Science and Technology Facilities Council

Technical Report
STFC-TR-2026-008

UK XFEL Science Case 2020 edition

J Marangos, J Collier, J Green,
D Dunning, et.al.

March 2026

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Enquiries concerning this report should be addressed to:

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DOI: 10.5286/stfctr.2026008

ISSN 2753-5797

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UK XFEL Science Case

The production team for the UK XFEL Science Case was as follows:

Editor: Jon Marangos

STFC Sponsor: John Collier

Production: Tracey Burge, Andrew Collins, James Green and Jon Marangos

Authors from the Science Team:

Andrew Burnett, Marco Borghesi, Andrew Comley, Mark Dean, Sofia Diaz-Moreno, David Dye, Jason Greenwood, Andrew Higginbotham, Adam Kirrander, Jon Marangos, Malcolm McMahon, Russell Minns, Marcus Newton, Allen Orville, Thomas Penfold, Anna Regoutz, Ian Robinson, David Rugg, Sven Schroeder, Jasper van Thor, Sam Vinko, Simon Wall, Justin Wark, Julia Weinstein, Amelle Zair and Xiaodong Zhang

Facility Science and Technology

Jim Clarke, John Collier, Louise Cowie, David Dunning, James Green, Neil Thompson and Peter Williams

Additional contributing authors

Massimo Altarelli, Frederico Alves Lima, Moatez Attallah, Shakil Awan, Stuart Bartlett, James Baxter, Uwe Bergmann, Tom Blackburn, Rebecca Boll, Stefano Bonetti, Christian Bressler, Bill Brocklesby, Colin Brown, Will Bryan, Phillip Bucksbaum, Richard Catlow, Roy Chantrell, Aina Cohen, Simon Coles, James Cryan, Georgi Dakovski, Sarnjeet Dhesi, John Dyke, Daniel Eakins, Gwyndaf Evans, Michael Foerst, Leszek Frasinski, Gianluca Gregori, Markus Guehr, Fahim Habib, Dave Hall, Samar Hasnain, Thomas Heinzl, Bernhard Hidding, Simon Hooker, Nils Huse, Olof Johansson, David Keen, Premysl Kolorenc, Adrian Mancuso, Stuart Mangles, Mattias Marklund, Steve Matthews, Stewart McWilliams, Martin McCoustra, Paul McKenna, Christopher Milne, Henrike Mueller-Werkmeister, Shaul Mukamel, James Naismith, Keith Nelson, Abbas Ourmazd, Robin Owen, Foivos Perakis, Paolo Radaelli, Dave Riley, Alex Robinson, John Rodenberg, Nina Rohringer, Kai Rossnagel, Marco Ruberti, Christopher Russo, Charlotte Sanders, Marcus Scheck, Paul Scherkl, Christopher Schofield, Robbie Scott, Edward Snell, Emma Springate, David Stuart, Geoff Thornton, Joachim von Zanthier, Martin Walsh, Mark Warren, Peter Weber, Philippe Wernet and Junko Yano

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Glossary

ARPES	Angle-resolved Photoemission Spectroscopy
CDI	Coherent Diffractive Imaging
CLF	Central Laser Facility
Cryo-EM	Cryogenic Electron Microscopy
ESCA	Electron Spectroscopy for Chemical Analysis
EUV /XUV	Extreme Ultraviolet (20 - 200 eV)
EXAFS	Extended X-ray Absorption Fine Structure
HAXPES	Hard X-ray Photoelectron Spectroscopy
HED	High Energy Density
HHG	High Harmonic Generation
HXR	Hard X-ray (4 keV - 100 keV)
ICS	Inverse Compton Scattering
IR	Infrared
Linac	Linear Accelerator
LWFA	Laser Wakefield Acceleration
MX	Macromolecular Crystallography
NC	Normal Conducting
ODL	Orbital Degeneracy Lifting
PDF	Pair Distribution Function
PWFA	Plasma Wakefield Acceleration
QED	Quantum Electro-Dynamics
RAL	Rutherford Appleton Laboratory
RIXS	Resonant Inelastic X-ray Scattering
SASE	Self-amplified Spontaneous Emission
SC	Super Conducting
SCO	Spin-crossover
SFX	Serial Femtosecond Crystallography
STFC	Science and Technology Facilities Council
SXR	Soft X-ray (200 - 4 keV)
THz	Terahertz (10^{12} Hz)
UED	Ultrafast Electron Diffraction
UKRI	UK Research and Innovation
UV	Ultraviolet
VUV	Vacuum Ultraviolet (10 - 20 eV)
WAXS	Wide Angle X-ray Scattering
WDM	Warm Dense Matter
XANES	X-ray Absorption Near Edge Structure
XAS	X-ray Absorption Spectroscopy
XES	X-ray Emission Spectroscopy
XFEL	X-ray Free Electron Laser
XFELO	XFEL Oscillator
XPCS	X-ray Photon Correlation Spectroscopy
XPS	X-ray Photoelectron Spectroscopy

Units

Time

Attosecond	1 as = 10^{-18} s
	Attosecond range 1 - 1000 as
Femtosecond	1 fs = 10^{-15} s
	Femtosecond range 1 - 1000 fs
Picosecond	1 ps = 10^{-12} s
	Picosecond range 1 - 1000 ps
Nanosecond	1 ns = 10^{-9} s
	Nanosecond range 1 - 1000 ns

Length

Ångstrom	1 Å = 10^{-10} m
Nanometre	1 nm = 10^{-9} m

Metric prefixes

exa	E	10^{18}
peta	P	10^{15}
tera	T	10^{12}
giga	G	10^{9}
mega	M	10^{6}
kilo	k	10^{3}
hecto	h	10^{2}
deca	da	10^{1}
		10^{0}
deci	d	10^{-1}
centi	c	10^{-2}
milli	m	10^{-3}
micro	μ	10^{-6}
nano	n	10^{-9}
pico	p	10^{-12}
femto	f	10^{-15}
atto	a	10^{-18}

> The question that the current UK XFEL Science Case seeks to address is how, over the coming decades, will the technological and scientific opportunities enabled by XFELs develop and what specific impact might there be from a UK machine aimed at offering new capabilities beyond those that exist today.

Foreword

The world's first X-ray free electron laser (XFEL) began operation in 2009 at Stanford, USA. In the following decade these machines have proven a powerful new tool for science. Using time resolved X ray methods, spectroscopy and scattering, they give a unique window into the structural and electronic dynamics of matter at the nanoscopic scale, imperative to further our understanding of critical natural processes in diverse settings from stellar and planetary cores, to biomolecules and chemical reactions, and to the development of new technologies based upon this understanding. There are now five XFELs operating in the world that have pioneered the application of new techniques across life, physical, chemical and material sciences, and generated important and transformative results. The UK is partner with one of these machine, the European XFEL in Hamburg operating since 2017, and UK users are active at all the other facilities. Although already proving highly impactful, XFELs are only at the beginning of their trajectory, and new capabilities are emerging that may prove still more significant. The question that the current UK XFEL Science Case seeks to address is how, over the coming decades, will the technological and scientific opportunities enabled by XFELs develop and what specific impact might there be from a UK machine aimed at offering new capabilities beyond those that exist today.

The process of preparing this Science Case began around a year ago with a broad-based community consultation that gathered data and ideas through a series on workshops involving key national and international scientists. The science team, comprising 25 scientific experts across a wide spectrum of fields and led by Prof. Jon Marangos of Imperial College, then distilled this input to form the current case. They were assisted by the expertise of 80 additional authors from the UK and overseas who contributed to the document. The intention is to look forward to what new capabilities a machine operating from around 2030 might be able to deliver. In the process the team drew on the expertise of the UK accelerator science and laser communities to identify a feasible set of advanced specifications that go beyond those currently available. The present case will now be shared with the UK scientific community and will be reviewed by external experts to establish whether or not there is a scientific "Mission Need" for such a machine. The establishment of "Mission Need" would then initiate a conceptual design study to examine the technical and financial feasibility of a UK XFEL.

The UK XFEL Science Case was developed through interaction with the UK scientific and technology communities and so it is natural now to share this output with those communities. It is hoped that this will enable further discussion informed by the substantial case now available for public examination and engagement. It is also hoped that this report will help to broaden the discussion to include other potential stakeholders in industry, academia, learned societies and government. A series of webinars will be held over the coming few months to present the main features of the case and to promote discussion. It is hoped that this will add to the Science Case and build a wider community support as well as promoting the wide benefits to science and technology that can be delivered by XFELs.

Professor Mark Thomson

Executive Chair, Science and Technology Facilities Council

1. UK XFEL Science Case – Executive Summary

An advanced X-ray free electron laser facility in the UK would create key new opportunities across the sciences and in technology, help to answer pressing scientific questions, and contribute to solving societal challenges of major importance. The facility would generate world-leading multidisciplinary advances. It would have a high impact in advancing technology, healthcare, frontiers of knowledge, net zero commitments and economic strengths, and provide a vital platform in creating a world-leading science and technology landscape in the UK, which will support advanced innovation. The facility would prove a vital resource for achieving step-changes in science and technology that address urgent societal challenges, e.g. in combating viral pandemics and attaining carbon neutrality and sustainability.

In this Science Case we address how construction of a UK X-ray free electron laser (XFEL) facility would create a national economic and industrial stimulus, forming an essential part of a science infrastructure landscape that ensures a vibrant, high technology environment, and helping to build and retain cutting-edge skills in the UK workforce. A UK XFEL will uphold national competitiveness in science, secure sovereign capabilities and grow new technologies of key importance to industry, healthcare and defence. We identify a path to create an XFEL infrastructure delivering a step-change in capability that will thrust UK science and technology ahead internationally in many vital areas.

The chief motivations for building a UK XFEL are:

- Unique X-ray and coupled capabilities can be optimised to create an ambitious, world-leading, UK XFEL for tackling emerging scientific and societal challenges
- Reinforces the UK as a centre for the most advanced science and innovation and will attract the best minds and boost skills in the national workforce
- Secures direct benefits to the UK economy from construction, procurement and operation, with high potential for levelling up R&D across the UK
- The UK will retain full control over the science and technology programme, and safeguard future sovereign capabilities and advances for industry, healthcare and defence.

In recognition of the growing importance of XFELs to current and future science and technology, leading industrial nations across the globe have established their own XFEL capability, with systems now in operation or under construction in the USA, Germany, Italy, Switzerland, Japan, Korea and China. XFELs are now recognised as indispensable to the development of new technologies where the quantum scale structural dynamics of matter must be understood and exploited. A primary driver for the Linac Coherent Light Source (LCLS) II in the USA has been its fundamental contribution to the Department of Energy's mission, most critically in Basic Energy Sciences, but also in National Security Science and aspects of the missions of other major agencies within the USA, including the National Institutes of Health (NIH) and the National Science Foundation (NSF). Similarly, the other international XFELs are seen as making essential contributions to science and to future economic and national strength.

Ultrafast X-rays from free electron lasers allow us to image the workings of matter at all relevant scales of both space and time. In common with neutron, synchrotron X-ray sources and electron microscopy, XFELs can establish the static structure of matter at the atomic scale. XFELs, however, are unique in that they can also allow us to follow the innumerable types of structural and electronic dynamics that are essential to understanding the workings of matter at the quantum scale, at their natural timescales of attoseconds to nanoseconds. They are therefore transformative in enabling the understanding and control of matter at the quantum *spatial* and *temporal* scales.

Intense X-ray pulses from XFELs open new windows into the understanding of light and matter in the universe, making possible a range of new opportunities, such as: probing properties of matter in solar and planetary interiors; understanding the basic interaction physics between photons (i.e. X-rays and gamma rays) and matter; and even providing new tests of the Standard Model. High brightness X-rays can be used to develop new technologies, for example X-ray lithography to engineer devices on the

nanometre scale. The energetic electron beam from the linear accelerator required to drive the X-ray laser can also be used directly to perform fundamental physics investigations, drive the world's brightest gamma ray source, and advance new accelerator technology.

Examples of big scientific questions that an advanced XFEL in the UK will be able to answer include:

- How do materials behave at the high pressures of planetary cores?
- How do enzyme-catalysed reactions occur in a living cell?
- How can we control states in quantum materials (e.g. superconductivity) with light?
- How do molecular machines efficiently cross energy barriers to drive biological processes?
- How do X-rays propagate in the interior of stars?
- How do liquids, like water, change and fluctuate at the nanoscopic scale?
- How can we optimally exploit quantum mechanics in solar and information technologies?

As well as underpinning a vast array of science, the capability and understanding delivered by an advanced UK XFEL will also be critical in the advancement of emerging technologies with great potential importance to UK industry and sovereign capability, including:

- Developing fast, energy efficient, compact data storage
- Optimising novel quantum sensors and quantum elements for information processing
- Advancing light harvesting, carbon capture with solar biofuel production, and energy storage technologies
- Discovering advanced drugs, antibiotics and antivirals
- Advancing catalysis and facilitating sustainable chemistry using Earth abundant elements
- Designing advanced materials for use in defence, industry and nuclear energy.

The new science and technology enabled by an advanced UK XFEL will boost delivery of the **UK government's Industrial Strategy**, through addressing the key challenges of **AI & Data Economy**, **Clean Growth**, **Future of Mobility** and an **Ageing Society**. For example, this facility will generate vast amounts of data that will require the development of cutting edge concepts to efficiently process, and so the UK XFEL will be a pioneering environment and incubator for new ideas in **Data, AI and Machine Learning** that can quickly propagate into the wider economy, along with the large numbers of highly trained scientists and engineers whose skills will be honed at the facility. In parallel to the Industrial Strategy, it will also address the themes integral to the **UKRI Strategy**. **Advancing technology** is addressed through the boost provided by space and time resolved understanding, leading to the development of new energy, data, nuclear and materials technologies. **Healthcare** is furthered by the profound advances in understanding of biochemical and biomolecular function, which allows better guidance in developing drugs and therapies. **Frontiers of knowledge** are advanced through the ability to probe quantum processes in matter and understand the couplings and interactions that underpin, for example, chemistry, materials science and life sciences, as well as through the potential to study matter at extreme conditions in the universe. **Net zero commitments** are underpinned by the space and time resolved data that is essential to developing sustainable approaches to catalysis, optimised combustion, carbon capture, and understanding the action of pollutants and particulates in the environment. In this latter area, the UK XFEL's mission resonates directly with the **UK government's Clean Growth Strategy**. Together these capabilities combine to boost **Economic strengths** as well as provide vital sovereign capabilities for the defence and the wellbeing of the nation.

In this Science Case, we explain these far-reaching science and technology opportunities, and detail how an advanced UK XFEL would deliver these opportunities. We outline ambitious XFEL facility options of realistic scale for the UK that would achieve this. The outline design options (an example is shown in **Figure 1.1** below) incorporate a wide array of unique features, in terms of the X-ray and accompanying capabilities, which will ensure a facility that will be both world-leading and able to tackle the most challenging research problems.

The international landscape of X-ray sources – synchrotron and XFEL – has seen rapid advances in the last decade. XFELs are now established in the USA, Germany, Switzerland, Italy, Japan, South Korea

and China, with multiple sources being planned at other locations. Similar growth has been seen with high brightness synchrotrons and, with the planned Diamond-II, the UK will maintain a strong presence in that technology and its application to increase understanding of the static structure of matter. What the UK must also secure is the capability for performing the most advanced time-resolved science that goes beyond the partial capabilities offered by ultrafast lasers, ultrafast electron diffraction and petawatt lasers. For this we will need extensive access to the very best XFEL facilities. A survey of research groups in the UK indicates that over 500 UK scientists have had active involvement in XFEL science in the last decade and the number is growing steadily. A huge advantage can be gained by developing a UK XFEL facility optimised with the most advanced features matched to our needs, ensuring long-term access and control, as well as direct benefits to the UK economy.

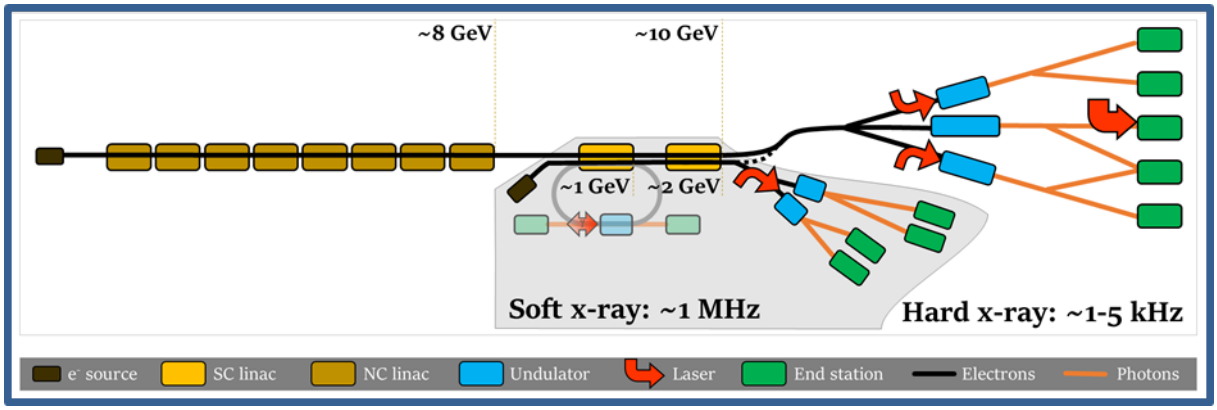

Figure 1.1: An outline design of one potential configuration with a unique combination of capabilities, able to deliver the science discussed in this case

We show that a UK XFEL can be designed to be a world-leading facility by integrating, in an optimised way, some of the exciting new developments emerging across the accelerator and X-ray science landscape. This ensures the highest quality and most versatile X-ray specifications, e.g. by moving beyond conventional X-ray generation schemes and exploiting developments in laser seeding, attosecond operation, and high brightness modes, to approach transform limited X-ray pulses of high spectral purity and brightness, and unprecedented temporal resolution. High repetition rate in the soft X-ray range, and moderately high repetition rate over the hard X-ray range, is a powerful combination and this would be both world-leading and cost effective. Access to the most advanced radiation sources (e.g. terahertz (THz), ultrafast laser and high harmonic generation (HHG)), relativistic electrons (from laser wakefield acceleration (LWFA)) and other charged particle beams to arrive synchronized to the X-rays at the interaction point, will allow for a wide range of unique science. Direct use of the high-quality relativistic electron beam can be harnessed to advance accelerator science (e.g. plasma wakefield accelerators) and deliver a gamma source brighter than any in the world, with substantial benefits to nuclear science and UK industry. Detector and sample delivery of the highest calibre will be developed alongside the light sources to provide best-in-the-world performance, with world-leading data handling and data science developments available to support the most advanced analysis. There is a timely opportunity to develop a world-leading XFEL facility with beyond state-of-the-art capability, to innovatively tackle vital science and technology challenges.

To allow the facility to deliver the fullest range of the potential science and technology, ease of accessibility for individual users, and for new user communities, is a critically important issue. In part, this can be addressed by designing appropriate technical configurations of instruments, end stations and data systems into the facility from the outset. The possibility of conducting experiments solely via user supplied samples, without on-site users, will be developed in scientific areas that are currently at an advanced level of technical maturity, such as serial nano-crystallography. This approach will significantly boost throughput and lower the threshold to access. The second part of the solution to lowering barriers to access will lie with offering improved training and support for new users, in order to develop, and widely propagate, the required expertise to use the facility effectively. We recommend that work on this should start now, building on the actions already undertaken by the Life and Physical Sciences Hubs at Harwell that currently support UK access. Related actions, such as establishing

dedicated Centres for Doctoral Training across a variety of science areas, should be undertaken with urgency. These measures are important to ensure readiness for a UK XFEL facility, but equally will allow UK science to successfully compete in using the existing international XFELs.

The transformative capabilities brought about by an advanced XFEL are in real-time imaging and measurement at the quantum scale that will underpin many future technological and scientific advances and developments in human health. No single technology, however, will solve all scientific problems. The solution to the challenges we face now, and the yet unforeseen challenges we will face in the future, will inevitably require a combination of technologies. An XFEL should be seen as an essential component in a wide-suite of capabilities that includes for example; lasers, spectroscopy, mass spectrometry, cryo-EM, synchrotron X-rays, ultrafast electron diffraction and neutrons. We further discuss these synergies in the Science Case.

The UK benefits from membership of the European XFEL in Hamburg. We must continue as a full member of this organisation, as this facility will remain one of the world's premier XFELs. In the longer term, the planned UK XFEL would deliver new capability beyond that at any existing facility and would remain complementary to the European XFEL. UK engagement with European science is likely to be maintained, but not substantially grow, over the coming decades. Clearly, we are now having to rethink strategies for protecting our best interests across a wide range of science and technology capabilities as geopolitical alignments evolve. **Secured access to the best XFEL facilities** is vital for ensuring, in the long-term, **sovereign** and **industrially critical capabilities**. A key advantage of building a UK XFEL infrastructure of international class is that it will ensure UK access to that capability, whilst being **a beacon to scientists from around the world** and a **catalyst for growing international collaborations**.

The direct national economic benefits of constructing and hosting a large scientific infrastructure in one's own country are substantial and well documented. Further benefits lie in opportunities for **greatly expanding the skills base in the UK workforce**, from PhDs and engineers, to technicians and apprentices. A UK XFEL would boost skills and attract and retain talent in areas critical to the economy, such as advanced electronics and control systems, optics, hardware and software for handling unprecedented data volumes, precision engineering and advanced manufacturing. The importance to future **key sovereign and industrial capabilities**, only available if we have **full control** on all decisions, must be at the core of making our plans. Without a UK XFEL programme, there is high risk of lost science and technology opportunities and, worse still, of a loss of skills in academia and industry and an accelerated brain drain. Building an XFEL is an essential part of a national strategy that ensures **we remain a technology maker**, and do not become merely a technology taker.

We should compare the current situation to that of the New Light Source (NLS) project in 2008-10, where high technical risks (*will XFELs work*?) and scientific risks (*will XFELs make a significant scientific impact*?) were seen. This encouraged a risk averse strategy, and led the UK to do nothing at the time. Now the situation is reversed. Today, the technical and scientific risks are looking low: these machines *work* and they *produce copious quantities of great science*. A 'do nothing' or a 'do little' strategy is now the riskiest (as we discuss in **Section 9**) and could severely damage national competitiveness, technology and sovereign capability, and scientific standing. The more ambitious the machine, the lower the future risks to UK science and technology.

In this Science Case, we discuss the main scientific opportunities as currently foreseen and identify the capabilities required to realise these opportunities. We recommend that the most effective way to proceed, that maximises national benefit, is to develop an ambitious, advanced UK XFEL that is world-leading in key respects. We map out how this might be done and further recommend that the UK now embarks on the next stages towards building this infrastructure. There is a **timely opportunity** to develop a **world-leading scientific infrastructure with unique capability**, that enhances the portfolio of international XFELs and provides a **huge boost to UK science and innovation**.

2. Introduction

X-ray pulses emitted by X-ray free electron lasers (XFELs) are a billion times brighter and more than ten-thousand times shorter than pulses from other X-ray sources. This makes possible time-resolved X-ray measurements that access the quantum scales of space and time in matter. The impact of this new capability on science and technology through the 21st century looks to be as large as the applications of lasers and synchrotrons were in the 20th century.

This draft UK XFEL Science Case has been developed over the period July 2019 to May 2020 through a wide community consultation, including a series of seven workshops, along with extensive analysis and discussion. Whilst much of the material has been prepared by the core science team and staff from STFC's RAL/Diamond and Daresbury sites, there has also been extensive input from many scientists around the country and overseas, for which we are immensely grateful. A further revision was undertaken between July and mid-September 2020 with input from the community. This input is reflected in the current authorship. The Science Case is anticipated to continue to evolve through further community engagement over the coming months.

This draft Science Case contains an analysis of the societal challenges and scientific opportunities that can be addressed by a unique UK XFEL. These opportunities exist across a broad range of disciplines: physics and X-ray photonics; matter at extreme conditions; quantum and nanomaterials; chemical sciences and energy; life sciences; and applications to industry, medicine and defence. These opportunities are discussed in their respective sections (**3 – 8**). In **Section 9**, we examine the technical capabilities required to capture these opportunities, and how the integration with other capabilities in the UK landscape will be vital; we also present and analyse a range of options to deliver this science, and discuss the next steps required in the development of this infrastructure. A series of Appendices is included that present: outline designs of machines that can satisfy all, or a large part, of the science demand (**Appendix 1**); the broader developing methodological landscape (**Appendix 2**); assessments of synergies with other technologies (**Appendix 3**); and a survey of the community development and the engagement exercises undertaken (**Appendix 4**).

We begin in this section with an introduction to the science and technology that underlies the draft Science Case, starting with a primer on XFEL sources and a broad-brush preview of the scientific opportunities. This introduces the dominant science driver for XFELs, which is access to the dynamical processes in matter on the quantum length and time scales that are relevant to chemistry, biology, materials and technology. We then go on to introduce the powerful time-resolved methods, i.e. X-ray spectroscopy and scattering, that are enabled by an XFEL. By way of establishing an international context for the UK XFEL, we present a brief survey of existing XFELs. Finally within this section, we discuss the array of new capabilities that could form part of an adventurous UK XFEL, and which would lead to ground-breaking scientific and technological opportunities, and enhance the international landscape. As a new facility, a UK XFEL would be superbly positioned to implement recent and emerging advances in X-ray modes, advancing the scientific reach made possible by XFELs to deliver transformative science.

2.1 Overview of the impact of XFELs on science

XFELs have led to transformative developments in light source science over the last decade. Numerous scientific applications have already been achieved, and original methods and approaches are being developed in many areas that anticipate future impact. The discoveries enabled by XFELs are still expanding and new ideas are being explored, but, after only ten years, the impact is already well demonstrated.

The mechanism of X-ray free electron laser radiation has its origins in the formation of self-modulation of a relativistic electron beam as it radiates in an undulator (**Figure 2.1**). In an XFEL, high quality relativistic (3 – 15 GeV) electron bunches of low emittance are required, necessitating the use of large-scale, high-performance linear electron accelerators. On entering the alternating polarity magnetic field structure of the undulator, the electrons begin to radiate and, critically, there is a back reaction of the radiation upon the electrons in the bunch. Passage through a sufficient length of undulators leads to a regular structuring of the electron density in the bunch, the consequence of which is coherent, high brightness X-ray radiation. This process, termed Self-Amplified Spontaneous Emission[1,2] (SASE), is the dominant principle of operation of free electron lasers in the X-ray region.

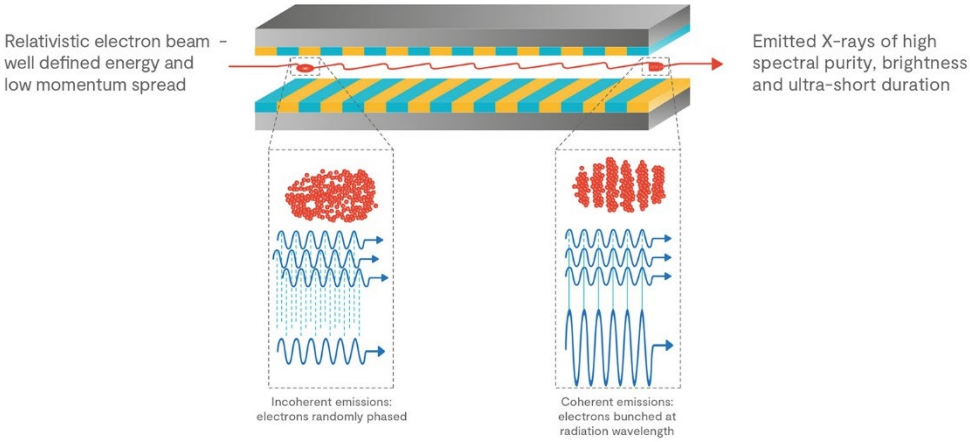

Figure 2.1: Principle of operation of a SASE X-ray Free Electron Laser
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Lasing in the vacuum ultra-violet range via this method was achieved at the Deutsches Elektronen-Synchrotron (DESY) in Hamburg, and this machine began operating as the FLASH user facility from 2005, with more recent extension into the soft X-ray (SXR) range.[3] The Linac Coherent Light Source (LCLS) at the SLAC National Accelerator Laboratory in California first lased in the X-ray range in April 2009,[4] heralding a new dawn in X-ray science. In the relatively short time since then, there have been numerous demonstrations of important new science (as discussed in this Science Case) and a number of new X-ray facilities have begun operation around the world.

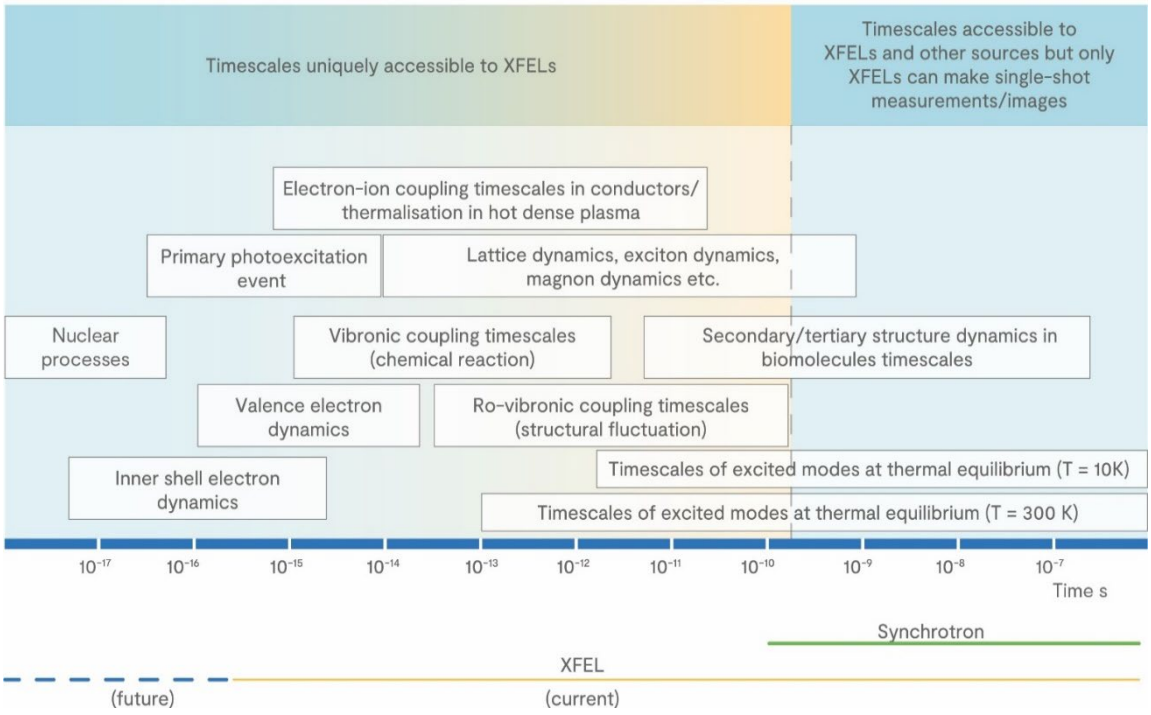
Other concepts are now being explored to extend the capabilities of X-ray lasers, including the consideration of oscillator-based lasing, as first envisioned by John Madey[5] (the inventor of the FEL concept). Laser preconditioning of the electron bunch (seeding) before it enters the undulator has proved effective at greatly improving the coherence properties and stability of the output, with this approach successfully demonstrated in the soft X-ray range at the FERMI facility[6] in Italy. Lasing on a very short, single SASE spike, leading to near transform limited operation, has also been developed through manipulation of the phase space of the incoming electron bunch, with the first demonstration of attosecond time domain isolated pulses[7] at LCLS within the last year.

With the capabilities of these light sources developing so rapidly, we are heading into the next generation of XFELs with far greater control of the X-ray pulses. It is these opportunities that the UK XFEL is positioned to progress and apply to a still wider range of scientific challenges.

The properties of light from free electron lasers are dramatically different from those of storage rings and conventional lasers. Storage ring synchrotron radiation has enormous spectral coverage and can deliver a high photon fluence (photons per second) up to hard X-rays (10s of keV), which has allowed these sources to be the dominant tool for crystallography, X-ray spectroscopy and many other areas of X-ray science for the last four decades. These sources do, however, have low peak brightness, especially if a narrow spectral bandwidth or a short pulse is selected. With advanced pulse slicing, they can provide sub-picosecond temporal resolution, but only with a tiny flux, which severely limits the utility for measuring rapid changes. Conventional lasers have advanced hugely in recent years and can produce extremely short pulses (~5 fs) at very high brightness, but these capabilities are limited to a restricted spectral range (0.5 – 5 eV). With high harmonic generation (HHG) the accessible range can be extended, but the low inherent conversion efficiency (< 10^{-6} in the extreme ultraviolet (XUV) and < 10^{-8} in the SXR) is a severe restriction to fully exploiting incisive X-ray techniques, like X-ray spectroscopy at atomic edges, and atomic position resolution by X-ray diffraction.

SASE free electron lasers deliver coherent radiation across an exceptional spectral range (< 10 eV to multiple-keV), with narrow bandwidth (~0.1% of photon energy) and very energetic (millijoule/10^{12} photons per pulse) short pulses (~1 fs duration), and therefore with exceptional brightness. A FEL undulator produces this very bright pulse at the fundamental frequency, but also bright pulses at three- and five-times that frequency (the harmonics), with the photon number dropping by a factor of around 100 at each harmonic step. This is a vastly wider spectral range than that covered by conventional lasers, and the pulses are typically a hundred thousand times shorter and millions of times brighter than those that a storage ring can provide. XFELs are having a revolutionary impact on the science we do with light, potentially as far-reaching in impact as that created by the laser and synchrotron radiation in earlier decades.

Box 2.1: XFELs provide unique access to the structure and dynamics of matter at the quantum scale: nanometre spatial and ultrafast temporal scales



Ultrafast X-rays from free electron lasers allow us to image the workings of matter at all relevant scales of both space and time. XFELs, in common with neutron, synchrotron X-ray sources and electron microscopy, can establish the static structure of matter at the atomic scale. XFELs, however, are unique in that they also allow us to follow, at their natural attosecond – nanosecond timescales, the myriad structural dynamics that are essential to understanding the workings of matter at the quantum scale. They are transformative in enabling the understanding and control of matter at the quantum spatial and temporal scales.

The main science driver for X-ray FELs is the access to the structural dynamics of matter at the quantum scale (see **Box 2.1**). XFELs provide access to the atomic (ångstrom) spatial and few-to-sub-femtosecond temporal scales of matter. This is achieved by way of time-resolved X-ray scattering and X-ray spectroscopy (**Section 2.2**), which together enable determination of the instantaneous geometric structure and electronic-state characteristics. Incisive time-resolved probing allows us to measure dynamical processes and the coupling between different components of a quantum system, including that between electronic excitations, and vibrational and rotational dynamics, in molecules and macromolecules, as well as collective modes, such as phonons, excitons, polaritons and magnons, in condensed-phase systems. The practical importance of understanding these couplings and quantum dynamics is clear, for example, if we consider that much sustainable technology is energized by the absorption of light from the Sun, and that efficient and cost-effective devices and processes require a quantum-level understanding of the chain of processes that follow the initial electronic photoexcitation.

In the decade since their first operation, numerous XFEL applications have been demonstrated. It is impossible to detail all of this work, but we cover a representative sample through this Science Case. Here, we offer a few recent examples of significant results that serve to illustrate the impact of XFELs across multiple scientific disciplines: these topics are discussed further in **Sections 3 – 8**.

The opportunities afforded by XFELs in time-resolved studies have already advanced research in the chemical and physical sciences. Recent liquid and gas phase chemistry studies have improved our understanding of chemical dynamics of relevance to catalysis,[8,9] where X-ray emission spectroscopy has proved a decisive method in resolving research questions. Combining X-ray diffraction and X-ray emission from molecules of interest in biochemistry is also proving very promising, with some recent work by Kern *et al.*[10] leading to new insights on the photosystem II complex photocycle. Much opportunity has also been enabled in physics, where pump-probe methods have allowed the interrogation and study of dynamics in states only transiently accessible, for example, high pressure shocks, hot dense matter, matter dressed by lasers and matter in extreme electric and magnetic fields. Recent examples for matter at extreme conditions include probing shock compression of materials[11] and probing laser generated dense matter.[12] Optical and terahertz (THz) field dressing of quantum materials probed by XFEL pulses is leading to the discovery of hidden phases of significance to high T_c superconductivity and other functional properties.[13,14] Further opportunities in time-resolved X-ray emission spectroscopy (XES) and X-ray photoelectron spectroscopy (XPS) for chemical dynamics and resonant inelastic X-ray scattering (RIXS) for materials science will be enabled by the far higher sensitivity offered by the high repetition rate XFELs that are now becoming operational.

In life sciences, an important early scientific breakthrough with FLASH, the XUV FEL at Hamburg, was the coherent diffractive single shot imaging of biological and non-biological structures led by Hajdu and Chapman.[15] These same ideas have since been implemented at LCLS, and promising results are emerging on imaging non-periodic, non-reproducible structures and nanocrystals utilising the single shot coherent diffraction imaging (CDI) methodology. In the future, there is potential for such a technique to provide nanoscopic imaging of biological assemblies and molecular machines within the necessary time resolution and under operating conditions (i.e. living cell temperatures). It has been in the sphere of serial femtosecond nano-crystallography (SFX) that XFELs have had the largest impact, so far, in life sciences. SFX is opening up the study of otherwise inaccessible proteins, such as membrane proteins that frequently cannot be made to form macroscopic crystals, and also allowing structures to be studied free of radiation damage and potential cryo-artefacts. Recent examples include investigations of light harvesting in photosystem II,[16] and studies of the protein that is a critical agent in sleeping sickness[17] and of the machinery of neuronal molecular transport.[18] Although not yet competing with the rate of protein structures deposited in the data banks by synchrotron studies, the opportunity to solve structures not otherwise tractable makes XFEL-based crystallography very valuable to structural biology. Moreover, XFELs bring the unique possibility of studying the structural dynamics of light-activated proteins, something that has not been possible before, as illustrated in Pande *et al*.[19] which resolved the structural dynamics occurring in the photo-excited cis/trans isomerization induced in the photo-active yellow protein. A recent ground-breaking study has shown

the possibility of using the snap-shot imaging capability of an XFEL to study rare, but functionally critical, conformational changes in a virus.[20]

These are a few examples from a rapidly growing body of scientific literature all enabled by XFELs; there are several recent reviews and special issues that offer a detailed and up-to-date survey.[21,22] Although these achievements are already impressive, we should keep in mind that XFEL light sources have only been available for just over a decade. Much development has taken place and much more must be anticipated as the newer and upgraded facilities start to operate.

There remains enormous, as yet untapped, scientific and technological potential for these light sources. A UK XFEL with increased control over the X-ray output, a large data acquisition rate and the most innovative accompanying capabilities at the interaction point (e.g. lasers, THz, ebeams) will be transformative in tapping this full potential. Key questions that an advanced UK XFEL can answer include:

- How do materials behave at the high pressures of planetary cores?
- How do enzyme-catalysed reactions occur in a living cell?
- How can we control states in quantum materials (e.g. superconductivity) with light?
- How do molecular machines efficiently cross energy barriers to drive biological processes?
- How do X-rays propagate in the cores of stars?
- How do liquids, like water, change and fluctuate at the nanoscopic scale?
- How can we optimally exploit quantum mechanics in solar technologies?
- How can intense X-ray pulses be used for advanced semiconductor chip manufacturing?

In the Sections that follow, these topics and many others are considered in greater detail and emerging opportunities across a wide range of science are highlighted and discussed.

2.2 Time and space resolved measurement with an XFEL

The combination of time-resolved X-ray scattering and X-ray spectroscopy that can be performed at XFELs is proving transformative. These methods enable measurements, resolved in space and time, of the electronic and structural dynamics at the fundamental quantum scales for solids, liquids, nano-assemblies and molecules relevant to physics, chemistry, material and life sciences.

2.2.1 X-ray structural and electronic probes

The short wavelengths of X-ray photons, and the short de Broglie wavelengths of electrons and neutrons of appropriate energy, permit diffraction imaging of the structure of matter at the atomic spatial scale. In contrast to the case for neutrons and electrons, with X-rays it is also possible to interrogate the electronic states of matter through various types of spectroscopy, and this has proved key to elucidating the electronic and geometric structure of materials, molecules and biomolecules. The frontier challenge is also to measure the dynamics of these electronic and structural properties, which at the nanoscopic/quantum scale are typically very fast (attosecond – nanosecond) (see **Box 2.1**). Such time-resolved measurements require very short duration X-ray probes, to enable this structural information to be sampled at a sufficiently high temporal resolution. X-ray pulses from XFELs are routinely generated with 10 fs or shorter duration, with sub-femtosecond modes now available, which match to this task. In this Section, we briefly overview the classes of time-resolved X-ray probing techniques that are available, and then discuss the types of measurements that are currently being made (see **Box 2.2**).

2.2.2 Time-resolved X-ray scattering

X-rays may interact with matter via either elastic or inelastic scattering (the latter is discussed with X-ray spectroscopy in **Section 2.2.3**). The elastic scattering signal is dominated by Thomson scattering from the large number of electrons localised to the atomic sites. If the scattering is from a periodic structure (see **Figure 2.2)**, such as a crystal lattice, constructive interference between the scattered X-ray waves leads to strong peaks at certain angles (Bragg peaks),[23] which give the reciprocal space information from which the lattice structure can be readily retrieved. Through serial exposures, high brightness X-rays, such as those available from an XFEL, enable the lattice structure of nanocrystals to be retrieved with atomic resolution. This has proven of significant value, as many proteins can only be crystallized to form nanoscopic, rather than macroscopic, crystals.[24]

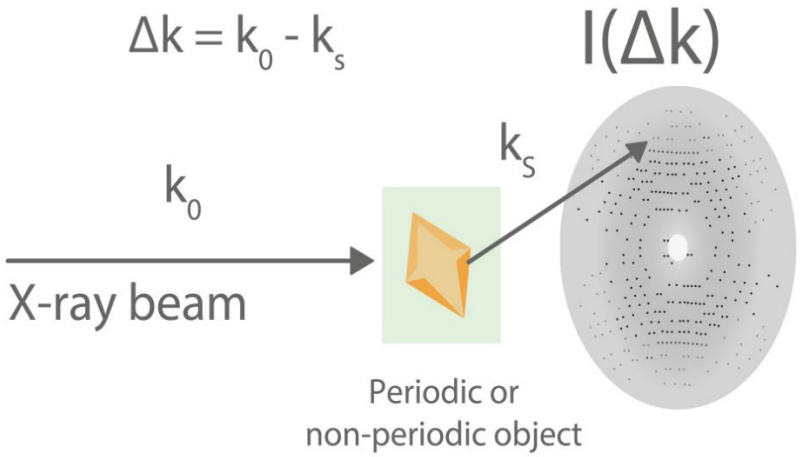


Figure 2.2: X-ray scattering, from either a crystal or a non-periodic object, leads to a distinct diffraction pattern from which the structure can be reconstructed. Through the high temporal resolution now available at XFELs structural dynamics can be followed in full detail

Even in a non-periodic structure, the X-ray scattering signal for spatially coherent X-rays can give a complex diffraction pattern from which the structure can be retrieved, using powerful algorithms that numerically solve the phase problem by applying various physical constraints in an iterative retrieval procedure.[25,26] This coherent diffraction imaging (CDI) procedure is well suited to the high brightness coherent X-rays from XFELs, and the concept of "diffract-before-destroy" for imaging non-periodic structures has been used to gain nanometre resolution in a variety of biological[27] and non-biological[28] nanoscale structures. Although not yet reaching atomic resolution, advances towards 0.5 nm resolution are being made as the technique develops. The possibilities for static nanoscale imaging of single particles by CDI are being actively pursued at all of the XFELs currently in operation and progress is regularly being reported (see **Sections 3.4** and **7.5**).

The X-ray pulses from XFELs have a very short duration, as well as a very high brightness; consequently, if they are applied time synchronized with another interaction that can initiate structural change, then time-resolved X-ray diffraction becomes possible. Such a scenario is termed a 'pump-probe measurement', with temporal information gained by repeating the measurement over the appropriate range of pump-probe delays. A significant number of recent experiments illustrating this possibility have been carried out at the LCLS and SACLA (SPring-8 Angstrom Compact free-electron LAser in Japan) XFELs. The X-ray brightness is high enough even to capture structural changes in an ensemble of gas phase small molecules,[29] and pump-probe measurements of laser activated molecular dynamics have revealed photochemical structural changes that occur over a few hundreds of femtoseconds. Structural changes of much larger photoactive protein molecules, in a nanocrystalline form, have also been captured in a number of cases.[19] Optical and THz fields can be used to induce non-equilibrium phases in strongly correlated quantum condensed phase materials with new emergent properties, and these too have been captured by time-resolved X-ray diffraction.[16] Recently, progress has been made on short electron pulse generation for ultrafast electron diffraction (UED),[30,31,32] although accessing the sub-10 fs temporal range remains challenging and UED returns no information on the electronic quantum states. The synergy of XFEL and UED techniques is discussed in **Appendix 2.1**.

For time-resolved studies, unless picosecond resolution is sufficient, technical effort must be applied to establish the relative timing of X-ray and optical pulses. In the LCLS (the first X-ray FEL), there was an intrinsic temporal jitter of up to several hundred femtoseconds; in the newer facilities, this has been reduced through improved temporal synchronization technology and the development of a number of so called "time-tools",[33,34] at LCLS and elsewhere, that can sort the pulse timing to a fidelity of better than 10 femtoseconds. Future machines with lower intrinsic jitter and higher resolution time-tools are under development;[35,36] these are anticipated for widespread use that will improve the achievable resolution eventually to better than 1 fs. This timing technology is also vital for the time-resolved X-ray spectroscopy techniques discussed in **Section 2.2.3** below.

2.2.3 Time-resolved X-ray spectroscopy

Inelastic X-ray interactions can be enormously powerful, and their measurement via various channels forms the basis of several well-established X-ray spectroscopy techniques (see **Figure 2.3**): X-ray photoelectron spectroscopy (XPS); Auger electron spectroscopy; X-ray absorption spectroscopy (XAS); X-ray emission spectroscopies (XES) and resonant inelastic X-ray scattering (RIXS). With XFEL pulses, these X-ray spectroscopy tools can be made time-resolved, with temporal resolution in the femtosecond and, in the near future, even the sub-femtosecond range.

Photoelectron emission results when an X-ray photon is absorbed by the target and a bound electron is excited to the continuum from valence to inner shell states. If X-rays of well-defined energy are used, the energy analysis of the photoelectrons emitted from the valence and inner shells gives direct information on the binding energies of these states. Angularly-resolved measurements of the photoelectrons can give additional detailed information on state symmetries. This technique has been widely exploited to investigate the chemical state of materials and, in this form, is often termed Electron Spectroscopy for Chemical Analysis (ESCA), following the pioneering developments by Siegbahn[37] that led to his Nobel Prize in Physics in 1981.

Ionisation of an inner shell electron can lead to an unstable electronic hole, which can undergo decay through electron-electron correlation with the emission of further Auger electrons.[38] Auger electrons carry information on the energy levels of the involved ionic forms. It has been shown to be possible to track mechanisms of radiation damage in biomolecules[39] using time-resolved X-ray Auger and absorption spectroscopy probing of optically excited molecules at an XFEL. Streaking in a laser field of atomic photoelectrons and Auger electrons has been used to resolve temporal delays in emissions from different states, with as little as a few tens of attosecond difference,[40] and these methods are being developed at XFELs.

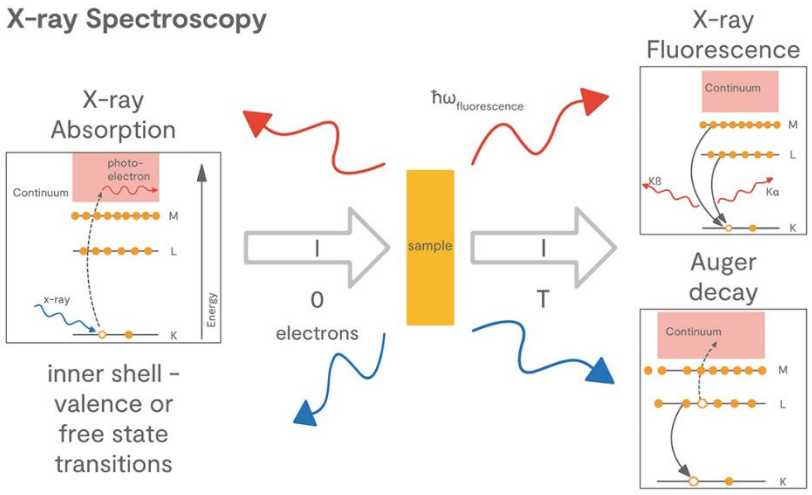


Figure 2.3: X-ray spectroscopy is sensitive to the electronic states, their energies, populations, symmetries and interactions. Utilising the specificity afforded by atomic X-ray absorption edges time-resolved X-ray spectroscopy can give access to the local evolution of states in space and time

Resonant ionisation close to an absorption edge of a particular atom, corresponding to a transition from an inner shell state to an unoccupied valence or low-lying continuum state, is a powerful way to learn about the electronic structure in the vicinity of that atom. The cross-section for photo-absorption at different X-ray energies can be determined from absorption or electron yield measurements in a condensed phase or gaseous system, and can reveal the details of the unoccupied and partially occupied valence and low continuum states near the ionisation threshold. This method of X-ray absorption near edge structure (XANES) is widely used to establish critical local electronic structure information.[41] Further into the continuum, the absorption modulations are termed extended X-ray absorption fine structure (EXAFS) and have been used for many years to establish local bond lengths around a specific atomic site.[42] Time-resolved X-ray absorption and emission (XAS and XES) using XFELs are now proven techniques for photochemistry studies.[10]

X-ray photon emission measurement methods are now being used in time-resolved mode using XFELs. For example, with RIXS, a core excited intermediate state relaxes to one or other of the neutral valence states by emission of a photon, and the energy and direction (momentum transfer) of the emitted photons are measured using an angularly resolving X-ray spectrometer. In the language of non-linear optics, this process is termed spontaneous Raman scattering. The energy levels of the occupied and partially occupied states can be registered from this signal, as well as the existence of the low energy collective excitation modes and their momenta. This provides a powerful way to probe low energy (eV to meV) excitation modes in a condensed phase material. Time-resolved RIXS studies have proved valuable in elucidating the nature of excitations in photoexcited correlated materials.[43]

RIXS and other photon in/photon out methods using spontaneous emission are two-photon in nature, although scale only linearly with X-ray field intensity. The spontaneous emission is, however, into unoccupied field modes and is therefore not controlled by the applied X-ray fields. High brightness X-ray sources provide new opportunities for controlled non-linear X-ray processes. One example is stimulated X-ray Raman, demonstrated experimentally by Rohringer *et al*.[44,45]

High brightness, high repetition rate XFELs open the possibility of non-linear X-ray spectroscopy with entirely new capabilities. An early proposal in this direction is the possibility of impulsive X-ray electronic Raman creating and probing atomically localised valence electronic excitation, and so tracking ultrafast electronic coupling through a molecule even on attosecond timescales.[46] This is just becoming possible through recent advances with attosecond pulses and is discussed further in **Section 3.3**. Another new concept is for non-linear X-ray diffraction involving a two-photon (optical and X-ray) scattering into an X-ray mode that can be heterodyne detected against an applied X-ray field in the same mode. This method is predicted to have the potential to image the charge density evolution of excited electronic states.[47]

2.2.4 Classes of measurements with XFELs

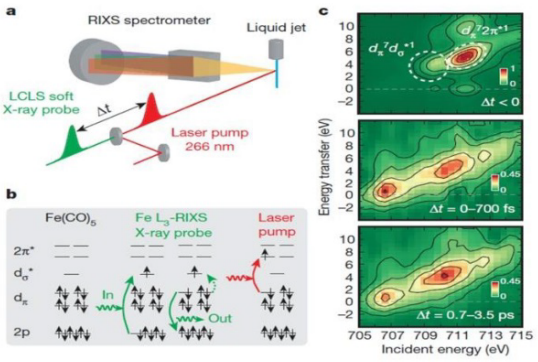
To date, the majority of studies conducted at XFELs have fitted into the categories of measurements of **structural dynamics**, **properties of transient state**, or **nano-crystallography**. These use a combination of X-ray scattering and spectroscopy. As repetition rates increase and the X-ray properties become more controlled, it is likely that classes of measurement based around coherent diffraction imaging, and studying fluctuations with X-ray correlation spectroscopy, time-resolved pair distribution functions and **mapping out conformational trajectories**, will become more important. The current state-of-the-art is illustrated in **Box 2.2**.

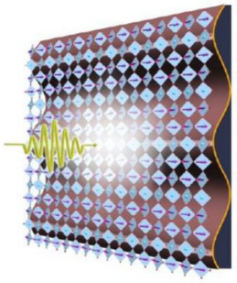
Looking ahead we anticipate a UK XFEL, with its suite of leading capabilities, will provide transformative opportunities including: higher temporal resolution, access to matter in a wider range of extreme states, greater data rates to capture the full range of fluctuations and rare events, and time-resolved structural information on scarce samples. In this way, it will be able to expand the scope of scientific investigation of the electronic and structural dynamics of matter, thereby profoundly increasing our understanding of the nanoscopic world that underpins so much of science and technology.

Box 2.2: Current forms of measurement being made at XFELs

Access to structural dynamics: Dynamical phenomena can be probed after laser excitation on a timescale down to femtoseconds, thus covering electronic dynamics, lattice dynamics and chemical bonds breaking/forming.

*Figure reproduced from P. Wernet et al., "Orbital-specific mapping of the ligand exchange dynamics of $Fe(CO)_5$ in solution" Nature **520**, 78 (2015), Springer Nature. DOI: 10.1038/nature14296*



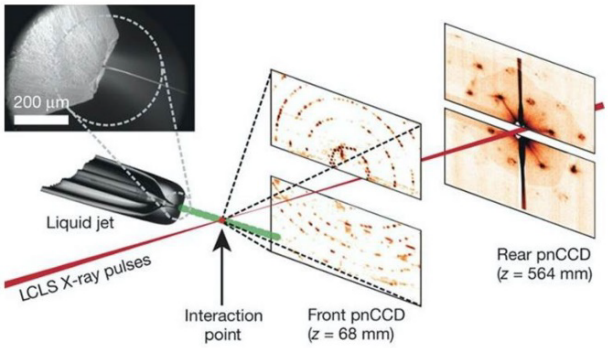


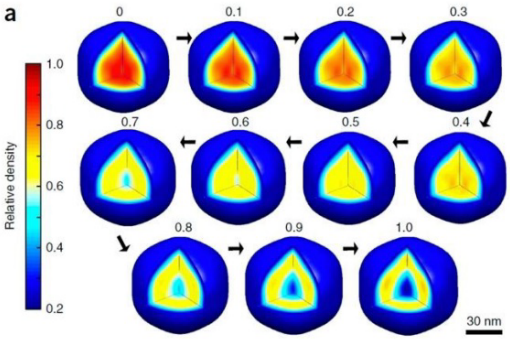
Access to transient states: Matter can be probed under only transiently attainable conditions of extreme pressure, high E and B fields, laser dressing and high energy density.

Courtesy of A. Cavalleri

New modes of crystallography and nanoscopic imaging: For seeing the nanoscopic arrangements relevant to nanotechnology and life-sciences free from radiation damage and adverse effects of sample preparation.

*Reprinted by permission from Springer Nature: H.N. Chapman et al. Nature **470**, 73 (2011). DOI: 10.1038/nature09750*





Capturing rare events: In physical, chemical and biological systems, critical processes can proceed through brief rare events (e.g. barrier crossings) arising from intrinsic fluctuations.

*Reprinted by permission from Springer Nature: A. Hosseinizadeh et al. Nature Methods **14**, 877 (2017). DOI: 10.1038/nmeth.4395*

2.3 Survey of existing facilities and capabilities

For the next decade, the UK will remain reliant on the international XFEL facilities in Germany, the USA, Japan, Switzerland, Italy, South Korea and China. To develop a future UK XFEL facility with unique capability, it is essential to plan this in the context of these existing facilities and other planned facilities in the pipeline. Here we briefly review the capabilities of the existing facilities and others due to start operating during the decade.

Now, and in the coming decades, the key frontier for a broad range of important scientific and technological disciplines will develop into the quantum realm, i.e. in a domain requiring measurement and understanding on ultra-small length scales, simultaneously with associated ultra-fast time scales. Accessing this domain, which is crucial for new knowledge, discovery and technological progress, is possible with an XFEL that provides insight into structural and electronic dynamics at the quantum scale.

Recognising this, there are currently five XFELs and three soft X-ray machines operating in the world, with several others under construction, notably in Asia. These few machines are already having significant global scientific impact, with a high proportion of their scientific output published in high impact journals. It is a signpost to the future, in much the same way that, decades ago, early synchrotrons, lasers, electron microscopy, etc. signalled new multi-disciplinary tools that we take for granted today.

Table 2.1: Summary of existing XFELs (March 2020)

Facility (Year of First Operation)	Max Photon Energy (keV)	Beam Energy (GeV)	Pulses/s	Bunch Charge (nC)	Facility Length (km)	RF Technology
FLASH, Hamburg (2005)	0.3	1.2	27000	1	0.32	SC
LCLS-I, Stanford (2009)	11	13.6	120	0.25	1.7	NC
SACLA, Harima (2011)	15	8.5	60	0.2	0.8	NC
FERMI, Trieste (2011)	0.3	1.5	50	0.5	0.5	NC
European XFEL, Hamburg (2017)	25	17.5	27000	1	3.4	SC
SwissFEL, Viligen (2017)	12	5.8	100	0.2	0.7	NC
PAL XFEL, Pohang (2017)	12	10	60	0.2	1	NC
LCLS-II, Stanford (2021)	5	4	10^6	0.1	4	SC
	25	15	120	0.125	4	NC
HE UPGRADE	12	8	10^6	0.1	4	SC
SHINE, Shanghai (2025)	25	8	10^6	0.1	3.1	SC

Table 2.1 lists the main parameters of short-wavelength FEL facilities in order of their coming online, and includes two facilities which are under construction and will be online in the next five years. The colour coding relates to the RF technology – superconducting (SC) or normal conducting (NC). The first facility to offer short-wavelength FEL light to users was the pioneering FLASH in 2005, recently upgraded to FLASH-II by including gap tunable undulators. FLASH was originally constructed as an SC linac test facility and the technological advances it produced were critical to the design and success of the European XFEL. The first hard X-ray facility was LCLS-I, which started operations in 2009, and has since been joined by facilities in Japan, the EU, Switzerland and South Korea.

SC technology permits a higher pulse repetition rate than NC. European XFEL (in common with FLASH) operates in a pulsed mode, where the RF cavities are switched on and off 10 times per second. This limits the total number of FEL pulses per second and is not favourable for some uses. When LCLS-II comes online from 2022, it will operate in a continuous wave (CW) mode, generating evenly spaced pulses at 1 MHz and photon energies up to 5 keV. For higher photon energies, the beam will be accelerated up to 15 GeV using the existing NC linac sections, so the FEL output will be limited to

120 Hz. The high-energy (HE) upgrade to LCLS-II will add extra SC linac sections to allow 1 MHz operation at 8 GeV, with expected photon energy 12 keV. Finally, the SHINE facility is under construction in a tunnel underneath Shanghai and is expected to be operational by 2025. SHINE will also be driven by an 8 GeV SC accelerator and will produce 1 MHz FEL pulses at energies up to 25 keV.

It should be noted that the accelerating gradients available from SC cavities are significantly less than those available from NC cavities – this is the reason that although LCLS-I and European XFEL have similar beam energies, European XFEL is twice as long. Another trend revealed by **Table 2.1** is that the required beam energy to produce hard X-ray photons has reduced over time. This is due to advances in undulator technology, such as narrow-gap in-vacuum devices or superconducting devices, which mean that shorter periods with stronger on-axis fields are now available.

All the operational machines listed have large international user communities, built up in the time since they first began operating. UK users have been very actively involved in science at FLASH, LCLS and SACLA (see **Figure 2.4**). User communities have rapidly grown around FERMI, European XFEL and PAL-XFEL, and are starting to turn their attention to Swiss-FEL. The UK user community is currently relatively small, compared to the synchrotron user community and, critically, to the XFEL, to the user communities in Germany, USA and other countries hosting these facilities. The UK community is, however, growing steadily, aided by initiatives such as the Life and Physical Sciences Hubs at Diamond and the CLF, respectively, and the new capabilities being offered as these international facilities evolve. It is vital for the strength of UK science across a wide range of areas that we do everything possible to grow this community substantially, otherwise we face losing our standing compared to the competition in key areas of frontier science and advanced technology, regardless of whether or not we build a UK XFEL.

Figure 2.4: Aerial views of operating XFELs: LCLS, USA (top left) started operating in 2009; SACLA, Japan (top right) operating since 2012; Swiss FEL, Switzerland (bottom left) operating since 2017; European XFEL, Germany (bottom right) operating since 2017

2.4 Outlook for a unique UK XFEL

In barely a decade since the first XFEL, remarkable progress has been made in adding new capabilities to this technology. Furthermore, the progress to-date represents only the very early stages in XFEL development – a host of further capabilities are being developed that would be incorporated into a UK XFEL. Building a new XFEL offers the opportunity to integrate the most exciting emerging features in an optimal way, to provide a combination of capabilities that will establish a facility of scientifically transformative potential.

The time is ripe to consider a new XFEL that builds upon what has been learnt from the first generation of machines. The first light from a free electron laser in the X-ray range was observed just 11 years ago (March 2009). The intervening decade has not only seen the construction of some half dozen machines around the world, but also enormous advances in the ability to simulate and implement new X-ray modes that are constantly advancing the scientific reach made possible by XFELs. These capabilities offer for example: two-colour, two pulse X-rays; variable polarization states; high spectral purity X-rays; higher brightness X-rays; and sub-femtosecond X-ray pulses. Many of these new capabilities go beyond SASE by manipulating the electron bunch (e.g. pre-modulation of density or controlled emittance spoiling) prior to it entering the undulator. Although all of these modes are underpinned by access to an excellent electron beam driver, they are ultimately controlled by the operating modes of the undulator and so, by using a versatile undulator design, all can be made available at a single facility if properly configured.

Existing facilities are often constrained by site and machine design factors, making it hard to offer all of these newer options or the combinations needed to optimise scientific impact. A UK XFEL, starting from a clean slate, could therefore leapfrog the existing facilities and would be superbly positioned to implement all of these advances, and to add to them other emerging capabilities.

In this section we briefly review a selection of the possibilities that can combine to deliver a facility of unique capability, one that can drive discovery and transformation in science. The majority of these modes are close to realisation or will need only moderate additional R&D (e.g. high repetition rate laser seeding, self-seeding, attosecond pulses, tapered undulators and additional external sources), whilst others still require demonstration and further R&D (e.g. external seeding for hard X-rays and return loop operation).

2.4.1 High repetition rate laser seeding

One area with exceptionally high potential for a UK XFEL is to extend the range of seeding[6] (introduced in **Section 2.1**) to much higher repetition rates and to higher photon energy. Seeding greatly improves the coherence properties and stability of the output. The FERMI facility in Italy has demonstrated seeding up to approximately 400 eV at a repetition rate of 50 Hz. In a recent demonstration,[48] two external lasers were used to precisely tailor the longitudinal phase space in the electron bunch before it entered the undulator. A UK XFEL could operate with a thousand times as many seeded pulses per second by utilising superconducting linear acceleration with high repetition rate (~100 kHz) lasers – both areas of UK expertise. In combination with high repetition rate sample delivery and detectors, the massively enhanced data acquisition rate would greatly speed up existing experimental techniques. In addition, this would also open up entirely new classes of experiment due to the excellent X-ray coherence and stability, for example in: X-ray emission spectroscopy[10] of dilute samples; X-ray angularly resolved photoelectron spectroscopy using the high repetition-rate to gain sufficient signal in the low space-charge limit; and transient grating measurements[49] of transport rates at sub-nanometre scales in materials. Furthermore, using the latest non-linear optical laser technology (see **Section 9.2.1**) to generate the appropriate seeding would extend the range over which seeding operates to reach higher photon energies (> 1 keV), thereby extending the benefits to new areas of science by spanning an important range of critical absorption edges in carbon, nitrogen, oxygen and metals.

2.4.2 High spectral purity X-rays

Laser seeding is anticipated to be less effective above 1 keV, but alternative technologies are being developed to improve coherence and stability at the higher photon energies. A useful figure of merit related to coherence is the relative spectral bandwidth, with smaller values indicating a higher degree of spectral purity. While existing XFELs typically operate with bandwidth between 1×10^{-3} for the default SASE mode and 2×10^{-4} for self-seeding (already introduced), new techniques are expected to far surpass this performance. Double self-seeding,[50] employing two monochromatisation stages within the FEL, has the potential to achieve bandwidths < 10^{-4}. High-Brightness SASE (HB-SASE),[51,52] a scheme developed by UK FEL physicists, could achieve a bandwidth of ~2×10^{-5}, and will be tested at soft X-ray at SwissFEL in 2021. Its use of magnetic delay chicanes rather than optics could prove more flexible to different energies and higher repetition rates.

A method that may promise the highest spectral purity in the future is the XFELO[53] (X-ray FEL Oscillator), which uses a low gain FEL enclosed in an optical cavity comprising diamond crystal Bragg mirrors with a geometry allowing a tunability of a few percent. Bandwidths of ~1×10^{-7} are anticipated, with modest pulse energies but exceptional shot-to-shot stability. Experiments to address the challenging cavity alignment tolerances are planned at LCLS-II. Such a scheme is, however, only possible on an accelerator with a repetition rate of around 1 MHz or higher, as below this optical cavity lengths become unfeasibly large. A facility with a high repetition beam at lower energy only (e.g. 2 GeV) could employ an oscillator FEL at soft X-ray/EUV wavelength, to provide good stability and spectral purity, and potentially provide seed pulses for an XFEL. Another future possibility is to seed directly at hard X-ray wavelengths. A potential seed source is under development at Arizona State University.[54] With this source, a compact low energy accelerator transforms a transverse electron diffraction pattern into coherent longitudinal electron bunching, into which a laser pulse is counter-propagated to produce a pulse of coherent hard X-rays with sufficient power to act as a seed for a longer XFEL amplifier. Experiments are underway and the results will be important to further planning.

2.4.3 Higher pulse energy

Pulses of high spectral purity, produced via any of the methods above, can be further amplified very efficiently by extending the FEL undulator beyond the normal saturation point, whilst tapering down the field strength to keep the FEL pulse in resonance with the decreasing electron bunch energy.[55] It is expected that increases in pulse energy of 1 – 2 orders of magnitude can be achieved using this tapering technique, with a simultaneous damping of the shot-to-shot fluctuations to a few percent. For example, by using low charge, highly compressed electron bunches in combination with self-seeding/HB-SASE and post-saturation tapering, it is anticipated that few-femtosecond, nearly transform-limited pulses, with > mJ pulse energies and few-percent shot-to-shot stability, could be produced.

2.4.4 Attosecond pulses

The recent demonstration of ~400 attosecond duration pulses at the LCLS facility (2018)[7] is a particularly significant development, and is a feature that would be a major focus of a new UK XFEL facility. The LCLS study reports one- and two-colour attosecond pulse generation over the photon energy range 500 eV – 1 keV, but it is anticipated that the same method will work through to the hard X-ray range. The study of dynamics on ultrafast timescales is one of the defining features of XFELs and is made possible by the ultrashort duration of the XFEL pulses. Moreover, the large coherent bandwidth (5 – 8 eV in the pulses generated so far) is a key resource for future multi-dimensional, non-linear X-ray spectroscopies. A number of demonstration experiments have already been carried out at LCLS using the attosecond X-rays, e.g. measuring relative photo-electron emission delays for ionisation from different states of a molecule, and demonstrating impulsive electronic X-ray Raman excitation.

The techniques demonstrated to-date all effectively ‘slice’ the electron bunch in order to generate a short X-ray pulse. This slicing has been done using the self-field generated in a wiggler section, with the phase space manipulated in a chicane before entering the undulator. The possibility of using lasers

instead of the self-field is also attractive, because, as the function of the laser is to slice rather than to seed, it could be performed at any photon energy, and would increase control and improve synchronisation to external sources. The pulses at higher photon energy would also be significantly shorter, to access even faster time-scales.

2.4.5 High average power

As well as high pulse energy, high average power from the X-rays and from the electron beam would open up unprecedented opportunities. The potential of XFELs in direct industrial processing, for example for photolithography at soft X-ray wavelengths to achieve deep sub-nanometre feature resolutions, is a little explored area, so far. Interest in this from companies in the semiconductor chip sector was registered in our information gathering exercise, but it is clear that, even for a test facility to prove the concepts, an exceptionally high repetition rate (multi-MHz) will be required. Adding a return loop or an energy recovery configured accelerator section at the front end (perhaps up to 1 GeV) could be used for such a purpose, before the bunches to be accelerated to a higher energy pass through a conventional linac section (see **Appendix 1**). This would also create opportunities for direct science access to a GeV range electron beam at a high repetition rate. An additional potential benefit of this is the construction of an ultra-high average brightness gamma source based upon inverse Compton scattering (discussed in **Sections 3 and 8**). Opportunities to develop a high repetition rate electron acceleration test facility will also be provided by the development of the relativistic high brightness linac required to drive the X-ray laser.

2.4.6 Combining X-rays with other sources

Beyond the potential for advanced X-ray modes sketched above, an enormous extension of science reach can be accomplished by combining other advanced capability at the X-ray interaction point. Ultrafast lasers, used with the X-rays in pump-probe configuration, are a mainstay of time-resolved XFEL research. Hitherto the laser photon energy ranges on offer at XFELs, and their pulse duration, have typically been rather limited due to practicalities and budgetary issues. In a machine designed to optimise these capabilities from scratch, the full range of pulse compressed laser/non-linear optical sources spanning from < 100 nm to 10 µm can be used for science (see **Section 9.2.1**), and with a repetition rate commensurate with experimental demands. By developing synchronised electron gun technology (in the 1 – 10 MeV energy range) at a number of end-stations, new opportunities in THz and electron-initiated biology, chemistry and physics, will become possible (see **Section 9.2.3**). A state-of-the-art, high repetition-rate, high power laser – essential for science in the area of X-ray non-linear interactions (see **Section 3**) and matter at extreme conditions research (see **Section 4**) – will also be able to launch synchronised energetic electrons or ions/protons into the sample at the interaction point, permitting a wide range of new experiments for material science, defence and astrophysical applications.

2.4.7 Conclusion

Only a sample of the possibilities for unique capability in a UK XFEL are covered above. It is also expected that advanced undulators[56] (e.g. superconducting) and ultra-low emittance electron sources will **extend photon energy reach** for a given electron beam energy, as well as facilitating higher energy per pulse. Harmonic lasing[57] will increase intensity at higher photon energies, too. In addition to combining X-rays with other advanced capabilities, **the two-colour (or multi-colour) FEL capability**[58] **could be greatly enhanced** in a facility designed for this purpose, with broader ranges of temporal and spectral separation. Advances are anticipated in the control of pulse structures beyond that already described, to include **control of polarisation, orbital angular momentum and carrier-envelope phase**. It is expected that **facility capacity can be increased**, e.g. following the approach of using fast-kickers demonstrated at European XFEL, and advanced controls incorporating machine learning will enable more **rapid optimisation and restoration of setups**.

In short, there are **clear opportunities for world-leading capabilities at a UK XFEL**, which can be optimised **to deliver transformative science.**

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3. Science Opportunities in Physics and X-ray Photonics

High intensity, ultrashort pulses of X-rays create new possibilities in physics and new potential in X-ray photonics that will find future application across the sciences. Here we consider new basic physics enabled by XFELs, and the exciting science opportunities provided by new X-ray based measurement methods.

Physics, and the exploration of new physical principles and methods, has been a major driver in the development of new light sources and their applications in science. From X-ray diffraction to the broad range of X-ray spectroscopy, the initial steps required the elucidation of physical principles, refinement of the measurement and analysis methods, and development of new instrumentation, in which physics played a primary and driving role. Given the unique new X-ray properties on offer from next-generation XFELs, for instance ultrashort pulses, large coherent bandwidth and ultra-high brightness, it is imperative that the new X-ray photonics and the physics of their interaction with matter is fully explored, not only because of the basic physics interest in its own right, but also in order to spur the development of new measurement methods and applications for future science. Moreover, these unique X-ray characteristics provide opportunities for fundamental physics experiments and tests. This section deals with a range of these opportunities, with an emphasis on looking forward to exciting new discoveries and frontiers.

The new capabilities are poised to answer some basic questions in the physical sciences, many of which can lead to wide application in other disciplines, including:

- What role does electronic quantum coherence play in the photo-excitation of matter?
- How do electron-nuclear couplings proceed and what role do conical intersections play in chemical reactions?
- What are the dynamical mechanisms for radiation damage in biomolecules?
- Can we map the conformational pathways of macromolecules traversing their energy landscape as they undergo function?
- Can we use X-rays to detect dark matter and for other fundamental tests?

First, in **Section 3.1**, we examine the basic interaction of intense X-rays with matter, and the opportunity this affords in chemical physics and solving basic questions of energy and charge transfer following photoexcitation. This has application to understanding the dynamics of radiation damage of biomolecules, probing and controlling chirality, and developing new probes for ultrafast quantum coherent phenomena. Next, in **Section 3.2**, we examine new opportunities in X-ray scattering that go beyond the conventional approaches of elastic non-resonant scattering and employ new concepts, by exploiting higher order photon correlation functions, quantum imaging concepts, inelastic scattering and signatures of electronic coherence in scattering. In **Section 3.3** we examine the new opportunities unlocked by the attosecond domain X-ray pulses that are now available. This includes the ultrafast probing of electronic coherence in new pump-probe X-ray spectroscopies, and the potential to exploit the large coherent bandwidth to develop new classes of non-linear X-ray spectroscopy. Non-linear X-ray spectroscopy has the potential to fully follow the propagation in space and time, and the decoherence pathways of electronic superposition states in matter. In **Section 3.4** we look at the potential opened by using high repetition-rate coherent diffraction imaging and related methods, along with advanced data sorting algorithms, to track the trajectory of molecular conformational change through the complex energy landscapes typical of biological and liquid systems. In **Section 3.5** we turn to tests of fundamental X-ray interaction physics, looking at non-linear QED physics and the potential for tests of the Standard Model using X-rays of extreme brightness in a facility offering a high repetition rate in order to capture rare events. Finally, in **Section 3.6**, we look at the added opportunity to directly use the high-quality relativistic electron beam that drives the XFEL to investigate new approaches in future accelerator and light source physics, and to drive the world's brightest gamma ray source.

3.1 Frontiers in ultrafast chemical physics

Ultrafast X-ray probing provides unprecedented insight into how energy and charge is transferred within and between molecules in processes such as photoexcitation or X-ray ionisation. Taking inspiration from non-linear optical spectroscopy techniques, and implementing them in the X-ray regime, will enable dynamic probing of electronic properties and how they couple to molecular structure. These techniques will prove key in finding answers to questions such as how DNA responds to ionising radiation and how to control photophysical processes at the quantum level.

3.1.1 Introduction

Light interactions with molecules were essential to the development of the conditions that made possible life on Earth. Irradiation of interstellar media created the molecular building blocks of life, while absorption and conversion of solar energy continues to sustain the processes that allow complex life to thrive. Light interactions are also critical for studying molecules during chemical reactions and biological processes, illuminating the structure and dynamics of reactants, catalysts and products as they evolve in time.

Conversion of light energy into molecular potential energy is initiated by the displacement of electrons in the molecule by an electromagnetic field. Coupling of electronic states results in charge displacement, which occurs on extremely fast (attosecond) timescales. Understanding and/or controlling how this charge is subsequently transferred and coupled to the molecular structure is key to determining how this energy is used to break or form bonds.

Photochemical processes are found in natural systems, such as those that govern vision,[1] vitamin D production,[2] photosynthesis,[3] UV photo-protection of DNA bases,[4] and the magnetic "vision" of migrating birds.[5] The charge transfer at the heart of these processes is equally relevant in determining the function of catalysts and batteries, and combustion and corrosion/degradation processes, such that these are optimised for particular applications. Questions remain about how electromagnetic energy is converted into chemical or electrical energy via coupling of electronic excitation into the molecular framework, with the experimental and theoretical tools available today unable to provide comprehensive answers.

Chemistry has predominantly relied upon an adiabatic description of chemical processes, where any atomic motion results in an almost instantaneous rearrangement of the electrons that "glue" the atoms together via bonds. In most situations, this assumption, known as the Born-Oppenheimer (BO) approximation, is reasonable, as the electrons are lighter and therefore move faster than the atoms. Following absorption of a photon, however, the potential energy surface of the excited electronic state has points or seams, called conical intersections, which cross with other electronic states. Near these intersections, as the separation of the electronic states becomes smaller, electron wavepacket motion slows down to the point where it becomes similar in magnitude to the motion of the atoms, and the BO approximation breaks down. This non-BO behaviour becomes more prevalent as the complexity and number of degrees of freedom of the molecules increases.

Theoretical simulations of molecules at conical intersections are particularly challenging to model, as the electronic and atomic motion cannot be de-coupled. With current models and computing power, this complex behaviour cannot be described accurately, even for relatively simple molecules, without significant approximation. Likewise, experimental methods currently lack the tools and observables that can broadly probe the motion of the system through a conical intersection.

3.1.2 New X-ray spectroscopy techniques

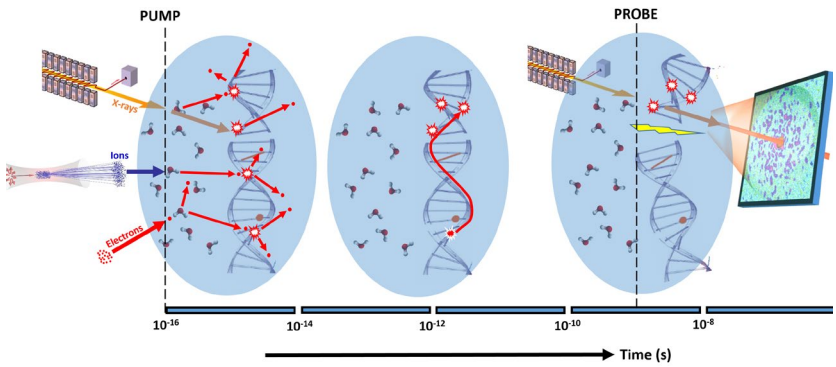
A range of ultrafast X-ray spectroscopy techniques has been developed at XFELs to exploit site-selective absorption by inner shell electrons in molecules. For example, X-ray near edge absorption spectroscopy, X-ray fluorescence spectroscopy, resonant inelastic X-ray scattering, and X-ray angle resolved photoelectron spectroscopy have been used as sensitive probes of chemical states and electronic structure. The advent of beamlines producing circularly polarised X-rays[6] has also enabled the chiral and magnetic properties of molecules and materials to be probed.

The high brightness and ultrafast pulse capability of a free electron laser will revolutionise X-ray spectroscopy by bringing it into the non-linear regime, facilitating the study of dynamical chemical processes with unprecedented temporal and spatial resolution. Non-linear spectroscopy, based on various absorption, fluorescence, wave mixing, and Raman schemes, has already been exploited in the optical domain to reveal details of the inter- and intra-molecular processes that govern transient chemical dynamics. This has shown how motion at the atomic level influences complex molecules and their biological function, but by translating these techniques into the X-ray regime with an XFEL, researchers will be able to delve down to the level of the electrons which underpin all molecular behaviour. As a result the critical electronic-nuclear couplings will be probed with atomic specificity, unravelling the behaviour at conical intersections and determining how charge and energy flows across and between molecules,[7,8] with sub-ångstrom resolution.

A range of X-ray spectroscopy techniques, coupled with optical techniques and X-ray diffraction imaging, can be combined in multi-pulse schemes to stimulate, observe, and even control chemical dynamics. This provides a powerful toolbox to answer some fundamental questions, such as how DNA reacts to ionising radiation[9] so that the mechanisms for cancer induction are understood and new ways of enhancing radiotherapy outcomes can be developed. For example, exciting new research has shown that high dose rate radiotherapy, which can be simulated in FEL experiments, is less toxic to healthy cells compared to cancer cells.[10]

Box 3.1 illustrates how an XFEL could be used to study the effects of radiation on isolated or solvated DNA in extraordinary detail. Different pulsed radiation sources (electrons, ions, X-rays) would initiate an interaction. The ionisation process and initial charge migration proceeds on an attosecond timescale, but, after as little as a few femtoseconds, the electron displacement couples to the molecular structure: this determines the ultimate destination of the charge, weakening or breaking bonds and transferring energy within the molecule or to its surroundings, on timescales from femtoseconds to microseconds. The electronic and nuclear coupling could be tracked over these timescales using the new non-linear spectroscopies and ultrafast diffraction available with XFEL pulses, in combination with synchronised optical lasers.

Box 3.1: Studying the effects of radiation on isolated or solvated DNA



Ionisation of DNA and its surroundings is initiated by a short burst of radiation (electrons, ions or X-rays). Charge is transferred on attosecond to picosecond timescales, ultimately causing bond cleavage and damage to the DNA. These steps can be probed at different times by XFEL pulses with linear and non-linear X-ray spectroscopies or ultrafast diffraction imaging.

Diffraction image and undulator illustration by Horst Frank, reproduced under terms of the Creative Commons Attribution License 3.0 BY

3.1.3 Chiral X-ray probes

One of the most intriguing scientific questions is why the molecular building blocks of life on Earth, such as amino acids and sugars, exist predominantly with 'one handedness'. This reflection asymmetry in molecules was termed *chirality* by Kelvin, and the mirror images are known as *enantiomers*. As a consequence of this chirality, the action of most biological processes depends critically on the handedness of receptors, enzymes, and drugs. Currently, the only way of identifying enantiomers is through interaction with another chiral object of known handedness. While circularly polarised light has long been exploited to help reveal structural asymmetries in molecules, the very small differences in the interaction of circularly polarized light with the opposite enantiomers limits the ability of light to identify and control molecular chirality. These chiroptical effects are weak because, from a molecule's perspective, the electric field's spiral rotation is much longer than the dimensions of the molecule itself, *i.e*. it is not present in the dipole approximation. Chiral differentiation relies on magnetic dipole interactions, which are orders of magnitude weaker, such that differences in the excitation rates of left- and right-handed enantiomers (circular dichroism) is typically <0.1%. However, as the wavelength of the light shortens and the chiral electric dipole interaction becomes stronger, XFEL pulses open up the possibility of probing the chirality of molecules and the magnetic properties of nanostructures on ultrafast timescales.

Recent discoveries have shown that asymmetries of 10% or more can be present in photoelectron angular distributions via electric dipole transitions to the continuum.[11,12,13] This photoelectron circular dichroism (PECD) originates from the interaction of the outgoing electron with the chiral potential of the molecule, with the electron being preferentially scattered parallel or anti-parallel to the light direction. This behaviour has been shown to be present for photoionisation of valence and inner shell electrons,[14] and in the single photon, multiphoton, and tunnelling ionisation regimes.[15] PECD therefore has the potential to become a universal sensitive observable for chiral dynamics.

Other developments have revealed that optical pulses can have more exotic configurations of their spin and orbital angular momentum. Pulses can now be produced where the local chirality changes rapidly in space and time, *e.g*. pulses with polarisations that map out all of the Poincaré sphere across the wavefront[16] or that have sub-cycle changes in the electric field rotation.[17]

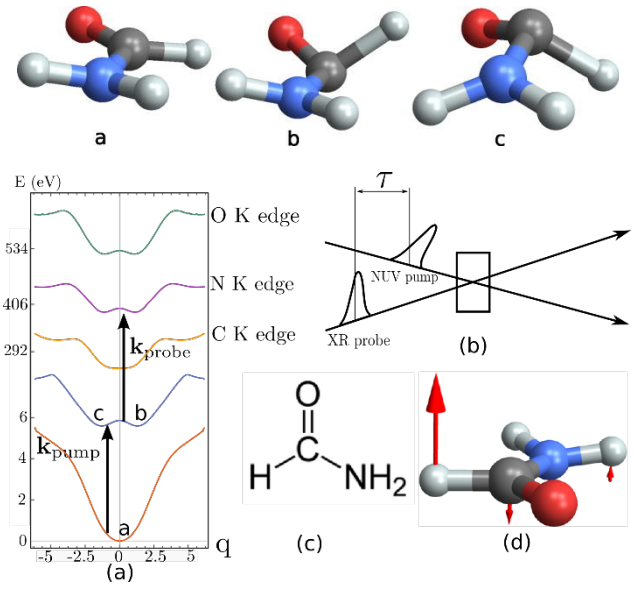


Figure 3.1: Potential for inducing, probing and controlling chirality.[20]

Chiral induction and ultrafast reversal in the planar molecule formamide: The formamide molecule is excited into a state which oscillates between two opposite chiral configurations. This transient chirality could be probed by circular dichroism in X-ray absorption or photoionization. Such a flagship experiment offers a first step on the road to exploiting light to control the creation and/or separation of specific enantiomers

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There are already proposals to implement some of these schemes for XFEL undulators.[18] Future developments will see pulses produced with electric fields that trace out 3D Lissajou patterns in space, enabling strong, direct coupling of the electric field to the chiral properties of the molecules via exclusively electric dipole interactions.[19] Combining optical and XFEL pulses of this nature will offer an unprecedented way of sensitively probing global and local changes in the symmetry of molecules on sub-optical cycle timescales. These fields also have the potential to induce chirality in achiral molecules and control the handedness of the products of chemical reactions.

Figure 3.1 demonstrates a formative experiment in which a chiral UV pulse projects the planar molecule formamide[20] from its achiral ground state (a) into an excited state with an initially chiral configuration (b). This creates a vibrational wavepacket in which the molecule flips between enantiomeric states (b,c) with a period of about 100 fs. This chiral induction and ultrafast reversal could be observed with an XFEL pulse through the circular dichroism in the absorption spectrum, or the asymmetry in photoelectron angular distributions.

A powerful XFEL which is capable of generating sychronised multi-colour X-ray pulses would enable such a scheme to be implemented so that chirality can be induced, controlled and probed at different centres within highly complex molecules. This opens up, for instance, the possibility of identifying the loss of chiral specificity within single proteins, which is believed to contribute to age-related illnesses such as cateracts and Alzheimer's disease.[21] These techniques could also transform the design and production of future chiral pharmaceutical and agrochemical products, which facilitate selective pharmacological and species targeting required to reduce health and environmental side effects.

3.1.4 Molecules in intense X-ray fields

The high brightness of XFEL pulses presents opportunities to perform diffraction imaging of single molecules. At intensities of up to 10^{20} W cm^{-2}, however, is it possible to obtain scattering data from an unperturbed molecule before it is inevitably destroyed by the pulse? Conversely, could complementary structural information be derived from the resulting fragmentation dynamics? To answer these questions requires a fundamental understanding of how complex molecules couple to intense X-ray fields.

One would expect the molecules to attain high ionisation states before they explode through Coulomb repulsion of the multiply-charged fragments, as with intense optical laser pulses; however, for X-rays, sequential single photon ionisation of inner shell electrons is prevalent. If a heavy atom is present in the molecules, the X-ray field efficiently ionises its inner shell electrons. Within a few femtoseconds, Auger processes ionize outer electrons while re-filling the inner shell holes. This results in sequential photoionisation-Auger events, generating an even higher charge state of the atom.[22] This charge has been found to quickly distribute around the molecule, via processes such as inter-atomic Coulombic decay (ICD), so that further absorption and ionisation of X-ray photons takes place. These mechanisms produce a charge state of the molecule which is higher than could be obtained for the atom by itself.[23]

This dramatic and ultrafast shift in electrons within the molecule means that it suffers radiation damage, since the initial electron distribution is altered substantially. Additionally, on timescales as short as 10 fs, Coulomb repulsion is already pushing the atoms from their equilibrium positions. This has consequences for XFEL diffraction imaging of single molecules, and these effects need to be considered to enable correct interpretation of single-molecule scattering patterns.

These processes have been observed in atoms and small molecules,[24] and very recently in fullerene,[25] but much more complex molecules need to be studied in order to see how electronic coupling behaves over greater spatial extents. Fragmentation patterns of complex molecules can themselves yield important structural information and can reveal details of how biological structures are damaged by ionizing radiation. Coulomb explosion imaging (CEI) has been established using intense optical pulses, with the momentum vectors of the fragment ions used to recreate the molecular structure,[26] and has already been applied to obtain the absolute configuration of some simple chiral molecules.[27] The higher charge states that can be reached by XFEL pulses will improve the resolution of the molecular

reconstruction obtained from CEI. Molecular models are also being developed to include the initial vibrational motion of the atoms and the subsequent nuclear dynamics,[28] giving multi-pulse schemes the potential to generate high resolution, ultrafast molecular movies of atomic motion in the molecule. The ability to observe fast proton migration within molecules is particularly important, as this migration drives many chemical processes, but cannot been seen with X-ray diffraction techniques that rely on scattering from electrons.

These developments will depend upon the continued development of multi-hit detector technology[29] and correlation mapping,[30] to enable the complex fragmentation patterns generated from large molecules to be interpreted meaningfully. For instance, co-variance mapping has recently been used to study the fragmentation patterns of trapped peptide ions, enabling detailed information on amino acid sequences and chemical modifications to be obtained.[31] Similar schemes could be highly valuable for studying how biological molecules suffer radiation damage following irradiation with ionizing particles.

3.1.5 Future vision

The development of a next-generation XFEL with high repetition rates, high pulse energies, multi-pulse sequences consisting of individually configurable wavelengths and polarisation states, and attosecond pulse durations will revolutionise how molecular systems are studied and understood. Huge steps forward in detector technology, capable of handling MHz repetition rates and manifold coincident hits (100s per pulse), will herald the dawn of multi-dimensional non-linear X-ray spectroscopy and fragmentation imaging. When placed alongside innovative X-ray diffraction techniques, this will provide sub-ångstrom and sub-femtosecond resolution of all molecular components – electrons, protons and ions. Using the comprehensive data provided by these complementary techniques, artificial intelligence advances will be exploited to re-create accurate, multi-faceted movies of the structure and dynamics of complex molecular systems, such as real-time atomic resolution of enzymatic action (see **Section 7.3**).

In addition, site-selective X-ray absorption within complex molecules, combined with spatial and temporal control of the pulse's electric field, will be a powerful probe of localised quantum properties within the molecule. In this way the properties of chromophores, reaction nodes, and chiral centres critical to molecular functionality will be revealed, by mapping out the electronic and nuclear motion on the multi-dimensional landscape that is found near conical intersections. These will provide insight, for instance, into how photosynthetic systems efficiently convert light into charge separation and how the chirality of life can be compromised, thus leading to age-related diseases.

Ultimately, this knowledge will enable the design of functionalised molecules, which can: emit light of different colours and polarisation depending on the environment and nature of the stimulus; transform the efficiency of solar harvesting devices; or change their pharmacological action inside patients following absorption of infrared light or X-rays.

3.2 New concepts in scattering

The arrangement of atoms in matter and the motion of those atoms is fundamental for comprehension of the function of material systems. XFELs enable us to determine dynamic changes in structure, providing insight that will allow us to engineer molecular machines and devise new catalytic processes. By combining ultrafast X-ray scattering with novel ideas from quantum optics and scattering physics, we will be able to explore new physics, circumvent the phase problem that currently restricts imaging of matter, study samples that are too disordered or fragile for today's technologies, and image important but elusive phenomena such as electron dynamics and coherent transport phenomena.

3.2.1 Introduction

X-ray scattering has shaped our understanding of the structure of matter. The iconic renderings of the arrangement of atoms in the DNA double-helix,[32] in proteins,[33] and in crystalline matter[34] constitute early breakthroughs that were rightfully awarded Nobel prizes. The number of known structures is growing exponentially[35] (see also **Section 7**), reflecting the importance of structure-function relationships in many branches of modern science and high-tech industries. This success notwithstanding, great opportunities remain to be explored.

The large photon-flux and coherence of XFELs, combined with cutting-edge ideas from, for example, quantum optics, may enable forms of single-particle imaging[36] that circumvent the requirement of crystalline targets and allow molecules to be observed in their natural state, avoiding distortion due to the crystalline environment. In many systems, the structure constantly fluctuates between many distinct thermodynamic states, with the rarest, and thus most difficult to observe, states playing important roles in the function of molecular machines such as enzymes. XFELs may allow us to image the whole range of thermodynamic states (see also **Section 3.4**). Furthermore, greater information might be extracted for delicate, fragile, or disordered materials that are challenging or impossible to study with the technologies available today. Perhaps most revolutionary, concepts are advanced that may overcome the *phase problem*, arguably the most defining challenge for all forms of x-ray imaging (see **Box 3.2**).

The short pulse duration at XFELs can have even greater impact. The absence of dynamics from the current structure-function dogma reflects the limitations of current imaging methods, which provide static and time-averaged images. The ability to measure the transformation of one structure into another made possible by XFELs may transform the development of future nanoscale technologies and bring greater understanding to all aspects of structural science. For instance, by measuring time-resolved sequences of molecular structures on a femtosecond timescale, the motion of atoms in a molecule following the interaction with light can be revealed, with great impact on our understanding of energy and charge transport and chemical reactivity, which could be exploited in areas such as photonics, catalysis and molecular electronics.

These new opportunities come alongside new and exciting physics. Imaging techniques, such as ghost imaging, exploit ideas from quantum optics and involve the detection of photons that never interact with the sample, with the quantum version of ghost imaging going one step further by using entangled photons. Likewise, ultrafast measurements with hard X-rays may transgress current distinctions between structural dynamics and spectroscopy, and provide insights into the fundamental nature of the combined motions of electrons and nuclei that cannot be achieved by other means. Finally, theoretical predictions indicate that, for sufficient time-resolution and coherence, new quantum interference phenomena in scattering will appear, carrying unique information about ultrafast electron dynamics and transient coherences in material systems.

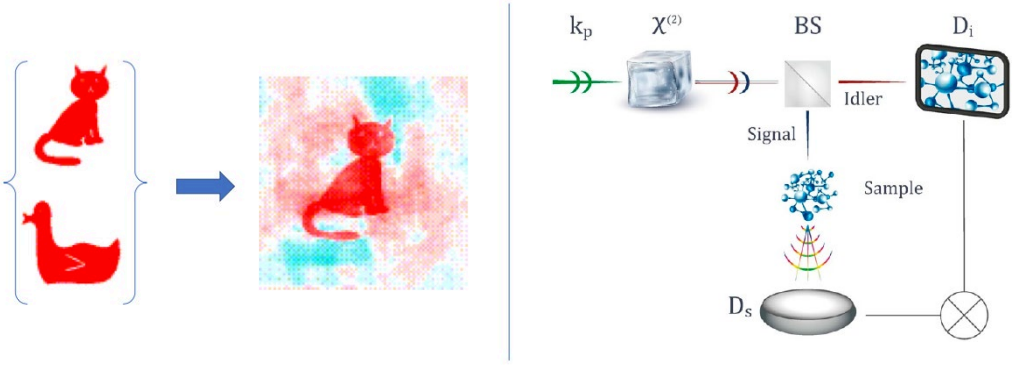
3.2.2 New imaging techniques

Correlated X-ray scattering, or fluctuation X-ray scattering, detects momentum-transfer correlations between two or more photons scattered by the same molecule, making it possible to determine structure in the absence or short- or long-range order. The concept, advanced in the late 1970s,[37,38]

remained largely undeveloped until the emergence XFELs, which finally provided sufficient photon fluence and pulse durations shorter than rotational diffusion times. In 2017, it was demonstrated at LCLS that angular correlations can determine nanoscale structural features of viruses.[39] With currently existing XFELs, the signal to noise ratio is still insufficient to determine the atomic structure of particles as complex as proteins, but with further improvements in photon fluence, the technology may attain this goal. Apart from studies in native environments, the method could also become instrumental in single-particle imaging, where it could overcome the issue of unknown sample orientations.[40]

Ghost imaging originates in quantum optics[41] and exploits the observation of photon correlations. These protocols have been extended to classical light,[42,43] making them relevant to non-seeded XFEL sources. The immediate advantage of ghost imaging is that the radiation dose absorbed by a fragile sample can be lowered dramatically.[44] The approach also offers distinct improvements in resolution, signal to noise, and, under specific circumstances, greater efficiency in data collection.[45] At optical wavelengths, it has been demonstrated that ghost imaging can provide special performance when parametric down-conversion is phase-matched to give non-degenerate signal and idler wavelengths.[46] This allows an object to be illuminated at one wavelength and the spatial information recorded at another, perhaps where the imaging detector is more sensitive or less noisy. Ghost tomography schemes have been proposed that aim at atomic resolution of complex targets,[47] and analogous ideas have been put forward that exploit the random time-structure of SASE pulses to achieve pump-probe resolution of dynamics without actual time-delay scans.[48] An interesting opportunity at future high-flux XFELs is quantum ghost imaging via parametric down-conversion of X-ray photons, allowing one photon of an entangled pair to be diffracted off a sample and detected in coincidence with its twin.[49] By scanning the photon that did not interact with the target, the phase information imprinted in the state of the field can be detected, which could yield real-space images that avoid the phase problem altogether (see **Box 3.2**).

Box 3.2: Real-space imaging with XFELs



Current imaging techniques measure the amplitudes but not the phases of the light. This so-called phase problem imposes significant limitations on imaging, as illustrated on the left. If we combine the phases for the cat with the amplitudes for the duck, the resulting image looks more like a cat than a duck (http://www.ysbl.york.ac.uk/~cowtan/fourier/fourier.html). Ideas from quantum optics, e.g. ghost imaging or incoherent diffraction, may overcome this problem. On the right, a proposed quantum diffraction setup is shown that would be capable of measuring phase. [49]

*Figure reproduced from S. Asban et al. PNAS **116** 11673-11678. Copyright (2019) National Academy of Sciences*

Another exciting technique that originates in ideas originally put forward by Hanbury Brown and Twiss is incoherent diffractive imaging,[50,51,52] which exploits higher-order correlations between fluorescence emission from different atoms to retrieve structural information. This approach may provide striking advantages, such as element specificity, and opportunities for phasing in a manner analogous to anomalous dispersion when performed in conjunction with coherent diffraction.[50] Since the cross-section for incoherent fluorescence emission is higher than that for elastic scattering, incoherent diffraction can produce stronger signals than standard coherent diffraction and detect higher

momentum transfer, thanks to the uniform angular distribution of fluorescence emission. The cumulative result is a potential for rapid structure determination that requires a significantly smaller number of observations to fill the full 3D Fourier space than conventional methods,[50] and sub-Abbe resolution may be achieved if higher than second order correlations are exploited.[49,53] The concept has recently been demonstrated at the FLASH XFEL using a patterned mask,[52] as shown in **Figure 3.2**. Similarly to the other techniques discussed in this section, incoherent diffractive imaging requires the extreme brilliance and high pulse repetition rate of new XFEL sources. It also requires pulse durations shorter than the radiative lifetime of fluorescence (e.g. 2.6 fs for the K_α fluorescence in Fe atoms). A striking prospective application could be ultra-high resolution of yet unresolved structural changes in metal clusters in Photosystem II, which are essential for the manner in which water is oxidised during photosynthesis.

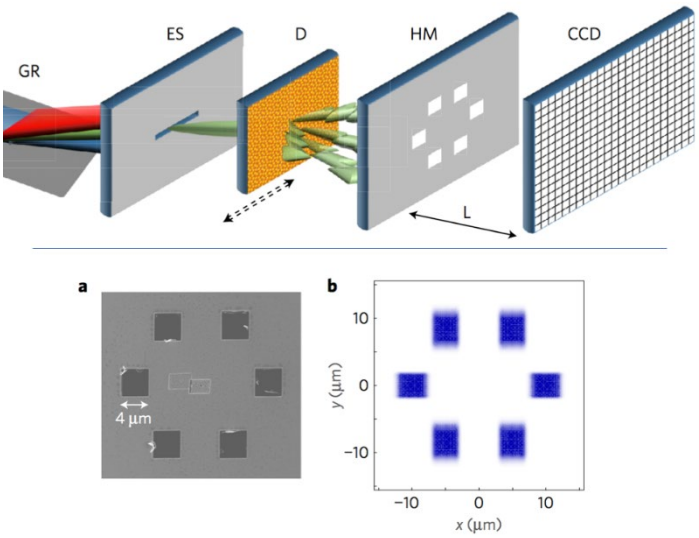


Figure 3.2: The first demonstration of incoherent diffraction using a microscale patterned mask at the FLASH XFEL.[52] (Top) Experimental setup with grating (GR), exit slit (ES), diffusor (D), hole mask (HM), and a CCD detector. a) Hole mask, b) reconstructed image.

*Figure reproduced from R. Schneider et al. "Quantum imaging with incoherently scattered light from a free-electron laser" Nat. Phys. **14**, 126-129 (2018), Springer Nature. DOI: 10.1038/nphys4301*

3.2.3 Structural dynamics and beyond

Ultrafast X-ray scattering at XFELs is opening the door to observations of structural dynamics at the fundamental timescale of nuclear motion, on the order of femtoseconds (10^{-15} s). This information is not readily available from ultrafast spectroscopy and brings unique insights into the atomic motions that underpin transformations in matter. With sufficient spatial and temporal resolution, it is possible to observe the fundamental steps in bond-breaking, bond-making, and atomic re-arrangements, for instance following photoexcitation. Recent experiments at LCLS demonstrated structure determination in excited molecules undergoing coherent vibrations,[54] as shown in **Figure 3.3** (*Right*), and the dynamics associated with rapid electrocyclic ring-opening reactions.[55] The measurements will transgress simplistic notions of structural dynamics, as analysis of the ultrafast X-ray scattering data can reveal normal modes and associated frequencies, thus combining sub-ångström resolution of atomic displacements with resolution of e.g. harmonic spectroscopic modes.[56,57] As the resolution increases, it will become possible to track the time-evolution of the quantum wavepacket for excited systems, identify excited electronic states, and directly observe intrinsically quantum phenomena such as dispersion, coherence, and interference.[58, 59,60]

Importantly, the scattered X-ray photons carry an imprint of the actual electron density of the material system. A recent experiment shown in **Figure 3.3** (*Left*) demonstrates that short-lived electronic states can be observed using ultrafast X-ray scattering at XFELs.[61] Taking into account expected improvements in signal-to-noise at future XFELs with a higher repetition rate, it is reasonable to expect

that we will succeed in simultaneously tracking both the structural dynamics and the changes in electronic structure which drive the nuclear motion. The ability to characterise nuclear and electronic motions in a single experiment will boost our ability to diagnose and improve molecular devices such as fluorescent probes, photocatalyst, and photovoltaics. On a more fundamental level, accurate measurements made possible by the large X-ray photon flux may reveal intrinsic correlation effects in electronic structure, leading to advances in electronic structure theory and the computational modeling of materials.

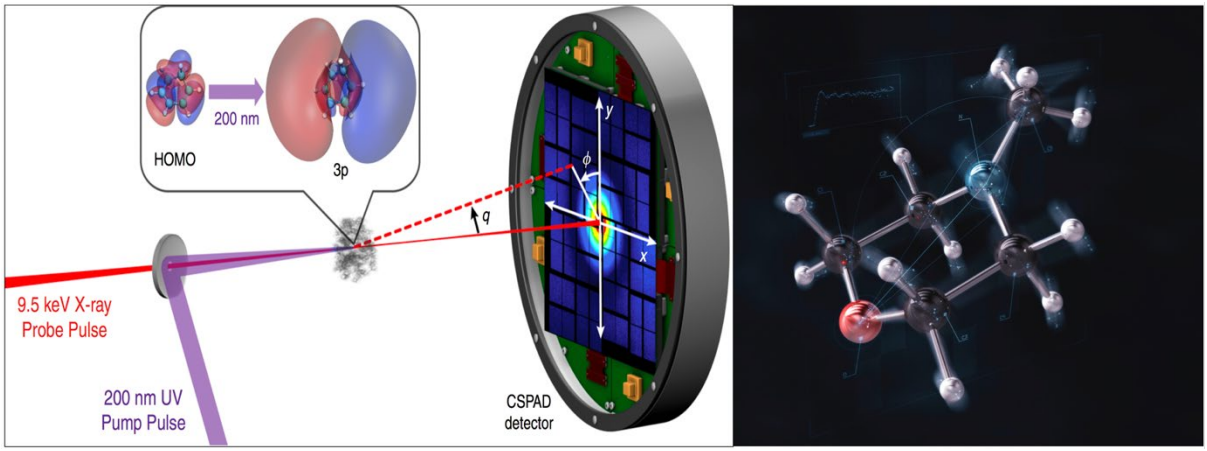


Figure 3.3: (Left) Schematic of the first experiment to directly observe an excited electronic state in a molecule using ultrafast x-ray scattering.[61] (Right) A recent experiment has been able to accurately measure bond distances in an excited molecule undergoing harmonic vibration.[54]

Figure reproduced from H. Yong et al. "Observation of the molecular response to light upon photoexcitation" Nat. Comms. ***11****, 2157 (2018), Springer Nature. DOI: 10.1038/s41467-020-15680-4*

3.2.4 Physics of scattering with coherent X-rays

The coherence in the incident X-ray radiation, combined with the ultrashort time-duration of the pulses, is expected to lead to new observable phenomena due to interferences between different inelastic transitions. Such interferences in X-ray scattering, sometimes referred to as coherent mixed scattering,[62] have been theoretically predicted to carry the signatures of ultrafast electron dynamics,[63] transient nuclear coherences,[62] and transitions between different electronic states due to nonadiabatic coupling[64] or at conical intersections.[65] **Figure 3.4** shows how transient nuclear coherences may manifest in scattering.

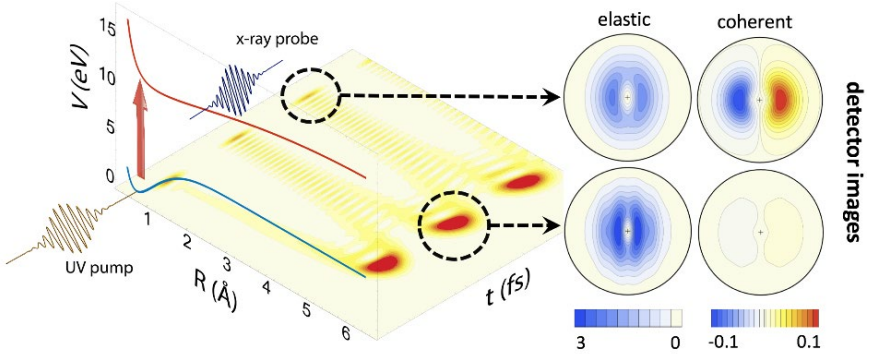


Figure 3.4: Coherent mixed scattering appears as a consequence of coherent electron dynamics and may help characterise complex dynamic processes in matter. On the left-hand side, an optically pumped wavepacket is shown, with the X-ray scattering detector images showing elastic and coherent mixed scattering shown on the right[62,66]

Figure reproduced from M. Simmermacher et al. "Electronic Coherence in Ultrafast X-Ray Scattering from Molecular Wave Packets" Phys. Rev. Lett ***122****, 073003 (2019), American Physical Society. DOI: 10.1103/PhysRevLett.122.073003*

The coherent mixed scattering will appear alongside elastic and inelastic scattering, and stems from an interference of scattering amplitudes from different electronic states populated in an excited

molecule,[62,66] as shown in **Figure 3.4** and **Figure 3.5**. The effect requires coherence between populated electronic states, meaning that their nuclear wavefunctions must overlap. Such coherences emerge transiently during photochemical reactions, when electronic states are coupled and transitions between them occur. Coherent mixed scattering should thus provide distinct fingerprints of internal conversion and intersystem crossing during photochemical and photophysical processes. It could furthermore be used to measure the role of coherence in energy transport[67] and charge migration.[68]

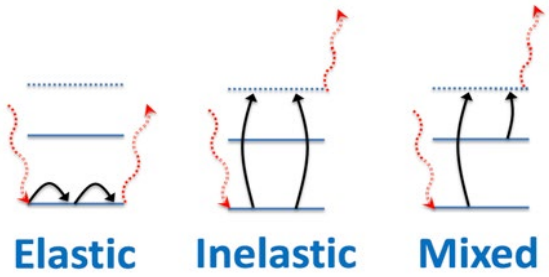


Figure 3.5: Schematic illustration of the components in X-ray scattering.
Populated states are shown as solid horizontal lines, vacant electronic states are shown as horizontal dotted lines, with the scattering transitions shown as curved black arrows (one for each scattering matrix element) and incident and scattered photons as curly red arrows. Elastic (left) and inelastic (middle) scattering are well known, but coherent mixed scattering constitutes a new predicted phenomenon that requires the coherence of XFELs to be observed.[62-66]

3.2.5 Conclusion and future outlook

The opportunities provided by XFELs paint an exciting picture for the future of X-ray science. Advances in X-ray imaging will make it possible to accurately determine structure and structural dynamics across large ranges of timescales, from femtoseconds to minutes, of complex molecular machines such as Photosystem II at sub-Abbe resolution, providing unprecedented insight into their workings. It is clear that imaging at XFELs will extend beyond the narrow definitions of imaging as a determination of the 3D structure of matter. Imaging experiments will be able to address specific atoms and atomic species, determine energetic properties of the system, probe electronic states and electronic motion, determine vibrational modes, and even probe subtle yet important quantum phenomena such as dispersion, interference and coherence.

Attosecond X-ray pulses with high repetition rate, at tuneable energy, and with transform limited bandwidth and high shot-to-shot reproducibility will be needed. These must be married to high-performance detectors that are possibly energy-resolved. Advanced optical laser facilities must accompany the X-rays, with sub-fs pump-probe synchronisation required to capture electronic coherences induced by optical pump pulses. It is to be expected that many of these auxiliary technologies will be developed over the next decade to be incorporated into a UK XFEL facility.

3.3 Attosecond science and non-linear X-ray spectroscopy

Electron dynamics, typically occurring on attosecond to femtosecond timescales, play a crucial role in a vast array of physical, biological and technological processes. High temporal resolution X-ray probes are essential to the understanding and harnessing of these processes, and will impact on knowledge and control of, for example, excitons in light harvesting systems, primary steps in photocatalysis, advanced photodetectors, and photodynamic therapy.

3.3.1 Introduction to new attosecond XFEL capability

There has been a rapid advance in short pulse operation modes at XFELs since LCLS first started operation in 2009.[69] Low-bunch charge modes were soon found to produce self-amplified spontaneous emission (SASE) pulses as short as 3 fs[70]; emittance spoiler based methods followed,[71] and the two-colour fresh-slice mode[72] was developed and is now routinely used.[25] Two-pulse/two-colour X-ray modes are subject to orders of magnitude less inherent jitter (sub-femtosecond) than laser-X-ray experiments and so, at present, offer the highest temporal resolution pump-probe capabilities. When millijoule-level femtosecond duration SASE pulses are focused, high intensities (> 10^{18} W cm^{-2}) are routinely attainable. Such high intensities are required to drive even relatively low order non-linear X-ray processes, since the relevant interaction strengths scale strongly with wavelength, leading to much diminished non-linear cross-sections in the X-ray range. Nevertheless, two-photon ionisation,[73] stimulated Raman[74] and stimulated emission[75] have been observed, as well as XFEL-pumped atomic X-ray lasers.[76] The challenge now is to go beyond multi-spiked stochastic SASE pulses, to permit more controllable non-linear interactions.

The introduction of seeding[77] and echo-enabled seeding at FERMI[78] has shown that almost transform-limited (fully temporally coherent) femtosecond pulses can be delivered in the XUV and soft-X-ray range. These seeded pulses have enabled the first transient grating XUV FEL experiments[79] and prospects to scale these to higher photon energies look promising. Utilising phase-locked harmonics of the seeded FEL provides attosecond pulse train capabilities in the VUV spectral region.[80] Enhanced SASE (eSASE) has been discussed for some time as it offers[81] a way to restrict the SASE lasing to a single SASE spike, with a field that much more closely approaches the *ideal* transform limit. This technique was recently demonstrated[82] with the generation of one- and two-colour eSASE isolated attosecond pulses and large coherent bandwidth. Using a circularly polarised laser field streaking method, these pulses were fully characterized in the 500 – 1000 eV range and found to give 200 – 500 attosecond pulse durations (**Figure 3.6**), with a relatively narrow distribution over multiple shots. Moreover, these short pulses were accompanied by a large coherent bandwidth in the range 5 – 10 eV, and the pulse energy was some nine orders of magnitude higher than that obtained by high harmonic generation (HHG), the only other source of attosecond pulses. This breakthrough development is opening the path to important new opportunities in attosecond domain pump-probe measurements, and non-linear X-ray spectroscopy.

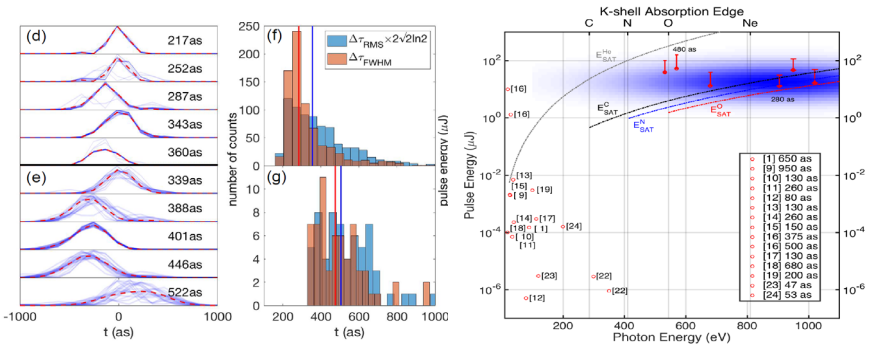


Figure 3.6: Recent results from LCLS showing (left) the measured 200 – 500 attosecond pulses in the SXR region, and (right) the comparison to HHG attosecond sources[82]

Figure reproduced from J. Duris et al. "Tunable isolated attosecond X-ray pulses with gigawatt peak power from a free-electron laser" Nat. Phot. 14, 30-36 (2020), Springer Nature. DOI: 10.1038/s41566-019-0549-5

3.3.2 Attosecond science

The timescale of electronic dynamics in matter is naturally very fast; for example, the orbit time of an electron in the lowest Bohr level of the hydrogen atom is just 150 attoseconds. When superpositions of electronic valence states are formed, fast electronic dynamics are manifested as an observable effect, e.g. through the ultrafast time-dependent localisation of charge density. Given that the typical energy spacings of valence states can span several electron-volts or more, the resulting beating timescale is typically a few-femtoseconds to sub-femtoseconds. The primary events of photoexcitation and radiolysis will intrinsically occur on such timescales when considered at the single system quantum level. The wider impact of this on science and technology is through the importance of photo-excitation/photo-ionisation in renewable energy (e.g. light harvesting technology), photocatalysis (e.g. photo-driven water splitting and biofuel generation) and biomedicine (e.g. photodynamic therapy, photoactivated fragmentation of biomolecules in mass spectrometry, and radiation damage and therapy).

The new X-ray attosecond pulse capability from eSASE provides the prospect of applying X-ray spectroscopic probes that allow, for the first time, the study of electron dynamics with full spatial resolution through atomically localised probing as well as the required temporal resolution. For example, in the X-ray ionisation of matter by a short pulse, the high kinetic energy of the outgoing electron leads to a "sudden ionisation" event that can project the resulting charged system into superposition of valence states, resulting in large amplitude charge density oscillation across the system with attosecond timescales. This "*charge migration*" situation has been widely studied theoretically, but can only now be realised in the context of true sudden ionisation. Ultrafast charge migration following sudden ionisation or excitation is believed to be a universal response of extended molecules, and is also likely to occur in some form in many condensed phase systems.[83] It is now understood that there is intrinsic coupling to the nuclear wavefunction through both zero-point geometry spread and subsequent rapid motion,[84] which will take place on a short (< 10 fs) timescale, so it is expected that coupling to nuclear modes will rapidly become important.[85] Understanding ultrafast electron-nuclear coupling poses an enormous challenge, requiring fully quantum dynamics calculations that go beyond the Born-Oppenheimer approximation, and experimental benchmarking is now vital.

Electron wavepackets excited by attosecond pulses lead to a new regime in photochemistry where the electronic state dynamics drive the reaction and the nuclear dynamics follow, in contrast to the usual case where nuclear dynamics drive the reaction and the electronic motion follows. Such charge directed reactivity has been suggested as a way to explain laser ionisation experiments in some molecules,[86] and may offer routes to control reactions in the future.

Ultrafast hole evolution and motion is of critical importance to many aspects of photochemistry and photophysics, where there is hitherto little experimental data at these short timescales. At present, attosecond science relies heavily on the process of HHG as a means to generate attosecond pulses in the soft-X-ray photon energy range,[87,88] but, despite progress in the generation efficiency and shortness of the pulse duration,[89] the power levels are currently found to be very low (picojoules in the soft X-ray range). This has prohibited applications to direct pump-probe measurements and instead techniques have been developed that use an intense IR field either as the pump[90] or the probe.[91 92] The strong IR field will, however, induce profound modifications to any extended multi-electron system[93] and so inhibit the ability to make measurements on the native charge migration process without unwanted strong field distortion.

3.3.3 Attosecond spectroscopy and impulsive X-ray Raman interactions: Electronic excitation in matter localised in space and time

X-ray attosecond pulse pairs open up new routes for the pump-probe study of charge migration and other attosecond timescale electronic processes. A resonant core state to valence hole probing scheme enabled by attosecond X-ray pulses is far superior to current methods, in that the interaction ensures a non-perturbative measurement of the intrinsic electron dynamics, whilst it also permits an

atomically localised probing of the electronic state through the atomic specificity of core state spectroscopy.[94] In addition, attosecond streaking with circularly polarised fields is now being used to time-resolve the electron photoemission process and subsequent Auger cascades,[95] and future extensions of such streaking based methods are anticipated to be extended to the XUV and hard X-ray ranges as new attosecond capabilities are developed.

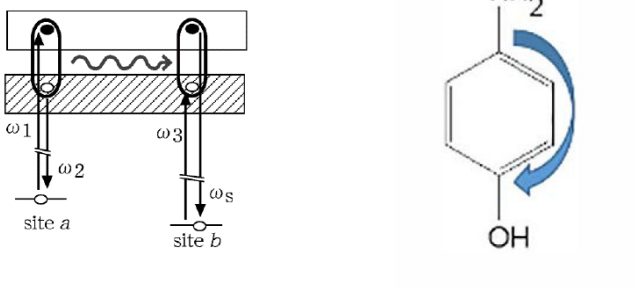
With the new generation of eSASE capability likely to be extended across a wide photon energy range in a future light source, we will have the means to measure time-dependent information on the electron-hole evolution, and localisation in a wide range of situations in both gas and condensed phase systems. We also anticipate better synchronisation and better time-stamping (e.g. via circular streaking offering sub-femtosecond measurement resolution) between laser fields and X-rays in future facilities. Such advances will allow attosecond resolved measurements on excited state neutrals that will extend these X-ray probing methods to chemical excited state dynamics in gas and liquid phases and excitons in condensed phase materials, and open-up prospects for control of photo-processes through manipulation using this new resource of electronic state superpositions.

New concepts in nonlinear X-ray spectroscopy have been proposed and explored theoretically, including 1D[96] and 2D coherent X-ray Raman scattering.[97] One method already being realised is *impulsive* X-ray Raman scattering (IXRS), which relies upon the large coherent bandwidth within a single attosecond X-ray pulse to provide both the pump and the Stokes transition frequencies required to excite a valence *electronic* state in the neutral. This is analogous to stimulated impulsive Raman in the optical domain (visible to UV), which primarily couples to *vibrational* states of matter. IXRS offers unprecedented opportunities for creating localised coherent electronic wave packets in *un-ionised* states that can be employed to probe electronic couplings between atomic sites in a molecule or a condensed phase material.

Early experiments on IXRS in the NO molecule tuned near the O 1s-π* resonance have shown promising results. Tuning the X-ray photon energy resonances between inner shell and valence states in the molecule boosts the two-photon (Raman) excitation of excited state neutral atoms by a large factor. Through strong resonance enhancement, the Raman process can select only atoms of a single species through a virtual transition to this core-excited intermediate state. The process can, therefore, lead to localised excitation at a specific site (site *a* in **Box 3.3**) within a neutral molecule, and it is possible to control which sites are excited by tuning the X-ray photon energy. A second delayed pulse, tuned to a different resonance, can then be used to induce a Raman transition at a nearby atomic site (site *b*). The electronic excitation transfer from site *a* to site *b* can then be determined through observation of changes to the stimulated X-ray emission spectrum induced in the second Raman transition. As a result, this process provides the perfect tool to probe the transfer of electronic excitation within a molecule or a condensed phase system with atomic spatial and sub-fs temporal resolution, and is ultimately a *photon in – photon-out* method that lends itself to gas, solid and liquid phase systems.

Box 3.3: New concepts to create and track coherent electronic wavepackets through materials

SPACE TIME LOCALIZED MEASUREMENTS OF ELECTRONIC COUPLING



A double impulsive Raman sequence can excite a valence state wave-packet localised at one atomic site and probe at a second atomic site after a controlled delay.[96] This creates a unique opportunity for spatial/temporal resolved probing and quantum control. Such a flagship experiment is a stepping-stone to attosecond multi-dimensional spectroscopy, with creation and probing of localised electronic wave-packets in matter of all kinds.

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3.3.4 Conclusion and future directions

Building on these ideas we can envision the development of new experimental techniques to probe electronic dynamics on femtosecond to attosecond timescales. In the future, with multi-pulse/multi-colour attosecond operation, it will become feasible to create a localised electronic excitation at one atomic site and then probe, with attosecond resolution, the motion of that excitation to *multiple* other atomic sites within the molecule or material, by observing stimulated emission at different X-ray frequencies (see **Box 3.3**). Further developments exploiting multi-colour attosecond pulses at high repetition rate will permit us to realise more elaborate X-ray four-wave mixing scenarios, currently at the level of theoretical investigation. These ideas promise to yield new types of multi-dimensional spectroscopy that can, in principle, examine the full range of nuclear, electronic and electronic-nuclear couplings in a material. Extension of the transient grating method to the X-ray range to investigate ultrafast transport in materials is one prospect, but this will require fully coherent broad-bandwidth pulses (such as those available with eSASE) with a high measure of phase coherence across a wide range of frequencies. With appropriate high repetition rate X-ray sources giving access to measurement of weak signals at high fidelity, the extension of the methods to more complex materials, liquids and larger molecules is feasible.

Attosecond X-ray pulses, with provision for two- and multi-colour pulses, will be needed at high repetition rate. Each pulse will have ~ 10 eV of coherent bandwidth, and this capability will be needed across the soft X-ray to hard X-ray range to enable the full range of research. Hard X-ray attosecond pulses would enable impulsive Raman site specific probing in bulk condensed phase materials that minimises damage to, and backgrounds from, the surrounding material. Optimal approaches to synchronise and time-sort the delay with external lasers will permit the development of a wide range of attosecond measurements, e.g. with an XUV pump (from HHG) and an X-ray probe. It is likely that the full array of X-ray tools needed for these advanced spectroscopies can be developed over the next decade and incorporated into a UK XFEL facility.

3.4 Capturing conformational dynamics and rare thermo-dynamic states

Chemical reactions catalysed by biomolecules and transformations between states of matter, such as crystallisation or phase transitions, progress via complex trajectories across rare thermodynamic states. Many of the transitions and fluctuations critical to these processes happen at timescales too fast to be captured by any existing methods. XFEL imaging methods, coupled to advanced data sorting algorithms, offer a unique way to capture these changes essential to understanding how, for instance, biomolecules function in their native state and deliver improved control of crystalline matter for the benefit of material science.

3.4.1 Introduction

For many decades the key to our scientific understanding and control of matter in its various forms – molecules, polymers, solid materials (metals, semi-conductors, dielectrics) and biomolecules – has stemmed in large part from our ability to determine their atomic scale structure. In structural biology, the tight connection between structure and function is an underpinning paradigm that supports nearly all of biology and is responsible for the vast majority of new treatments linked to human health. Our scientific understanding of structure was delivered by the capability to use X-ray, neutron and electron diffraction, and imaging methods to determine the atomic scale arrangement of complex material. As successful as this picture has been, it nevertheless misses a key part of the story.

The challenge is that many processes in condensed phases, such as enzyme catalysis, crystallisation,[98,99] phase transitions,[100,101,102] or dynamic heterogeneity[103] occur via rare states accessed via thermodynamic fluctuations. Yet, we only detect an ensemble averaged behaviour, strongly dominated by the stable endpoints of the process, rather than capturing the underlying transformational dynamics at a single molecule level. For example, in the context of biomolecules, scientists fit an atomic model to X-ray diffraction data from crystal comprised of 10^6 copies of the macromolecule, each of which may include tens of thousands of atoms in a complex 3D arrangement. Functional information often comes from measuring the reaction kinetics and/or spectroscopic signals of an ensemble average reaction in solution. Overall reaction rates are typically rather slow (microseconds or longer) for biomolecules, although the dynamics of the critical sub-steps that manifest the functional processes nearly always happen on a much faster timescale (picosecond to nanosecond). Up until very recently, we have not had the appropriate tools to capture the atomic structures of dynamic systems engaged in performing their function. Thus, the ability to routinely measure the structure and function of macromolecules engaged in physiological processes, under physiological temperature and pressure, would be transformative.

If we can directly image key conformational steps, i.e. the rare thermodynamic states crucial to function, then the ensuing mechanistic insights will answer profound questions in condensed phase, including physics, biology and chemistry:

- How do enzyme-catalysed reactions occur in a living cell?
- How do molecular machines efficiently cross energy barriers to drive biological processes?
- What are the fluctuation dynamics of solvation networks in liquids?
- What are the initial steps in crystallisation and how do the initial crystal seeds grow?
- What are the mechanistic aspects that control phase transitions?
- How do spontaneous fluctuations and nanoscale heterogeneity relate in functional materials?

New X-ray diffraction and coherent diffraction imaging capabilities at XFELs enable single-shot structure determination/imaging, which exploit pulses short enough to capture individual conformations. For each single molecular or biomolecular assembly probed with femtosecond pulses,

we will capture an instantaneous conformation that is not smeared by a long exposure time. This capability, combined with advanced data analysis techniques, offers a route to resolve the questions posed above and many others.[104,105] Using these methods, and with sufficient data, it is possible to map out the conformational trajectory through the free-energy landscape associated with a particular reaction path,[106] and address fundamental questions in statistical mechanics and rare events. In common with cryo-EM, this potential capability for single-particle imaging sets X-ray scattering data apart from ensemble-averaged methods, such as X-ray crystallography and NMR spectroscopy, that cannot capture the single-molecule conformations.

Whilst the most common technique to measure dynamics is by the pump-probe methodology, this is *not* viable for capturing the plethora of reactions occurring at room temperature but driven by far from equilibrium transient conformational changes (e.g. barrier crossings). For instance, the molecular conformation(s) required by enzyme catalysis are very likely to be significantly different from the equilibrium structure of the macromolecule in its ground state. An alternative to pump-probe strategies is to take multiple short pulsed data points and then splice these together to create stop-motion views of the functional cycle. This often exploits either X-ray diffraction from a periodic array, as in serial micro-crystallography methods, or coherent diffraction imaging from non-regular specimens, as in single-particle imaging techniques, at high spatial localisation to avoid spatial averaging. Importantly, the density of the data sampling must be high enough that the rarely occupied high-energy states of the system are present within the data set. Moreover, the exposure time must be short enough to capture the various stages of these conformational changes without time averaging, scrambling or blurring. If these criteria are met, then the data techniques can in principle retrieve the structural dynamics of these critical events at high atomic and temporal resolution.

3.4.2 Data driven approaches to structural dynamics

Pioneering work by the Ourmazd group [107] took pump-probe experimental data[108] that visualised the molecular rotational wavepacket in N_2 using Coulomb explosion. Despite that the original data had 300 fs timing uncertainty, Ourmazd *et al*. were able to reconstruct the dynamics with a few femtosecond precision, including transient aligned states of the molecule. The key feature of this data-analysis method is that it does not require precise control of timing, as would be the case in a conventional pump-probe experiment. Instead it uses random and essentially noisy data from the large dataset, and applies advanced algorithms for sorting the data in order to reconstruct the rare events.

For some cases, such as cryo-EM, the relatively low temporal resolution available from freeze-quench methods (~ a millisecond) are adequate to capture the dynamics of slow processes. The ability to go to much faster timescales, however, corresponding to the actual inherent timescales of many intermediate states, and the opportunity to avoid artefacts from low temperature conditions, presses us to explore the possibilities with ultrafast X-ray sources. Furthermore, cryo-EM data sets are typically rather small due to the time associated with the freeze-quench preparation and data collection, which limits the ability to "*see*" critical rate-limiting high-energy conformational states. Cryo-EM is, and will likely remain, the dominant method for single molecule conformational state determination with near atomic resolution. In contrast, lower resolution X-ray single-shot imaging may have a considerable role in uncovering the large conformational changes associated with high-energy, rate-limiting processes.

Another example, applied to single-molecule coherent diffractive imaging of the PR772 virus with low spatial resolution (in the 10 nanometre range), allowed Ourmazd *et al*. to visualize a rare event – the growth of a tubular structure from a portal vertex potentially associated with release of the virus genome as shown in **Figure 3.7**.[109] This indicates the potential for application to X-ray snapshot imaging. Success of the technique was also demonstrated with cryo-EM data, where the conformational and energy landscape of the 80S ribosome extracted from yeast was mapped.[110]

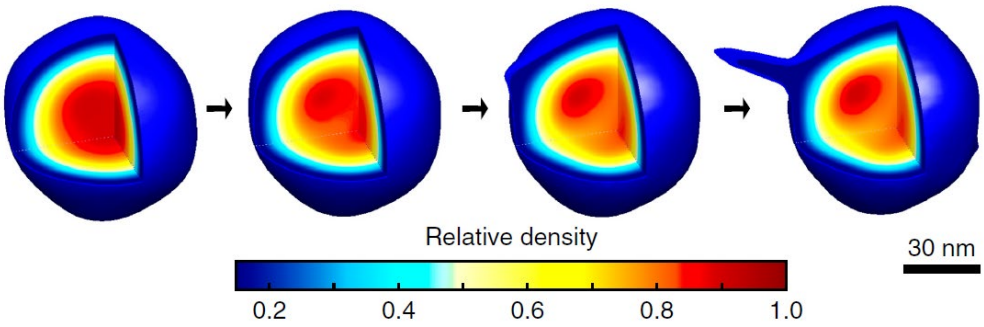

Figure 3.7: 3D structures revealed by conformational analysis of 37,550 single-particle X-ray snapshots of the PR772 virus grouped by conformational parameter. The rare tubular structure is captured in the rightmost conformer.[109]

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3.4.3 Developing methods for tracking conformational dynamics through the energy landscape

The further development of these methods will require some significant technical advances for which a UK XFEL facility can be optimised. Firstly, improved resolution of X-ray single-particle imaging is an important goal. The Single Particle Imaging Initiative at LCLS and other efforts globally have improved the methodology and resolution,[111] but it is believed there is still considerable scope for further improvement. This includes improved control of imaging conditions (X-ray intensity, spectrum, beam profile), an improved particle hit rate and higher precision positioning in the focus, less variation in the thickness of the hydrating water jacket around each sample, and further improvements on scattered background and on analysis algorithms. Evidence is emerging that the highest intensities are not required for imaging and that, if a nanometre resolution is sought, then soft or tender X-ray wavelengths rather than hard X-rays may be optimal.

The central advantage of the XFEL-based technique is the possibility of recording very large datasets. The probability of a specific conformer within the free energy landscape is determined by the Boltzmann factor, and hence the highest energy states furthest from equilibrium will also be the rarest. To be sure of sampling with sufficient numbers, *all* of the relevant conformers for a reaction with a high-energy transition state (as in processes driven by ATP hydrolysis) will require billions of individual snapshots. This will remain very challenging for cryo-EM, but is well within reach of an XFEL, even one at modest repetition rate of 10 kHz, which will require only hours under optimised conditions. Moreover, the very short pulses (few femtoseconds) of the XFEL will eliminate any possibility of temporal smearing, which remains a real issue given the freeze-quench time of cryo-EM.

It therefore appears that a high repetition rate seeded source operating at ~1 keV and with high flux harmonics (to 3 keV) may be a very appropriate source for furthering the method to sub-nanometre resolution. The seeding would ensure stable shot-to-shot conditions and a reproducible beam and spectrum. This would need to be coupled to the most innovative state-of-the-art sample delivery system. Another area where focused effort will be needed is in algorithm develop to support the efficient conformational determination and sorting from the large data sets. For ultimate resolutions a high rep-rate hard X-ray source with some form of seeding could prove optimal. These capabilities are also likely to have impact in capturing the complex structural dynamics in condensed phase systems and quantum materials, where fluctuations on the mesoscopic scale can play a critical role.

3.4.4 Future outlook

XFELs hold promise to bring new insight into the rare events and thermodynamic states that underpin the function of enzyme catalysis, phase transitions, crystallisation with its great importance for the properties of advanced materials, and the rate-controlling steps of many important processes in the chemical and biotech industries, food processing, and in the manufacture of materials. On a

fundamental level, direct access to rare states and rare events will allow scientists to fine-tune their understanding of equilibrium and non-equilibrium thermodynamic processes. Single particle imaging and imaging of a wide range of thermodynamic states is likely to grow into an important technique that could benefit a wide range of research groups in the UK.

To advance this work, a high repetition rate, seeded source operating at approximately 1 keV, with high flux harmonics up to 3 keV, would offer exciting opportunities. High repetition rate hard X-ray pulses with high shot-to-shot stability would be transformative. These X-ray capabilities would need to be coupled to a state-of-the-art sample delivery system, and the most advanced detectors and analysis algorithms.

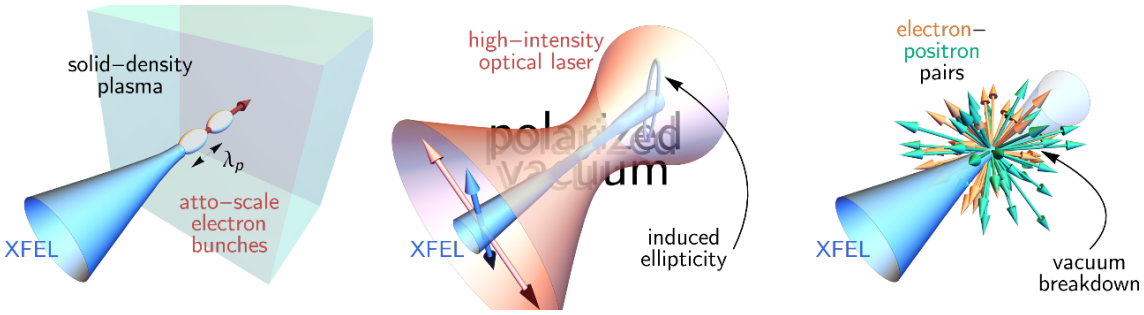
3.5 Non-linear X-ray physics and physics beyond the Standard Model with XFELs

With the development of high intensity X-ray lasers, one can envision new non-linear X-ray interaction physics in matter and with the quantum vacuum. The interaction physics of high intensity X-rays with matter is a largely unexplored problem. High intensity X-rays open the door to using multi-photon interaction in ground-breaking precision tests of observables that are normally manifest only in very high-energy collisions. This may allow tests for deviations from the Standard Model of particle physics, while being far below the Planck scale of 10^{19} GeV that is beyond the direct reach of any particle accelerator.

3.5.1 XFEL-driven nonlinear dynamics in matter and vacuum

The combination of high photon frequency and high intensity means that XFELs are ideally suited for studying matter in extreme conditions, as discussed in **Section 4.2**. However, a future XFEL system that aimed for *relativistic intensity*, at XUV to soft X-ray wavelengths, could be used to explore new non-linear, X-ray propagation physics in matter, or even the vacuum itself.[112,113] The latter is possible because, according to quantum field theory, light can interact with transient electron-positron pairs, whose lifetime is restricted by the uncertainty principle. There are longstanding theoretical predictions that the vacuum, through this coupling, behaves as a non-linear, birefringent medium, and can even "decay" to electron-positron pairs.[114] The highly multiphoton nature of these processes means that they belong to the *non-perturbative* sector of QED. While the perturbative regime has been thoroughly explored with collider platforms, there have been only a few investigations of non-perturbative QED.[115] Neither vacuum birefringence nor vacuum breakdown have been observed with real photons. Here we summarise three scientific opportunities, illustrated in **Box 3.4**, that would be available with XFEL pulses that are focused to high intensity.

Box 3.4: Example scientific opportunities available with XFEL pulses focused to high intensity



(Left) An XFEL drives a nonlinear plasma wake in a high-density plasma, accelerating atto-scale electron bunches at gradients of TeV/cm.

(Centre) An XFEL probes the vacuum polarised by a high-power optical laser.

(Right) An XFEL, focused to ultrahigh intensity, sparks electron-positron pair creation from the vacuum

The propagation of a high-intensity optical laser through dense media is known to give rise to a wide range of non-linear effects: non-linear refractive index, ionisation, beam self-focusing and filamentation, as well as frequency conversion through self-phase modulation, harmonic generation and Raman and Brillouin scattering. The basic physics of **non-linear X-ray interactions with solid density matter** has so far been little addressed, and a new facility with tightly focused, high energy pulses and a high repetition rate would allow these phenomena to be explored. This is in part stimulated by the desire to understand how extremely intense X-rays propagate through matter. The

properties of the plasma created by the excitation and acceleration of electrons in solids varies according the properties of the material: in a crystalline environment, for example, channelling and coherent bremsstrahlung give rise to radiation with novel properties.[116] Practical applications of such research include, for example, the development of extremely short pulse X-ray sources, a means of increasing the range of propagation of high intensity X-rays through matter, tailoring energy deposition for X-ray machining in bulk materials, and the possibility to develop time-resolved nanoscopic imaging with elemental sensitivity in dense systems.

One exciting possibility is to use an XFEL beam to drive a wakefield in a solid-density plasma,[2,117] thereby scaling a laser-plasma accelerator[118] from optical to XUV or soft-X-ray wavelengths. This leverages the considerably higher frequency of an XFEL; as the plasma frequency of a medium increases with the electron density n_e, increasing the driver frequency renders higher density targets transparent. The plasma wavelength, λ_p [μm] = $n_e^{-0.5}[10^{21}\ \mathrm{cm}^{-3}]$, which controls the size of the accelerating structure, and therefore the size of the electron bunches, is significantly reduced. For optical lasers, the use of high-pressure gas jet $10^{18} – 10^{19}$ cm^{-3} yields a cavity size of 10 μm and therefore electron bunches that are tens of femtoseconds in duration. Driving a solid of density $10^{23} – 10^{25}$ cm^{-3} with X-rays, focused to an intensity $\sim 10^{18}\lambda^{-2}$ [μm] W cm^{-2}, could yield electron bunches with durations as short as $10^{-17} – 10^{-15}$ s. These could be used to generate secondary beams of gamma rays of comparable duration.

Non-linear behaviour occurs not only in matter, but in the vacuum as well. While in classical electromagnetism, light does not interact with light, QED predicts that it is possible for photons to scatter off one another. In a collision between a high-intensity, optical laser and an XFEL beam, this scattering manifests itself as **vacuum birefringence**. An initially linearly polarised XFEL beam would acquire a small ellipticity, as if it had passed through a birefringent medium. The difference is that the medium is not a material, but the vacuum, which is polarised by the strong electromagnetic field of the optical laser. A lab-based measurement of vacuum birefringence is much in demand, as the same phenomenon should occur around highly magnetized compact objects, such as magnetars,[119] and claims of observation are disputed.[120,121] Furthermore, as the ellipticity change would be zero in Born-Infeld theory,[122] an experiment could rule out this alternative theory of non-linear electrodynamics.

The experimental challenge is the small size of the cross-section ($\sigma_{\gamma\gamma}$) for photon-photon scattering, and therefore the small size of the ellipticity change. Indeed, as $\sigma_{\gamma\gamma} = 10^{-31}(\hbar\omega^*/mc^2)^6\,\mathrm{cm}^{-2}$ for centre-of-mass photon energies $\hbar\omega^*$ much smaller than the electron rest energy mc^2, the necessary photon fluxes are so high that light-by-light scattering has not yet been observed with real photons. The combination of an XFEL and a high-intensity optical laser leverages the strong scaling of $\sigma_{\gamma\gamma}$ with photon frequency: the cross section is 11 orders of magnitude larger for XFEL-laser scattering than for laser-laser scattering, and 33 orders larger for XFEL-XFEL scattering (as attempted at SACLA[123]). The advantage of using a high-intensity optical laser is that signal is enhanced by coherence. The large separation in energy scales (keV vs. eV) means that the X-ray photons primarily scatter forward, with altered helicity, rather than momentum. The ellipticity induced in the probe beam, $\delta = \omega L \Delta n/2$, is proportional to the *difference* in the refractive indices $\Delta n = 2\alpha I_{laser} / 15 I_{crit}$. It is maximised by increasing the X-ray frequency ω and the laser intensity I_{laser} ($I_{crit} = 2 \times 10^{29}$ W cm^{-2}). As the ellipticity change is of order $\delta = 10^{-10}$, high initial polarisation purity and precision measurement capability are required.[124] Such experiments are already planned at European XFEL as part of the HIBEF project; a UK XFEL has the potential to leverage new laser technology to reach higher optical field intensities and repetition rates, which significantly enhances the signal statistics. A future possibility would be the probing of anomalous dispersion, at higher X-ray energy, where the refractive indices become energy dependent.

At higher field strengths, these same vacuum non-linearities become strong enough to drive **Schwinger pair creation**,[3] or **vacuum breakdown** to electron-positron pairs. This phenomenon, a landmark prediction of non-linear QED, becomes likely when the applied electromagnetic field can deliver work equal to $2mc^2$, i.e. twice the rest energy of an electron-positron pair, over a Compton length $\lambda_c = \hbar/(mc) \sim 386$ fm. This process should be distinguished from the gamma-X-ray pair creation discussed in

Section 4.3, which occurs in the linear or weakly multiphoton regime, and is therefore well described by perturbative QED. Schwinger pair creation is driven entirely by the field itself and cannot be described at any order of perturbation theory. Exponential suppression of the rate is overcome by fields that satisfy $E^2 - c^2B^2 > E^2_{cr}$, which requires either tight focusing or the overlap of two or more beams of extreme intensity. However, the characteristic field strength, $E_{cr} \sim 1.3 \times 10^{18}$ V m^{-1}, is so large that it is currently out of reach in a laboratory environment. In fields of critical strength, the electrons and positrons so created can be accelerated so strongly that they radiate hard gamma rays, which stimulate further pair creation, radiation emission, and thus an electromagnetic cascade. It is speculated that triggering such a cascade is what limits the highest intensity that could ever be achieved with a tightly focused optical laser.[125,126] However, the higher photon frequency of an XFEL, compared to an optical laser, means that it is possible to reduce the volume of the focal region, suppressing cascade growth that could limit the largest field achieved. It is predicted that a terawatt XFEL, focused close to the diffraction limit, could provide the first observation of Schwinger pair creation.[127] Here, capability for diffraction-limited focusing is essential: if the focal spot radius is 20 nm, rather than 0.1 nm, the power requirements increase from 2 TW to 50 PW. Progress towards this goal would also allow for the study of higher order, multiphoton effects in gamma-X-ray pair creation (see **Section 4.3**); non-linear effects increase with the X-ray focused intensity I_X as $I_X^{3/2}$.

3.5.2 Physics beyond the Standard Model with XFELs

The Standard Model of particle physics allows for charge-parity (CP) violation in the electroweak and strong sectors. While the former is experimentally established, the latter is constrained by neutron electromagnetic dipole measurements to be negligibly small, with no natural explanation. This is known as the strong CP problem. One of the most well-motivated solutions to this problem is the axion proposal by Peccei and Quinn.[128] It has been subsequently noted that such models have a pseudo-Goldstone boson, the QCD axion,[129,130] which can make up a substantial fraction or the entirety of the dark matter abundance[131,132,133] of the Universe. Similar pseudoscalars, known as axion-like particles (ALPs), readily arise in the low-energy spectrum of string theory.[134] In the following, we use the term axion to refer to both the QCD axion and CP-conserving ALPs.

If we consider the mass range around 1 eV, the strongest bounds are placed by the CAST experiment,[135] a helioscope sensitive to the axion flux produced in the sun. However, due to the astrophysical origin of the axions and the consequential lack of control over their production, the possibility of model dependence must be seriously taken into account. For example, the non-zero plasma frequency and high temperature conditions in the sun affect the axion-photon effective coupling.[136] Similar arguments apply to stellar cooling bounds. In the lower mass range (<10 μeV), microwave-cavity searches (such as ADMX[137]) look for dark matter ALPs and achieve bounds very close to the QCD predictions, but, of course, these bounds are heavily dependent on the underlying assumptions of the local dark matter distribution.

As such, model-independent bounds given by purely terrestrial experiments can be attractive, particularly if they can be comparable to those provided by CAST or ADMX. With the development of high intensity laser beams, searches using the light-shining-through-walls (LSW) scheme[138] have become possible. These are based on the idea that a laser beam propagating in a magnetic field can spontaneously create axions, which, being weakly coupled, pass through an intervening wall. Behind the wall, any axions entering the reconversion magnetic field mix back into photons and are detected. Other laboratory axion searches include the PVLAS collaboration,[139] looking at induced birefringence as a polarised laser beam traverses a magnetic field. This effect receives contributions from both QED and axion interactions, with the leading QED contribution a one-loop process, which competes against the tree-level axion contribution. Because of this limitation, PVLAS bounds, even if they provide an enhancement from laser LSW searches, are still significantly above those provided by CAST.[140]

The above discussion suggests that FEL searches could fill the gap in both exploring different mass ranges as well as in probing axion couplings below the PVLAS bounds. An XFEL facility could then be included in the worldwide effort of searches for dark matter, as synchrotrons have, in the past, been

used in LSW experiments, both at at ESRF[141] and SPring-8[142]. The advantage of an XFEL in LSW searches is the $10^{17} - 10^{18}$ increase in the number of photons/s, implying a factor 20 – 30 improvement in the predicted exclusion bounds (this is due to the very weak coupling of axions to ordinary matter). Moreover, recent work has shown that the collision of X-ray and optical laser photons may be able to circumvent the intrinsic limitation of laboratory-based searches using the LSW approach.[143] As shown in **Figure 3.8**, the collision of two beams can resonantly produce axions, with their presence inferred by a signal photon detected after magnetic reconversion, but with a much larger cross-section thanks to resonant excitation – achieving exclusion bounds comparable to CAST, but without any assumption on the axion generation in stars. The additional advantage of an XFEL-based search is the energy tunability, thus providing a natural means to scan across a broad energy range – which is needed, given that the ALP's mass is unconstrained by theory.

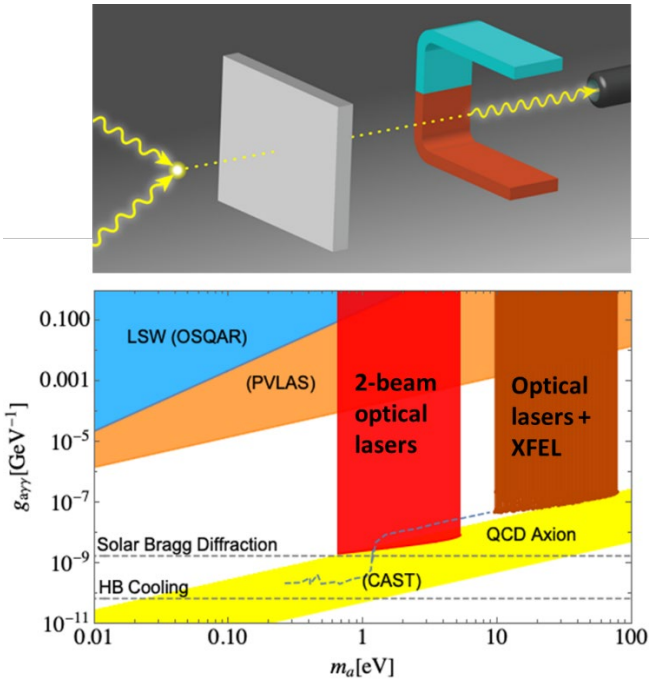


*Figure 3.8: Top: probing production of dark matter with the coherent interaction of two laser beams (from Physics **13**, s59, 2020; APS/Alan Stonebraker). Bottom: one optical laser beam forms a standing wave and a second beam (either optical or X-ray) interacts with the standing wave.[143]*

The proposed axion searches at an XFEL facility will be expected to further constrain the parameter space for axions and ALPs. While a positive detection would be a significant discovery, with a long-lasting impact to our understanding of fundamental physics, a null experiment would also be extremely important, allowing the exclusion of theories and narrowing down the allowable mass range of these dark matter candidates. As we know, while cosmological and astrophysical evidence for dark matter is very compelling, attempts to identify the elusive particle itself have yet resulted in a null detection. Recent satellite observations with XMM-Newton and Chandra in the *Perseus* cluster have shown an unidentified emission line near 3.5 keV.[144,145] It has been suggested that this line may be the result of resonant excitation of dark matter particles. XFEL experiments could then provide an ideal experimental tool (because of the narrow bandwidth and high photon number) to resonantly excite dark matter particles and then measure their subsequent decay into X-ray photons. Initial calculations shows that it might be possible to detect of order 1 – 10 photons a week in this way, thereby potentially opening up a new search strategy for dark matter.[146]

In addition to the above-mentioned dark matter searches, XFELs could also be envisioned as a test of other fundamental physics processes, particularly when focused to high intensities. Ultra-short pulsed X-ray beams are expected to deliver unprecedented intensities at very short wavelength, possibly achieving values in excess of 10^{20} W/cm^2. An electron placed at the focus of such beams should experience enormous acceleration,[147] comparable to what it would feel if placed near the event

horizon of a 6 x 10^{18} kg (= 3 x 10^{-12} M_{sun}) black hole. Indeed, for such low mass black holes, the surface gravity is strong enough that pairs of entangled photons can be produced from the vacuum, with one of the pair escaping to infinity. The black hole can then radiate, and the spectrum of such radiation is a blackbody at the so-called Hawking temperature.[148] This relation is at the foundation of quantum gravity phenomenology, since, by virtue of the equivalence principle, it is impossible to distinguish between an accelerated frame in flat space-time or gravitational effects. In flat space-time, the observation of thermal photons by an accelerated detector is called the Unruh effect.[149]

While the Unruh effect is well-established in the accelerated frame, its possible observation in the laboratory frame remains controversial.[150] This is because the calculation of what the observer sees in the rest frame involves non-trivial, non-equilibrium quantum field theory calculations, to the point that an experiment may be the only way to put the debate to rest.

Moreover, all proposals aimed at the observation of the Hawking/Unruh effect have so far been unable to reach the required conditions, but instead have focused on (classical) analogue systems.[151,152] Hawking radiation, information loss-paradox, as well as searches for dark-matter are now within the grasp of new high intensity optical laser facilities.[153,154] But, while optical laser experiments are in principle able to achieve the required acceleration, they also need to separate the Unruh emission from any other classical or QED (e.g. radiation reaction) effect, which is very challenging.[155,156] High-intensity, high-energy X-ray laser facilities thus offer a complementary approach that could provide a successful route towards the experimental validation of the Hawking/Unruh effect. For an electron accelerated by a 10^{19} W cm^{-2} laser, the Unruh temperature corresponds to the optical frequency band. Thus, it becomes much simpler to separate the Unruh emission from the X-ray background. In addition, at these high X-ray intensities, very light particles can also be created via similar mechanisms,[157] which then could complement the dark matter searches discussed above.

3.5.3 Conclusion and future outlook

The science outlined in this sub-section ranges from the basic science of non-linear high intensity X-ray matter interaction to tests of fundamental physics. Although all the research described will be very challenging, and at a range of risk levels from medium to high, the scientific rewards are commensurately high. It is possible that this research could lead to new understanding of the fundamental physics of the Universe. The high intensity X-rays required in the soft to hard X-ray range are feasible with current XFEL technology, and still higher intensities may be achieved as that technology and that of X-ray optics develops. As, in many cases, the limit will be that signals are weak, the use of high repetition rate (> 100 Hz to 100 kHz) is highly desirable. Here the restrictions may not be the XFEL itself, but rather the high-power optical lasers, which are needed to reach intensities as high as 10^{22} W cm^{-2} and for which scaling to higher repetition rates will be an important goal. That goal is synergistic with other high-power laser projects in the UK.

3.6 High brightness relativistic electron beam science

Monoenergetic relativistic electron beams with low emittance, in addition to powering the XFEL, can also be used directly for new research. This research includes: electron beam-driven plasma wakefield acceleration (PWFA), a unique inverse Compton scattering gamma source, and opportunities to use the electron beam for fundamental physics experiments. The incorporation of plasma photocathodes in PWFA can boost electron energy and brightness, which can have a transformative impact on photon pulses produced by the UK XFEL in the future. The gamma source would be a major research asset for nuclear science and the nuclear industry in the UK.

3.6.1 Introduction

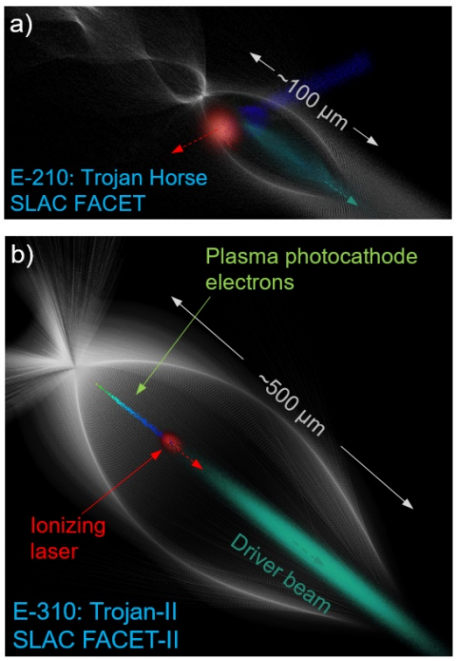
The low emittance relativistic electron beam from an accelerator that drives the X-ray production is an essential requirement for an XFEL. Here we consider additional exciting science that uses that electron beam directly. The first example is the possibility of establishing an experimental end-station for the electron beam, accelerated to multiple GeV, that can be used to conduct research into the plasma wakefield concept PWFA. In PWFA, a first electron bunch generates a wakefield that can accelerate a second following bunch to significantly higher energy. In this research, focus would be on the plasma photocathode concept that uses a laser pulse to generate the second electron bunch in situ in the wakefield at exactly the correct moment and location to enable optimal acceleration. This promises new ultra-low emittance electron beams of utility in future accelerators and photon sources. In the second opportunity, the electron beam is accelerated to an energy of ~ 1 GeV at high rep-rate in a return loop energy recovery linac (ERL) section of the accelerator. This can be used to generate high spectral brightness gamma rays using inverse Compton scattering (ICS) from a laser field. This ERL configuration would be fully compatible with the operation of the XFEL. We also examine the possibilities of using the electron beam directly in fundamental physics experiments.

3.6.2 Plasma photocathode production of ultrabright electron beams

By transferring energy from a *driver* electron pulse to a following *witness* electron pulse in a plasma wave, the energy of witness beam electrons can be multiplied on sub-metre-scale distance because of the ~100 GV m^{-1} scale plasma accelerator gradients.[158] However, challenges with regard to plasma-based generation of electron beams with sufficient quality, in terms of emittance and energy spread, have thus far prevented the achievement of lasing in undulators.

Now, the plasma photocathode approach, invented,[159] and computationally[160] and experimentally[161] pioneered, by a UK-led collaboration, opens a transformative path towards the controlled production of electron beams of substantially improved quality compared to state-of-the-art. Here, electrons are released with minimal transverse momenta by laser-based ionisation directly within the plasma wave. Subsequent rapid acceleration and focusing in ~100 GV m^{-1} plasma fields then produces electron bunches that are intrinsically compressed to ultrahigh brightness.

This combination of plasma photogun, compressor and accelerator in a single, compact plasma accelerator stage allows generation of ultrashort (fs to sub-fs-scale), high-current (multi-kA) electron beams with extremely low emittance $\varepsilon_{nx,ny}$ down to the nm rad-scale – three orders of magnitude smaller than state-of-the-art levels. In addition to its superior emittance capability, the plasma photocathode process is decoupled from the shot-to-shot jitter of the electron driver beam,[161] which gives rise to potential for very high stability, and in turn an extremely wide parameter range of ultrabright electron bunches, including multi-colour trains with variable separation in energy and time.



The first demonstration of a plasma photocathode was achieved at SLAC's FACET facility in the "E-210: Trojan Horse" experiment[160] in 90° geometry between electron drive beam and plasma photocathode laser. The figure to the right shows 3D particle-in-cell (VSim) representations of this experiment (top) and improved versions in collinear geometry (bottom). The electron driver beam from the linac (green) sets up the plasma wave, and the plasma photocathode laser pulse (red) liberates electrons, that are then captured by the plasma wave and constitute the witness beam. R&D on improvement of electron beam quality from this concept is ongoing in the UK and the US, aiming to demonstrate electron beams with 10-nm-scale emittance, sub-fs duration and kA-scale currents.

A further innovation enabled by plasma photocathodes can reduce the energy spread, from the typical few-%-level to relative energy spreads as low as the $\Delta W_{rms}/W < 0.01\%$ level already at $W \approx 3$ GeV witness beam energies.[160] This is well below the FEL energy threshold given by the Pierce parameter, even for very hard X-ray radiation, and also is crucial for beam quality preservation during transport. Since the emittance of plasma photocathodes can yield nm rad-scale emittance levels in both planes ε_{nx} and ε_{ny}, the corresponding 5D-beam brightness $B_{5D} = 2I_p / (\varepsilon_{nx}\varepsilon_{ny})$, where I_p is the peak current, as well as the 6D-brightness $B_{6D} = B_{5D} / (0.1\% \Delta W_{rms}/W)$ are many orders of magnitude larger than those of state-of-the-art electron beams from conventional accelerators.

While the experimental realisation and exploitation of the plasma photocathode technology is still in its infancy,[161] the experiments conducted to date are in very good agreement with the expectations of theory and simulation, and the confidence level is therefore high that ultrahigh beam qualities can be realised and harnessed. The UK XFEL is in a symbiotic relation with PWFA: the UK XFEL linac can be exploited to realize plasma photocathode PWFA and to produce increasingly bright electron beams, and in turn these brightness-boosted electron beams can be harnessed for accessing fundamentally new photon science regimes in the future.

3.6.3 Impact of ultrabright electron beams on photon science

The UK STFC has assumed leadership in the exploration of such ultrabright electron beams for photon science in the "PWFA-FEL" project ("Exploratory Study of PWFA-FEL at CLARA" 2019-2023), a UK-US collaboration that brings together plasma photocathode wakefield accelerator and XFEL experts.[162] Retroactive addition of PWFA-FEL capabilities into existing hard X-ray FEL facilities, such as LCLS[163] and/or LCLS-II, may be possible to some degree; these ambitions, however, have to deal with existing facility layouts which may be prohibitive for full exploitation. The timing of the UK XFEL may offer an ideal balance between maturity of PWFA-FEL R&D, and timely provision of capacities to be able to fully harness the opportunities for novel electron beams and photon science. Provision of dedicated beamlines for plasma accelerator boosters would enable exciting R&D capabilities, ranging from photon science to high field/energy physics without increasing the spatial and financial footprint of the facility significantly; they could even allow significant cost savings by reducing the electron energy and

undulator length requirements (see below). Intriguingly, in addition to, or alternatively to, dedicated plasma accelerator beamline(s) directly powered by the linac, one could also accommodate the use of linac-generated electron beams *after* their passage through the undulators. When propagating through an undulator, the electron beam transfers only a fraction of its energy to the photon field, and the concomitant loss in electron beam quality does not significantly compromise their capability to drive a PWFA. A particularly cost-effective and potentially 'high-gain' approach could therefore be integration of plasma wakefield brightness and energy afterburners into the linac-based UK XFEL after the undulator section, instead of only diagnosing and disposing the electron beam into a beam dump, as is usually done.

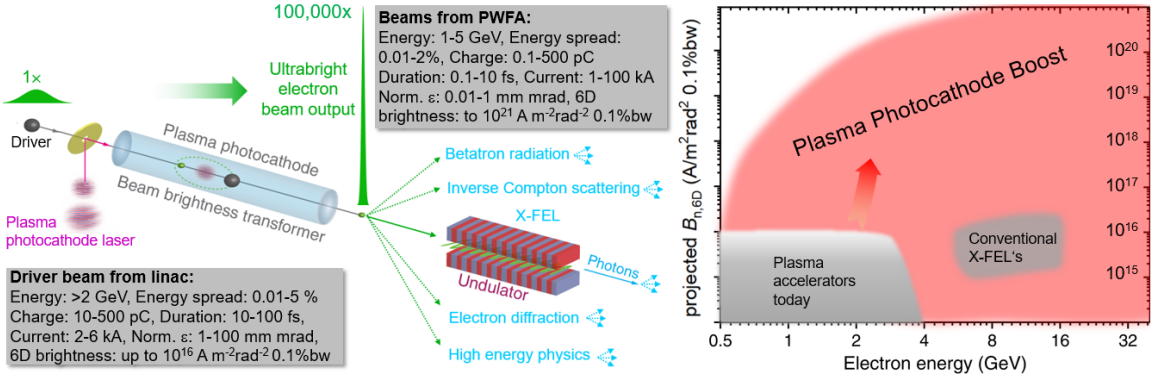


Figure 3.9: Layout for a plasma photocathode based PWFA (left) and the potential beam brightness boost (right)

Figure 3.9 above (left) summarises the scheme and potential parameters for a plasma-based accelerator stage driven by a linac-based UK XFEL precision machine, and the boosted output electron beam. The plasma photocathode will substantially increase the electron beam parameter range of the UK XFEL, and will provide a strategic advantage compared with other XFEL facilities. The overarching impact from plasma photocathodes for photon science arises from their capability to produce ultrashort, high-current electron beams with superior emittances – the emittance improvement being at the root of this impact. **Figure 3.9** above (right) highlights the boost in 6D brightness of the witness beam that may be realized from plasma photocathode PWFA stages. The plasma photocathode laser required needs to reach tunnel ionisation intensities for He ($\sim 10^{16}$ W cm^{-2}), which is compatible with commercially available kHz to MHz rep-rate laser systems generating ~ 1 mJ pulses.

Such ultrabright output electron beams potentially enable completely new photon science modalities to be explored. A core requirement for coherent emission of X-ray photons is reflected by the energy spread threshold $\Delta W_{rms}/W < \eta$, where $\Delta W_{rms}/W$ is the relative energy spread, which reduces as $1/\gamma$ during the acceleration process, and $\eta \propto 1/\gamma$ is the FEL Pierce parameter, and by the emittance threshold $\lambda_{min} \approx 4\pi\varepsilon_n/\gamma$ required to achieve saturation at x-ray wavelengths λ_{min}. First, the consequence of ultrahigh brightness electron beams is a significant reduction in gain length in the undulator section, because the 1D gain length scales as $L_{1D} \propto B_{6D}^{-1/3}$. Second, such high gain leads to rapid growth of the photon field, and thus minimises slippage between the emerging radiation and the electron beam. This enables a potential route towards operation of the FEL in a single-spike regime for fully coherent ultrashort photon pulses. Such photon pulses would enable novel scientific capabilities for femto-chemistry, material science, and imaging of electronic distributions, their motion and ultrafast charge transfer, e.g. in biomolecules on their natural timescale. Beyond this, the dramatically reduced emittance opens a path towards hard X-ray wavelengths λ_{min} for electron energies of only a few GeV, or conversely there can be a push towards even harder photon energies.[164] Lower electron energies are particularly interesting in this connection, because the rate of mean energy loss to incoherent radiation scales as $\propto \gamma^2$, and an even more severe fundamental limitation towards harder photon energies arises from the quantum fluctuation of synchrotron radiation, which scales with γ^4. These scalings[165] entail dramatic growth of energy spread for high energy beams and impose insurmountable challenges for realisation of gamma-FELs with conventional electron beams. In contrast, low energy,

ultralow emittance and high brightness beams from plasma photocathodes allow exploration of exciting possibilities towards gamma-ray FELs as well as for quantum FELs,[164] e.g. for precision studies of nuclear processes, and may allow realisation of photon-photon colliders, e.g. for Breit–Wheeler electron-positron pair production.

Further tailored '*designer*' electron beams can broaden the impact of plasma photocathode-generated electron beams on photon science at the UK XFEL, e.g. via synchronized and versatile multi-colour and pump-probe setups. Finally, as indicated in the conceptual **Figure 3.9** above (see also **Appendix 3.2**), ultralow emittance and ultrahigh brightness beams also allow for exploration of a range of wider opportunities, such as betatron and inverse Compton scattering sources, and ion channel lasers for photon science. While experimental realisation of PWFA plasma photocathode-based production of ultrahigh brightness beams is only beginning, the arising opportunities are potentially transformative. The integration of plasma wakefield accelerator beamlines for research and applications into the UK XFEL will allow full harnessing of this potential, and will provide unique capabilities and a broad path to future-proof competitiveness and upgrade options.

3.6.4 Inverse Compton scattering gamma source

The injector and first ~1 GeV of the superconducting electron accelerator for the MHz repetition rate soft X-ray FEL beamlines of UK XFEL can be readily adapted to include Energy Recovery (SC-ERL). The resulting capability to produce high average electron currents (10 – 100 mA) would enable a high-flux, narrowband gamma source based on inverse Compton scattering (ICS).[166,167]

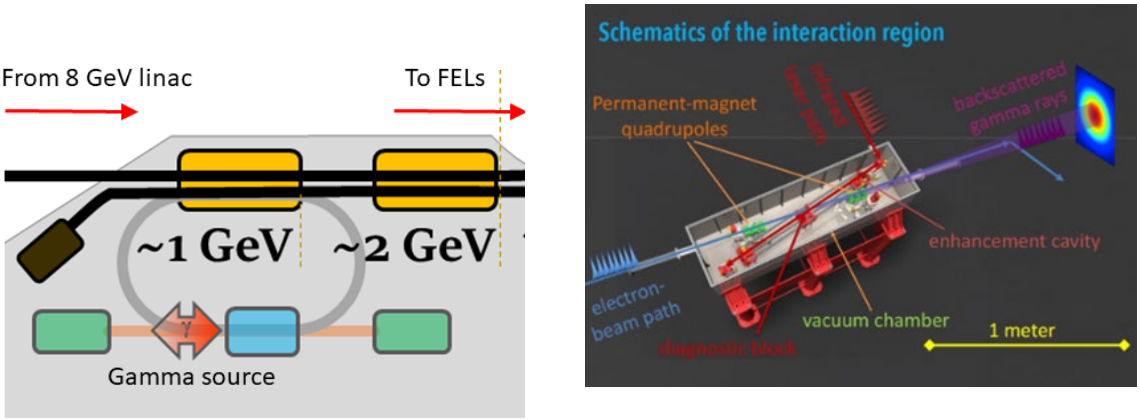


Figure 3.10: Left: Illustration of ERL-driven ICS gamma source located within a full UK XFEL facility. Right: Details of example laser-electron interaction point, comprising high finesse 4-mirror bowtie laser cavity and permanent magnet quadrupole focused electron spot.

Figure courtesy of Philippe Piot

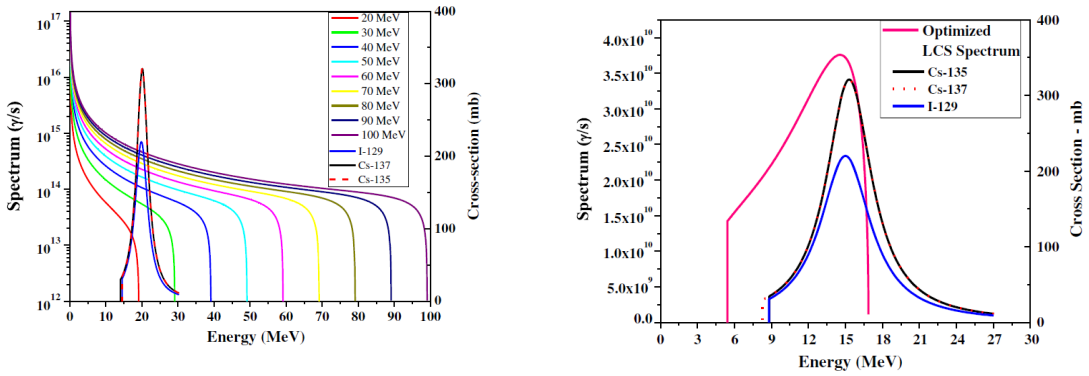


Figure 3.11: Bremsstrahlung (left) and collimated ICS (right) gamma spectra compared to photonuclear dipole resonances of Cs-135, Cs-135 and I-129 (right only).[168]

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The production of 1-100 MeV gammas via ICS of relativistic electrons in an external laser field results in gamma properties fundamentally improved with respect to standard bremsstrahlung generation. Bremsstrahlung is broadband emission peaked at low energy with a cut-off at the electron energy. ICS has a correlation between the angle of emission and energy; therefore in combination with angular collimation, narrowband (or "*monoenergetic*") gamma beams can be produced.[169,170] In addition, ICS preserves the polarisation of the incident laser. Presently the world's brightest narrowband gamma source is the High Intensity Gamma Source (HIGS) at Duke University.[169] The EU-funded Extreme Light Infrastructure – Nuclear Physics (ELI-NP) Gamma Beam System (GBS) is in the construction phase in Magurele, Romania.[170]

To quantify the potential of an ICS source driven by an SC-ERL enabled UK XFEL front end, initial calculations of the source properties have been produced and are shown in **Table 3.1** and **Figure 3.10**.

This ICS source has a spectral energy density at least two orders of magnitude greater than HIGS, and is likely to similarly exceed the performance of ELI-NP-GBS. It should be noted that this calculation assumes conservative, previously demonstrated parameters, and therefore should be viewed as a lower bound. Narrowing the energy bandwidth below 0.5% whilst retaining significant flux, as shown in **Table 3.1**, will enable the resolution of individual nuclear excitations according to the nuclear shell model.

Table 3.1: Conservative input parameters used for ICS source calculation for electron beam and laser system. We cover the nominal gamma energy from 1 to 100 MeV using electron beam extracted at three locations. For the laser-electron interaction point we assume a Fabry-Perot bow-tie like resonator cavity as demonstrated at KEK.[171]

Beam Parameters	**Value**		
Beam Energy (MeV)	340	680	1020
RF Frequency (MHz)	802		
Repetition Rate (MHz)	100		
Bunch Charge (pC)	100		
Average Beam Current (mA)	10		
Normalised Transverse Emittance (mm-mrad)	0.5		
Recoil Parameter	0.006	0.012	0.018
Nd:YAG Laser System Parameters	**Value**		
Wavelength (nm)	1064		
Repetition Rate (MHz)	100		
Pulse Energy (μJ)	100		
Average Stored Cavity Power (kW)	10		
Spot Size at IP (circular spot) (μm)	25		
Stored Pulse Width (ps)	5.7		
Field Strength of the Normalised Laser Vector Potential a_0	6.05×10^{-4}		

Table 3.2: Resulting ICS source brilliances and spectral energy densities for the three example extracted electron beam energies as detailed in Table 3.1

Parameter / Beam Energy	γ-ray Peak Energy (MeV)	Flux per Shot (ph)	Band-width	Flux	Average Brilliance (ph/s mm²-mrad²)	Peak Brilliance (ph/s mm²-mrad²)	Spectral Density (ph/s eV)
340 MeV	2.05	4076	raw	4.08×10^{11}	–	–	–
			0.50%	6.24×10^{9}	2.79×10^{14}	3.77×10^{16}	2.41×10^{5}
			0.10%	4.05×10^{9}	1.81×10^{13}	2.45×10^{15}	7.81×10^{4}
680 MeV	8.17	4750	raw	4.75×10^{11}	–	–	–
			0.50%	6.24×10^{9}	1.12×10^{15}	1.51×10^{17}	6.01×10^{4}
			0.10%	4.08×10^{8}	7.32×10^{13}	9.88×10^{15}	1.96×10^{4}
1020 MeV	18.27	5027	raw	5.03×10^{11}	–	–	–
			0.50%	6.24×10^{9}	2.52×10^{15}	3.40×10^{17}	2.67×10^{4}
			0.10%	4.11×10^{8}	1.66×10^{14}	2.24×10^{16}	8.79×10^{3}

Simulated improvement in the knowledge of an example photonuclear cross section is shown in **Figure 3.12**. The ICS source would be a step change in high-flux, tuneable, narrowband gamma production. As such, it would lead to the establishment / consolidation of a new field of science, Nuclear Photonics, named by analogy to the field of atomic photonics opened up by lasers from the 1960s.

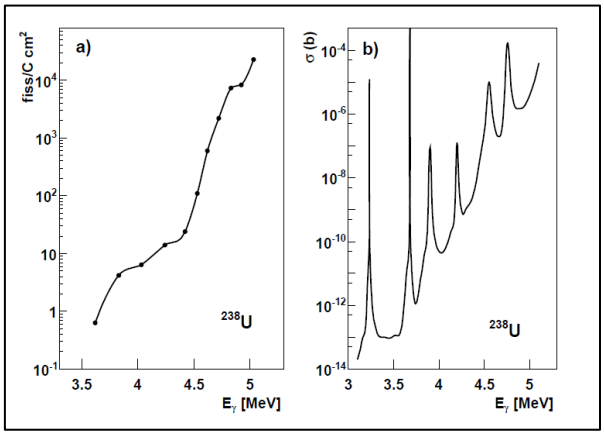

Figure 3.12: Left – Observed, bremsstrahlung induced photo-fission Giant Dipole Resonance (GDR) of ^{238}U. Right – predicted "hidden" resonances within GDR revealed by an ICS narrowband gamma source.[172]

Figure reproduced from P.G. Thirolf et al. EPJ Web of Conferences 38, 08001 (2012) under the terms of the Creative Commons Attribution License 2.0. DOI: 10.1051/epjconf/20123808001

In particular, the use of fully linearly-polarised gamma beams in photon induced reaction results in distinct angular distributions for the two transition multipolarities (electric E or magnetic M), and the associated excitation modes can then easily be disentangled. Hence, ICS gamma beams are a sensitive probe of the nuclear electric (E1)[173] and magnetic (M1)[174] dipole response. Since the photon is not charged, for an interaction it physically needs to hit the object nucleus, resulting in a low scattering cross section. In order to compensate for this, existing facilities use large amounts of target material (order of grams is required), which limits the application to stable or quasi-stable nuclei with a half-life in the order of 100 years. The 100-fold increase in flux enabled by an SC-ERL driven source will eliminate this restriction.

The E1 response is dominated by the well-known Giant Dipole Resonance (GDR);[175,176] however, in the last two decades an additional E1 contribution has been established on the low-energy tail of the GDR. This so-called Pygmy Dipole Resonance (PDR)[177,178] is located near the particle thresholds and has been shown to have an enormous influence on neutron capture rates as encountered in the astrophysical rapid and slow neutron capture processes,[179] which synthesise all chemical elements heavier than iron.

The PDR is often visualised as an oscillation of a neutron skin versus a core with nearly equal proton and neutron numbers, though this interpretation is controversial. Nevertheless, this geometric interpretation suggests a connection to the asymmetry term of the nuclear equation of state, required to describe properties of the heaviest known objects: neutron stars. Recently, the PDR has even been linked to the reactor antineutrino anomaly,[180] which causes a previously unexplained heat generation in operational nuclear reactors.

For the M1 response, the Gamow-Teller (spin-isospin) resonances are of particular importance, dominating inelastic neutrino-nucleus interactions. These provide an additional heating to supernova type-II events, which otherwise would not explode.[181] Furthermore, they are mandatory in order to reliably estimate the cross-sections for neutrino detectors (e.g. see [182]).

Various interesting physics cases are not feasible with the gamma fluxes presently available (HIGS) or at facilities under construction (ELI-NP-GBS), but would become so with an SC-ERL driven ICS source. One example is the investigation of the E1 response of the octupole-correlated nucleus ^{226}Ra ($T_{1/2}$ = 1600 years), which very likely has a strong quadrupole-octupole coupling enhanced CP-violating Schiff moment in the ground state.[183] Recently, admixtures of the low-lying E1 strength have been proposed as a second enhancement mechanism.[184] Another example is the measurement of parity violating physics exploiting $J^{\pi} = 1^{\pm}$ parity doublets (close lying 1- and 1+ levels) as, for example, found in ^{20}Ne.[185]

In the context of particle physics, the ICS gamma source would enable unprecedented measurements of Delbrück scattering (QED vacuum) and light-by-light scattering. A SC-ERL driven ICS source would not only be of great interest in academic physics and astrophysics, but also have direct societal and economic benefits in the nuclear security, civil nuclear power and medical radio-nuclide sectors. For further details, see **Section 8.5**.

High luminosity internal gas target interaction point

A ~ 1 GeV, high current (10 – 100 mA), high brightness (< 1 mm mrad), low energy spread (< 10^{-5}) electron beam, such as that capable of being produced by the UK XFEL SC front end with energy recovery, is recognised as having high potential for fundamental physics studies requiring highly intense electron beams.

High luminosity (> 10^{36} cm^{-2} s^{-1}) e-A scattering can be used as precision tests of Standard Model and Beyond the Standard Model physics; for example, measurements of the weak mixing angle and direct searches for dark matter particles. The DarkLight experiment at Jefferson Lab[186] and MAGIX at MESA, U. Mainz[187] are examples of present and future experiments of this type. The paradigm is to bring the electron beam into collision with a supersonic gas jet surrounded by a 4-pi tracking detector, then recover the energy of the electron beam after disruption to enable large currents (and the correspondingly high luminosities). This setup has potential to greatly exceed limits established by beam dump and storage ring alternatives, such as those at CEBAF. Of utmost importance in these types of experiment is the precision with which one knows the electron energy, and therefore the ERL transport should be optimised to minimise the energy spread. It should be possible to maintain the gun-projected energy spread to the IP (300 – 1000 MeV), leading to energy spreads potentially at the 10^{-5} level.

Integration of ERL into full UK-XFEL facility

With the exception of the repetition rate, the electron beam properties required within the ERL to drive the ICS gamma source will be the same as those required to drive the soft X-ray FELs. This allows sharing of the injector and indeed for one of the FELs to be located within the ERL itself, opening seeding and industrial opportunities from the high average power thereby enabled. The ~1 MHz bunches required to drive the soft X-ray FELs can be separated from the remaining 99 MHz energy recovery bunches using resonant RF kickers as demonstrated for the Electron-Ion collider project.[188,189] The hard X-ray bunches can be injected into, and separated from, the ERL accelerating section utilising standard magnetic separation. Simultaneous and mutually transparent operation of all three source types would therefore be possible.

3.7 References for Section 3

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4. Science opportunities for Matter in Extreme Conditions

Femtosecond X-ray pulses from XFELs enable the probing of the atomic and electronic structure of transiently produced extreme phases of matter in unprecedented detail. This provides new knowledge and understanding as to the behaviour and control of matter in widely diverse settings, including planetary interiors, stars, inertial confinement and in shocked engineering materials.

Matter at extreme pressures and temperatures dominates the interiors of planets, exoplanets and stars and is a rich source of novel phenomena in condensed matter physics, materials science, and plasma physics. Such matter can be created in the laboratory by compression and heating with high-powered optical lasers, but then only exists transiently. To probe the properties and structure of this matter under extreme conditions requires X-rays of ultrafast pulse duration, in order to achieve the required penetration of these highly opaque objects and to capture the rapidly evolving states.

Here we discuss this important area of science, with implications across engineering, defence, astrophysics, planetary science and geophysics. In **Section 4.1** we examine new science opportunities in studying shocked materials, in which high pressures are created using diamond anvil cells and high energy laser compression. The diverse phases of matter generated in these high pressure conditions are known to be highly complex and understanding them is vitally important to our knowledge of the Earth's interior and that of exoplanets. High energy density plasmas account for most of the visible universe, and in **Section 4.2** we discuss how these states can be generated and probed using X-rays, providing fundamental new understandings of hot and warm dense matter and resolving conundrums such as the X-ray opacity of stellar interiors. In **Section 4.3** we discuss completely new science experiments that can be carried out if we interact laser accelerated electrons and protons with high intensity X-rays from an XFEL. Finally, in **Section 4.4** we discuss the new science opportunities that would arise if we combine an XFEL with a kJ class spherical compression facility.

4.1 Shocked materials and matter at extremes

The experimental study of matter at extreme density, where ion cores overlap significantly and the electronic structure is unique to the high-density regime, holds the promise of breakthroughs in our understanding of both solid and liquid phases. The creation and study of such matter will enable us to describe, understand and predict what electrons and ions will do in other condensed matter systems, with direct relevance to exoplanetary science. It will also enable us determine how matter might be manipulated in the future, to design new and improved materials that cannot be predicted by more traditional "evolutionary" methods.

4.1.1 Introduction to Matter at Extremes

The study of materials at high energy densities, or equivalently very high pressures, is a rich source of novel phenomena in condensed matter physics and materials science, and offers a route to new phases and materials, and provides stringent tests of fundamental condensed matter theory, computation and simulation.[1] It is essential for understanding the interior of the Earth and exoplanets, for developing models of material response in aerospace engineering and defence applications, and is increasingly making an impact in chemistry and materials science.[2]

Matter can be compressed and heated dynamically to extreme pressures and temperatures on nanosecond (or even sub-nanosecond) timescales via illumination by high energy optical lasers, a method that has been at the forefront of recent international efforts to achieve Inertial Confinement Fusion (ICF). Laser compression offers the only means by which matter can be created at multi-megabar pressures and temperatures of 10^4 K in a laboratory environment,[3] the conditions that otherwise occur only deep within gas or ice-giant planets, such as Jupiter or Neptune, and within the very many exoplanets discovered by the likes of the Kepler space mission.

Understanding the internal structure of such planets relies on our knowledge of the densities and compressibilities of the solid and liquid phases that make up their interior, and on the crystalline structure adopted by the solid phases. For decades, these structures were assumed to be "simple", with the atoms packed closely together. The high density phases were also assumed to become free electron-like metals at high enough pressures as a result of the kinetic energy of the electrons (which scales as $V^{-2/3}$) increasingly dominating over their potential energy (which scales as $V^{-1/3}$ for Coulomb interactions). There was, however, little experimental evidence to support these very broad assumptions.

4.1.2 The importance of X-ray studies

The arrival of third-generation synchrotron sources in the 1990s, combined with novel diamond anvil cell diffraction techniques and advances in electronic structure calculations, completely overturned these assumptions. The new picture that emerged was one of complexity, where the structure of high-density matter was found to be as complex, if not more so, than that observed at ambient conditions. It was also found that materials might transform into semiconductors or insulators at high densities rather than metals, and new forms of bonding, involving core electrons, were seen to enrich the structural landscape.

Key to these breakthroughs was the advent of advanced X-ray diffraction and spectroscopic techniques using diamond anvil cells. Even the most advanced synchrotrons, however, remain insufficiently bright to probe the very short-lived extreme states created as a result of laser irradiation and/or dynamic compression, which is the route to approach the highest pressures. The ultra-high brightness X-ray pulses from XFELs, on the other hand, can be focused to sub-micron dimensions, are extremely well collimated, are spatially coherent, and the sub-100 fsec pulse length is well-matched to probing the shortest-lived extreme states. Indeed, the pulse length is so short that even "smearing" of the data resulting from hydrodynamic motion can be removed.

XFELs thus enable us to study the structure and dynamics of extreme states of dense matter for the first time. Using the LCLS, UK researchers have made the first measurement of material strength at the

same spatial (< 1 μm) and temporal (< 50 ps) scales as multimillion-atom molecular dynamics simulations;[4] shown that melting and solid-solid phase transitions in shocked compressed metals take place on ns timescales,[5,6] that complex, even incommensurate, forms are created on such timescales,[7,8] probed the equation of state and resolved the ionic interactions at atomic length scales in dense metals[9,10] and carbon;[11,12] and created and probed the absorption of solid-density plasmas (see **Section 4.2**). UK researchers also played leading roles in the first extreme conditions experiments in 2019 at the European XFEL.

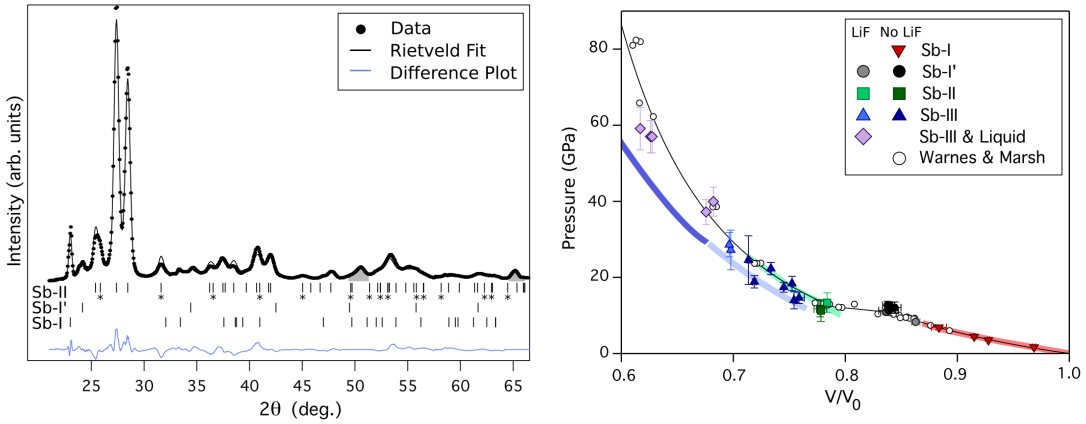


Figure 4.1: Examples of Synchrotron quality diffraction data from an ordered incommensurate host-guest structure (left) and complex phase evolution with pressure (right) in shock compressed antimony.[7]

Figure reproduced from A.L. Coleman et al. "Identification of Phase Transitions and Metastability in Dynamically Compressed Antimony Using Ultrafast X-Ray Diffraction" Phys. Rev. Lett 122, 255704 (2019), American Physical Society. DOI: 10.1103/PhysRevLett.122.255704

Although much of the work above has focused on elemental materials, work on more complex systems is becoming commonplace. This includes deformation of brittle materials such as ceramics,[13] compression of hydrocarbons[14,15] including the observation of precipitation of diamond-like carbon under loading,[16] and planetary relevant compounds such as SiO_2[17,18] and water.[19]

An example of the remarkable complexity present even in 'simple' elemental systems can be seen in **Figure 4.1**. This work on shock-compressed antimony followed structural evolution from ambient conditions up to melt along the shock Hugoniot. This study demonstrates two of the key themes permeating the field. Firstly, it was able to access complex phase transitions into an incommensurate host-guest phase on nanosecond timescales. Such structures, observed at moderate pressures in static experiments, are expected to be common at TPa pressures and, as such, their observation in nanosecond timescale experiments is a critical validation of the potential of dynamic compression to access complex stable structures at astrophysically relevant conditions (see **Box 4.1**).

The same work also shows the formation of the previously unobserved phase (Sb-I'), which appears to be unique to dynamic loading conditions. This demonstrates the potential for the large shear stresses and restricted deformation timescales inherent to dynamic loading to lead to unique material behaviour, hitherto unseen in static compression studies. An understanding of these phenomena is important not just to the interpretation of data of planetary relevance, but more fundamentally to understanding the dynamic compression and failure processes underlying key aeronautical and defence applications. Thus, it is key to explore and understand, at the microstructural level, the full sample journey through both compression and release.

The study of such systems has been made possible by the development of a suite of X-ray diagnostic capabilities. X-ray diffraction remains the workhorse of high energy density structural determination. More recently, this has been combined with imaging techniques to allow for detailed probing of systems with complex multi-wave loading, and thus spatially inhomogeneous structure.[20,21] Initial experiments have been conducted to demonstrate X-ray absorption spectroscopy as a tool for probing chemical environment within high density matter.[22] Most recently, inelastic scattering techniques have been demonstrated which hold the potential to provide temperature measurements in the 0.1 - 1 eV range likely to be accessed in these experiments, completing our understanding of material equation of state.[23]

4.1.3 Opportunities for future study

Despite the rapid advances made in the study of dynamically compressed matter since the advent of XFELs, there is still considerable scope for growth and innovation in the field.

In particular, there is still a significant range of pressure unexplored in XFEL science. Current capabilities at LCLS only allow studies up to 3 Mbar,[9] with the majority of work being at no more than 1 - 2 Mbar. This compares to the 3.5 Mbar of the Earth's core, or the 40 - 50 Mbar estimated core pressure of Jupiter. Studies will be extended at European-XFEL from 2021, where the UK's £8M DiPOLE diode-pumped, 100 J, 10 Hz optical laser, will be installed. DiPOLE is vastly superior to its LCLS equivalent, having three-times the energy, 2000-times the repetition rate, and, crucially, the ability to fine tune the time-profile of the laser pulses it provides in almost real time, thereby allowing routine access to an extremely wide range of P-T states at unparalleled rates. Even here, though, pressures will likely be limited to below 10 Mbar for most experiments. It should however be noted that both of these facilities have planned upgrade paths to low rep-rate kJ scale optical lasers within the early-mid 2020s.

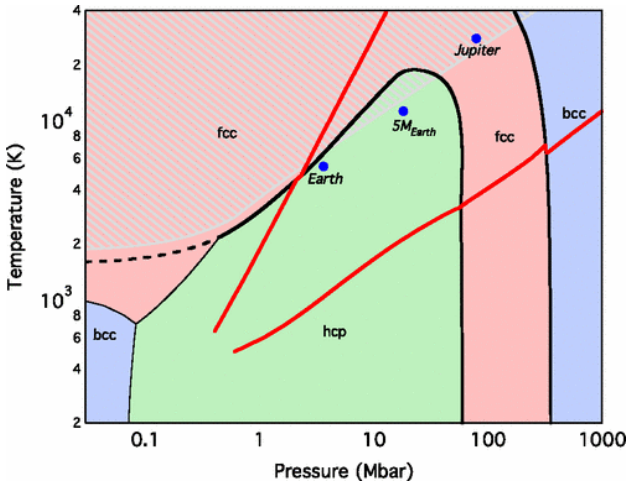
The potential of exploiting a wider range of pressure is significant. For example, in the same way that diamond is a familiar metastable high-pressure allotrope of carbon, a number of other high-pressure structures are predicted to be metastable at ambient conditions. One example is the proposed BC8 phase of carbon, which is notable for having a hardness comparable to, and potentially exceeding that of, diamond.[24] Any such metastability from a phase with a transition pressure above, or composition differing from, the Earth's mantle would potentially represent an entirely new material. The extreme structural and electronic properties of these phases means that such materials may exhibit extreme strength or density, have novel bandgaps suitable for exploitation in electronic or photovoltaic applications, or potentially exhibit superconductivity.[25]

In order to probe such materials, a full understanding of crystal and electronic structure *in situ* will be required. XRD as a structural probe, utilising 10 – 25 keV X-rays, is almost routine at XFELs, but accompanying spectroscopic techniques suitable for probing electronic properties often require quite disparate X-ray conditions. For example, techniques such as XANES[22] or XAS HEROS[26] require tuning to the vicinity of an absorption edge (typically <10 keV), which is usually avoided for scattering measurements. An XFEL capable of providing true two-colour modes of operation, allowing simultaneous structural and electronic probing, would open up new avenues for comprehensive understanding of high-pressure states, and potentially recoverable materials.

Box 4.1: Super-Earths and Beyond – Probing the cores of planetary giants

Ab-initio predictions of the solid phase and liquid (hatched) fields of stability in Fe – a key core constituent for planets.[27] Earth core conditions lie on the edge of current static technique capabilities, with 5 Earth-mass and Jupiter core lying in a regime accessible only to dynamic techniques with a multi kJ class optical laser driver. The two red lines denote the isentrope (lower) and the Hugoniot (upper).

Via a combination of X-ray diffraction and spectroscopic techniques an advanced UK XFEL could fully map this region, determining the equation of state, phase and chemical properties key to understanding planetary structure and evolution



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As discussed above, one key shortcoming of current experimental efforts is the inability to sample temperature due to the optically opaque nature of the material, and relatively low (typically sub eV) temperatures. One potential avenue to provide information on this final crucial component of equation of state is inelastic scattering, which employs high resolution (< 10 meV) X-ray scattering measurements to directly observe phonon (ion-acoustic) modes whose occupation is directly related to thermodynamic temperature.[23] However, the low efficiency of such scattering processes requires significant integration of shots, and thus limits exploration of configuration space. This limitation could be alleviated by a self-seeded FEL with the inherent capability to reach ~10 meV bandwidth in the hard X-ray regime. Once again, with suitable machine capability, such a technique is potentially compatible with diffraction/spectroscopy approaches, further broadening the information one can capture on these novel high pressure states.

4.1.4 Conclusions

The study of matter in extremes offers a window into the understanding of a wide range of phenomena from the astrophysical to fundamental material deformation. As a field experiencing rapid growth, there remains significant opportunity for discovery. Although both LCLS and the European XFEL have dedicated instruments for such studies, they are limited by the scale and ambition of the driver for compression, as well as the available X-ray parameters, and thus the viability of X-ray techniques.

The UK has world-leading capability in many of the underpinning technological requirements for this science. STFC efforts in high repetition laser technology and microtarget assembly have already been foundational for the European XFEL's HED instrument and early experiments on LCLS.

A UK XFEL offers a unique opportunity to collocate a world-class, large-scale laser compression platform alongside an advanced XFEL source. A high repetition rate, high energy (10 kJ class), temporally tuneable laser system would allow access to a plethora of hitherto unexplored structures in a range of materials. This would go meaningfully beyond the scale envisaged for existing FELs, allowing a UK system to access and explore a unique range of P-T states.

Coupled to this, a high photon energy, high pulse energy, narrow bandwidth, two-colour photon source would allow for the full suite of X-ray diagnostic techniques to be brought to bear, to allow for full structural, electronic and equation of state knowledge of the material to be acquired. All of this will lead to unprecedented understanding of the high pressure and dynamic deformation regimes, but will also open up routes to systematic searches for new metastable materials with potentially transformative scientific and industrial applications.

4.2 Quantum plasmas: warm and hot dense matter

The vast majority of the visible universe is in the plasma state, and extreme states of matter are routinely found in all astrophysical bodies from (exo)planets to stars. A comprehensive understanding of the structure and dynamics of such high energy density plasmas is thus of fundamental physical interest in its own right, but also forms the basis for progress in planetary physics, astrophysics, applications using laser-plasma interactions to generate compact radiation sources, and in providing the foundation to laboratory-based fusion energy. High temporal resolution X-ray probes, synchronized with high-energy drivers, will allow us to create these extreme conditions in a controlled laboratory setting and explore them on the fundamental temporal and spatial scales.

4.2.1 Introduction

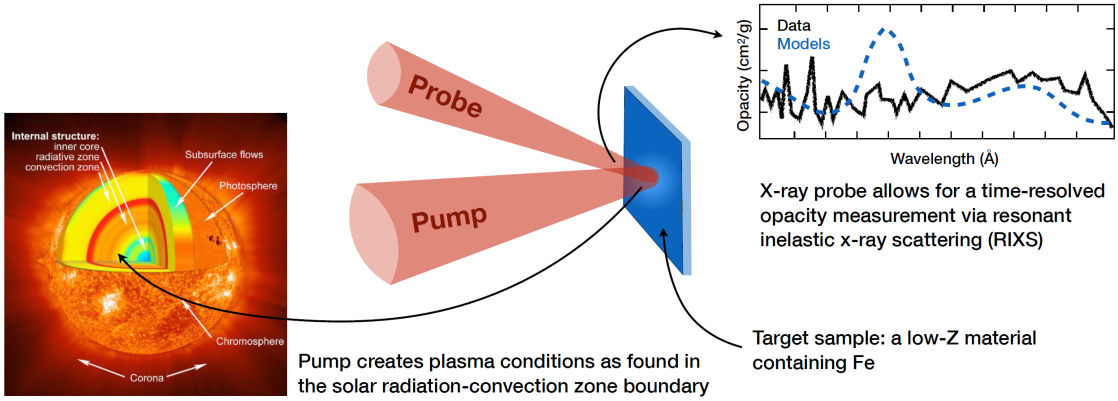
Significant advances in X-ray science over the past decade have transformed our capability to study how matter behaves in extreme conditions of pressure, temperature and density. Of particular interest is the dense plasma regime, where quantum effects and correlations are important and dominate plasma dynamics. Matter in these conditions is prevalent across the universe in stellar[28] and (exo)planetary interiors,[29] is commonly encountered in most laser-plasma interactions,[30] and is of considerable interest within the context of inertial confinement fusion energy research.[31] In contrast to high-temperature classical plasmas that are well described by kinetic theory, the properties of quantum plasmas are governed by the complex interplay between Coulomb interactions, quantum correlations and kinetics, all comparable in size. This leads to a rich spectrum of plasma properties, albeit one that has proven highly challenging to model computationally and to investigate experimentally.

Since energies from quantum interactions are in competition with thermal energies, the domain where quantum effects dominate has historically been confined to low-temperature (i.e. cryogenic) systems at relatively high densities. However, quantum effects and correlations remain important in systems up to temperatures on the order of their Fermi energy. Since Fermi energies can exceed 10s of eV in high density systems (see **Figure 4.2**), quantum effects can remain important even at high temperatures. Matter in this regime cannot be described by classical plasma theory and is known as warm-dense matter. Its equation of state has strong implications for planetary physics, as planetary cores are found in this regime, and its transport properties underly much of planetary formation and evolution. This research area is of growing interest in light of the observation of over a thousand planet candidates outside our solar system, many of which do not have analogues within our own solar system.[32]

While these observation-based discoveries are among the most exciting in a generation, they provide limited insight into the nature of these objects, i.e. their interior structure, evolutionary pathways, potential habitability, and physical and chemical processes that shape their geology and atmosphere. It is here that laboratory-based experiments can provide valuable insight into the behaviour of relevant high energy density (HED) systems, and guide future exploration. Similarly, our understanding of the structure, composition and evolution of stars also depends on a range of processes in the HED regime. Standard solar models[33] using the revised element abundances were found to disagree with helioseismic observations that determine the internal solar structure using acoustic oscillations. Recent experimental work on the Z-pinch machine at Sandia from Bailey and collaborators[28,34] showed that the opacity of Fe in the boundary region between the convective and radiative zones in the sun could be partially responsible for this discrepancy. From this work, it emerges that the opacity of open L-shell mid-Z ions (Cr, Fe) are relatively poorly understood and cannot be explained by current state-of-the-art modelling efforts, while closed-shell ions (Ni) do not lead to similar difficulties. This emphasises the importance of benchmarking astrophysical data in the HED regime to guide developments, and highlights the role of well-characterized HED experiments in supporting this effort. An example experiment that could address some of this physics is shown for illustration in **Box 4.2**. Other work from the LCLS FEL has shown more generally that our overall understanding of the electronic structure of partially-ionized plasmas in the hot-dense conditions relevant to stellar

envelopes remains incomplete,[35] and significant discrepancies remain between experiments and theoretical predictions of even fundamental quantities, such as degree of continuum lowering.[36,37,38]

Box 4.2: Time Resolved Iron Opacity Measurements in Stellar Envelopes



Schematic of an experimental platform to study the opacity of mid-Z elements such as Fe in stellar interior conditions. The plasma is generated isochorically by a soft X-ray pump and heated to the required conditions. After a time delay the system is probed at harder X-ray wavelengths and the L-shell opacity is determined via resonant inelastic X-ray scattering.

Illustration of the Sun courtesy of NASA/Goddard

4.2.2 HED science on XFELs to date

The first plasma experiments at FEL facilities[39] have successfully demonstrated the capability of X-rays to isochorically heat matter to temperatures between a few eV up to in excess of 100 eV (> 1 million K), providing access to the temperature-density conditions present in a range of stellar, white dwarf, and planetary interior conditions.[35,40,41] More recent work using nano-focused X-ray pulses suggests further isochoric heating of Fe to temperatures exceeding 1 keV at solid density, with electron densities well above 10^{24} cm^{-3}. The range of temperature-density conditions currently reachable via isochoric heating is schematically shown in **Figure 4.2**, alongside the temperature-density tracks for our sun and a typical white dwarf star. Such hot systems lend themselves well to be probed via X-ray emission spectroscopy, which has been successfully deployed to study the collisional dynamics of hot-dense plasmas,[42,43] their opacity,[44,45] and shed light on the physics of ionization potential depression,[36-38] all with unprecedented accuracy and control of experimental conditions. Investigations of warm-dense plasmas relevant to planetary astrophysics has also yielded important new insight into the structure and equation of state of planetary interiors,[16,46,47] their transport properties,[48,49] opacity,[50] and degree of ionization and continuum lowering.[51,52,53] To date, source limitations have constrained much of the high-temperature work to time-integrated experiments. Extending this research into the time domain, and to much higher densities, while accurately controlling the HED conditions of the generated plasmas (and independently measuring the

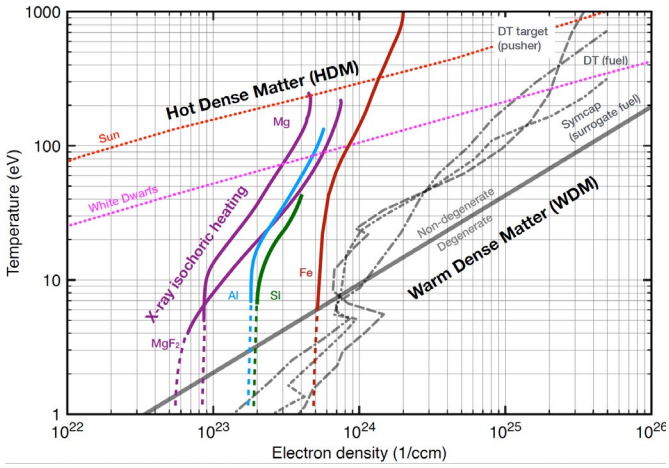


Figure 4.2: Temperatures and densities accessible in the laboratory using x-ray FEL isochoric heating: we can study a broad spectrum of extreme conditions, from planetary cores to stellar interiors. High energy compression drivers will allow us to investigate the unexplored regions at higher densities where quantum effects and correlations persist up to high temperatures.

temperature, ionisation and density), remain among the most promising future research avenues in this area.

4.2.3 Future opportunities

XFELs, coupled with energetic high-energy optical laser drivers, provide a unique opportunity to investigate extreme states of matter. X-ray isochoric heating has already been shown to heat solid density systems to temperatures exceeding 1 keV on femtosecond timescales, while compression experiments on large-scale laser facilities have shown how we can tune the inter-atomic spacing in matter to the point where it becomes comparable to the de Broglie wavelength, providing access to a new quantum frontier in high energy density science, potentially pushing quantum behaviour to the macro-scale. While these extreme capabilities are separately available at select flagship facilities around the world today, no one facility can currently both create such extreme conditions and subsequently probe them using the range of cutting-edge X-ray techniques provided by X-ray FELs. In addition to this, high repetition-rate lasers and FELs will prove revolutionary to HED physics in that they will enable, for the first time, statistical analyses of many identical HED events, rather than the current norm based on isolated-event experiments. Access to insight into how rare events (e.g. nucleation of phases and dislocations, ejecta and detonation) lead to transformations will also enable new science.

Future developments in FEL technology may provide viable approaches to significantly increasing the energy output of an FEL from the mJ level currently available towards 1 J. A joule-class X-ray FEL would have several transformative advantages to HED physics investigations, and would enable research opportunities unrivalled elsewhere. Firstly, it would allow us to access the ultra-high energy density regime via isochoric heating, generating dense plasmas at temperatures considerably in excess of those found in the centre of stars. It would further enable single-shot measurements of photon hungry diagnostics, such as inelastic or diffuse scattering, and would make it possible to apply novel non-linear spectroscopy techniques to HED investigations for the first time. A substantial increase in photons would also enhance the usefulness of beam-splitting techniques, and would, at least in principle, enable the generation of energetic X-ray comb pulse structures, which would provide new opportunities for multi-frame ultra-fast time-resolved studies.

The main future scientific objectives will be linked to the ability to perform well-characterised, time-resolved studies to drive progress in HED science. Of particular interest will be experiments aimed at observing the real-time dynamics of dense plasmas, and of phase transitions of dynamically compressed materials. This includes studies into the transport of heat, charge and particles across interfaces, and the experimental characterisation of conductivity, diffusivity, viscosity, instabilities, and plasma opacity. Transport properties, such as viscosity and thermal diffusivity in the warm dense matter regime in particular, are essential inputs for models of planetary evolution and nuclear fusion processes, and progress on this front will have an impact extending significantly beyond the realm of pure HED physics. Within this context, measurements of the opacity at the hot-dense conditions of relevance to the solar interior, performed in a well-characterised time-resolved experiment that demonstrates thermal equilibrium, may be possible for the first time, addressing key outstanding issues in solar modelling, as illustrated in **Box 4.2**.

The direct investigation of the electronic structure and excitation spectrum of highly compressed, dense plasmas is also of critical interest, not only because of its role in determining the overall partition functions and thermodynamics of extreme HED systems, but also because it will shed light on the mechanisms of core-electron interactions and on how they give rise to the observed emergence of structural complexity at high pressures. At the highest pressures it may be possible that such mechanisms lead to the discovery of new states of matter, where quantum effects emerge and dominate material structure and dynamics even at very high temperatures. While access to such extreme regimes may already be possible in some aspects on the largest facilities, such as the National Ignition Facility, key diagnostic techniques are still lacking and we currently cannot probe fundamental excitation mechanisms and ultra-fast electron dynamics in the most extreme conditions. These techniques, largely based on high-resolution inelastic X-ray scattering, necessitate a tuneable, narrow-bandwidth, bright X-ray source, which is where an XFEL with these capabilities would prove transformative.

4.3 X-ray interactions with laser accelerated electrons

By utilising compact, laser-driven, plasma-based accelerators we can generate X-ray and gamma ray sources synchronised with the X-rays available from the XFEL. Combining relativistic electron and XFEL sources would enable new science, for example allowing us to probe warm dense states, to access the extreme science of fundamental particle interactions, and to test the fundamental theories of quantum electrodynamics.

4.3.1 Laser wakefield accelerators

As described in more detail in **Appendix 3.2**, in a laser wakefield accelerator (LWFA) an intense laser pulse drives a plasma wakefield, within which are generated electric fields of order 100 GV m^{-1}, which can be used to accelerate charged particles. To date LWFAs have been used to generate electron beams with an energy up to 8 GeV from an accelerator stage only 20 cm long. The electron beams produced by LWFAs have been used to generate incoherent radiation from 100 eV to 1 MeV via magnetic undulators, betatron oscillations in the plasma wakefield, and by Compton scattering.

Since they are relatively compact and driven by the high power lasers that are necessarily part of an XFEL facility, LWFAs could be operated alongside an XFEL, greatly expanding the science which could be done on the facility whilst also providing an opportunity to drive advances in LWFAs themselves. As shown schematically in **Figure 4.3**, one or more LWFAs could be driven by using the optical lasers required for HED science, as decribed in **Sections 4.1** and **4.2,** to pump a short-pulse (50 fs) laser driver for an LWFA.

4.3.2 Science combining relativistic electrons and an XFEL beam

LWFA-driven photon sources can provide femtosecond-duration pulses of incoherent radiation in the keV range via betatron emission[54] or into the MeV range by Compton scattering an intense laser pulse from the electrons accelerated by a LWFA.[55,56,57] Compton scattering can generate narrow-band X-rays of sufficient brightness for single-shot radiography of dense material.[57] The Compton scattering beam can be supplied using a fraction of the LWFA drive beam or by using a plasma mirror to retro-reflect the LWFA drive laser. This latter technique provides a convenient, self-aligning geometry. The multi-keV X-rays produced by the betatron oscillations that occur within a LWFA are unique, in that they are both broadband and have a femtosecond duration. This makes them an ideal tool for X-ray absorption spectroscopy of rapidly evolving systems, such as those generated via laser compression or X-ray isochoric heating (see **Sections 4.1**and **4.2**). Work in this area has already started at the LCLS,[58] and is a focus of both UK[59] and international LWFA groups.[60]

The X-ray and gamma sources produced by these methods would be tightly synchronised both to each other and to the other lasers used at the XFEL (for example to those used to compress matter), and of course with the XFEL itself. Hence LWFA-driven photon sources could provide additional, synchronised ultrafast probes for X-ray imaging, scattering and absorption measurements where they can be used to probe, for example, XFEL generated WDM and HED states, as well as X-ray beam generated filaments and transient highly ionised states. Likewise a relativistic electron beam will interact with matter in highly novel ways that can then be probed by the XFEL with exceptional time resolution.

A laser capable of driving an LWFA is also capable of accelerating protons from thin foil targets, via a process called sheath acceleration. Depending on the laser parameters these broadband protons extend up into the 10s of MeV range. These picosecond duration proton beams can be used to isochorically heat samples into the warm dense matter regime, which can be interrogated with the full power of an XFEL. As described in the previous section, intense lasers can also be used to create warm dense matter directly, through the direct electron heating generated in a laser-solid interaction, or using the electron beams produced by a laser wakefield accelerator.

4.3.3 Probing fundamental physics

Combining LWFAs with an XFEL also offers some unique opportunities in fundamental science. One specific example is the study of photon-photon interactions. In 1934, Breit and Wheeler predicted that when two photons collide, they can produce an electron and a positron,[61] a process called "inelastic photon-photon scattering". This process is crucial in a range of astrophysical phenomena, and yet has never been observed in the laboratory. For example, extremely-high-energy gamma rays should not propagate across the universe due to their interaction with the cosmic microwave background,[62] and observations of TeV gamma rays are showing some tension with predictions based on the Breit-Wheeler process.[63]

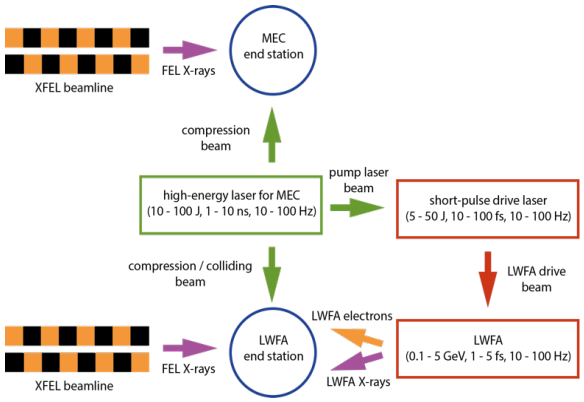


Figure 4.3: Schematic diagram illustrating how auxiliary lasers at an XFEL could drive a LWFA

Elastic photon-photon scattering, when two photons collide and change angle and energy, is one of the fundamental predictions of quantum electrodynamics, but it has never been observed with real photons. So far it has only been observed with very high-energy "virtual" photons.[64] In astrophysical scenarios, scattering of photons plays an important role in determining primordial abundances, and in the gamma-ray spectra we can observe from events early in the universe.[65] Attempts to measure low energy photon-photon scattering have not been successful (e.g. using keV photons from an XFEL[66] or eV photons using lasers) due to the very small cross-section at these low energies. Crucially, for both elastic and inelastic photon-photon scattering, the regime of relevance to astrophysics requires the invariant mass of the collision between two photons to be close to the rest mass of an electron-positron pair. With an XFEL pulse consisting few keV photons, this therefore requires collision with photon energies around a few hundred MeV. LWFAs are ideal sources of such photons, either through bremsstrahlung conversion or Compton back scattering.[67,68] Colliding ~100 MeV photons with 1 – 10 keV XFEL photons will enable fundamental studies of photon-photon physics in the laboratory for the first time.

4.3.4 Conclusion and future vision

Combining laser plasma accelerators with a UK-based XFEL would provide a unique capability that brings together a narrow energy spread relativistic electron beam with high brightness X-rays. This would be a cost-effective way of significantly broadening the science capabilities of a facility. Laser plasma accelerators can provide pulses of relativistic electrons, protons, gamma rays and broadband X-rays,which can be synchronised with the XFEL and other drivers, thereby allowing novel imaging, scattering, and absorption measurements. Such measurements can provide new insight into the behaviour of matter compressed and heated to extreme conditions, can be used to provide additional isochoric heating, or can provide the photon beams needed to probe the fundamental physics of photon-photon interactions for the first time.

The requirements for the XFEL are the same as those required for the other science described in this section – the ability to deliver high fluxes of high energy X-rays, ideally in the range 20 – 30 keV, but higher if possible. A LFWA requires driving by a high power optical laser. A focused intensity $> 10^{19}$ W cm^{-2} with a repetition rate exceeding 10 Hz (eventually to 100 Hz) would provide beyond state-of-the-art capability for these combined X-ray-electron experiments. We note that these laser requirements are similar to those needed for other science in this case (see **Section 3.5**).

4.4 Coupling an XFEL to a laser-driven spherical compression facility

The coupling of a laser-driven spherical-compression facility to a sufficiently hard X-ray FEL would enable the diagnosis of extreme states of matter in unprecedented detail, leading to advances both in the pursuit of fusion energy and our understanding of the universe. This would be a transformative marriage of technologies that would be globally unique, enabling the UK to attain a leadership position in the associated science and technologies.

4.4.1 Introduction

Laser-driven spherical-compression enables the creation of temperature and density states otherwise inaccessible within the laboratory. These conditions are similar to those in the cores of stars, supernovae and giant planets. Historically, research in this area has been focused on two main areas: laser inertial confinement fusion[69] (one of two 'mainline' routes to fusion energy) and nuclear weapons research. In recent years, High Energy Density Science (HEDS) research on such facilities has become increasingly diverse, and now includes areas such as Laboratory Astrophysics, Nuclear Astrophysics, Planetary Physics, Plasma Physics, Matter at Extreme Conditions, Warm Dense Matter, Opacity, Equations of State, Laser-Plasma Interactions and Quantum Electro-Dynamics (QED).

International spherical compression facilities include the USA's National Ignition Facility (~2 MJ of laser energy), France's Laser MegaJoule (similar to NIF), Russia's ISKRA-6 (2.8 MJ, under construction), China's SGIII (180 kJ) and SGII (320 kJ upgrade in progress), and the USA's Omega (30 kJ). However, due to the small spatial scales of the compressed plasma and the brief duration of peak compression, the limited precision of experimental diagnosis obstructs a detailed understanding of the physics of these extreme states of matter. Coupling a laser-driven spherical compression facility to the UK XFEL would enable a transformation in our understanding. For example, state-of-the-art experiments are typically limited to spatial resolutions of ~3 µm and temporal resolutions of 1×10^{-11} s (but usually significantly worse); in contrast, an XFEL can achieve spatial resolutions of ~30 nm and temporal resolutions of 1×10^{-14} s, an increase of 100- and 1000-fold respectively.

4.4.2 Applications

The key advantage of spherical compression is the capability to probe a *far* greater density and temperature parameter space than that which can be created through any other method, as illustrated in **Figure 4.4**.

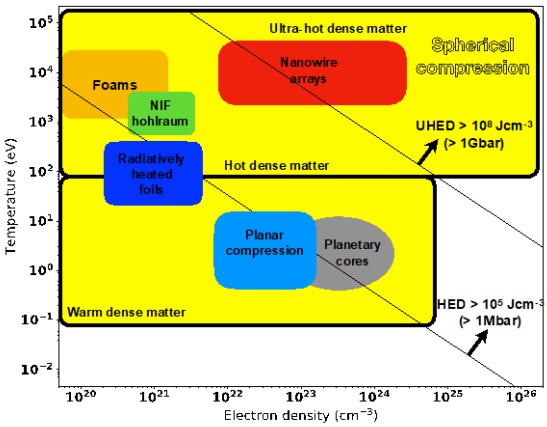


Figure 4.4: The region of density and temperature parameter space which can be explored via spherical compression (both yellow regions)

A laser-driven spherical compression facility sited alongside an XFEL would have a diverse range of applications in the fields of Laboratory Astrophysics, Nuclear Astrophysics, Planetary Physics, Plasma Physics, Matter at Extreme Conditions, Warm Dense Matter, Opacity, Equations of State, Laser-Plasma Interactions and Quantum Electro-Dynamics (QED). Rather than re-visiting these topics, which are detailed elsewhere within this section, we instead highlight that spherical compression would greatly increase the scope of these research areas by enlarging the accessible density and temperature parameter space.

Below we outline some areas where the coupling of a spherical compression facility to an XFEL would be truly transformative, creating a world-leading globally unique facility. This would enable these

systems to be studied in unprecedented detail, with concomitant improvements in our understanding of the underlying science.

4.4.2.1 Laser fusion

Laser inertial fusion is, along with magnetic confinement fusion, one of two highly advanced, credible approaches to fusion energy. Currently the National Ignition Facility (NIF) has entered the alpha heating regime and has made substantial progress towards meeting the Generalised Lawson Criterion for ignition. Further progress is expected to require either an improved understanding of the implosion performance and fuel assembly conditions, or an increase in the implosion scale; progress is ongoing on both fronts. The unprecedented spatio-temporal resolution of an XFEL would enable ultra-high-resolution X-ray Compton scattering or phase contrast imaging of the implosion with effectively no temporal blurring. Coupled to a more modest (e.g. 100 kJ) spherical compression facility, this would transform our understanding of the implosion process, accelerating progress towards fusion energy gain. Importantly, by exploring more energetically efficient implosion techniques such as Laser Direct Drive,[70,71] the insights gained on such a facility could pave the way to ignition on significantly smaller scale lasers than NIF, which in turn would enhance the economics of laser fusion power production through the reduction in capital cost.

4.4.2.2 Fusion materials

A key challenge for fusion is the engineering of materials able to withstand the fast ion and neutron irradiation created by fusion reactions. The coupling of a spherical compression facility to an XFEL may enable the real-time evaluation of damage mechanisms caused by atomic displacements within the lattice.

4.4.2.3 The intensity frontier

Spherical compression requires quite significant laser energy, meaning a system would likely be at least in the high 10s of kJ in order to be globally competitive. Chirped Pulse Amplification (CPA, the subject of the 2018 Physics Nobel Prize) enables this laser energy to be compressed in time. If the available laser energy were harnessed in this way, the achievable laser intensity would far exceed that of any existing or planned facility. Such a laser, when coupled to an XFEL, would enable the exploration of a raft of exotic fundamental physics (see **Section 3.5**).

4.4.2.4 Matter at extreme conditions

Studies of the mechanisms of deformation, melt, recrystallisation and polymorphic phase transitions in matter are currently limited to planar compression geometries, in which shear plays a significant role in the deformation dynamics, significantly complicating the interpretation of such experiments. A spherical implosion facility combined with an XFEL would enable hydrostatic (shear-free) compression to extreme states of matter to be studied in unprecedented detail, and to pressures and temperatures well beyond those currently accessible with planar compression.

4.4.2.5 Advanced manufacturing

The development of precision targetry for a spherical compression facility would greatly enhance existing cutting-edge UK manufacturing capabilities, such as those at Scitech Precision Ltd. Furthermore, the laser developments required for such a facility would consolidate the Central Laser Facility's position as world-leaders in the design and manufacture of high-energy, high repetition rate lasers. With these technologies in place, the UK would be excellently placed to capitalise on potential economic benefits if power production via Laser Fusion were to become a commercial reality.

4.4.2.6 Defence

The combination of spherical compression with an XFEL would enable opacity and equation of state studies to be performed with unprecedented fidelity at extreme densities and temperatures. Potentially such a facility could provide access to the burning plasma regime, unlocking a wealth of physics, the detailed understanding of which is critical in the nuclear test-ban era.

4.4.3 Facility needs

In terms of UK XFEL facility characteristics, the key parameter is the ability to deliver high fluxes of high energy X-rays, ideally in the range 20 – 30 keV, higher if possible.

The cost of a laser-driven spherical compression facility is highly dependent on its design characteristics and in particular total laser energy. The largest international laser-compression facilities cost more than an XFEL; however, investment at this level would not be required in order to make a significant impact. A detailed examination of the optimal design characteristics of a laser-driven spherical compression facility is beyond the scope of this report. Instead we briefly outline two approaches which might be considered in order to fund such a facility within a plausible funding envelope:

- a phased approach starting out at 1 - 10s kJ of laser energy, with a planned upgrade path; or
- an international collaborative approach, where the UK's investment in the XFEL forms a substantial part of its contribution to the construction of an international spherical compression laser facility.

Either way, given the scientific potential offered by such a facility, it is crucial at the FEL planning stage that sufficient physical space is left for the development of such a facility.

4.4.4 Conclusions and future vision

The coupling of a laser-driven spherical compression facility to an XFEL would be a transformative marriage of technologies. This globally unique capability would have the potential to revolutionise laser fusion research, accelerating the realisation of fusion energy, whilst enabling a plethora of diverse High Energy Density science, from Laboratory Astrophysics to Quantum Electro-Dynamics.

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5. Science Opportunities in Quantum and Nanomaterials

Quantum and nanomaterials represent an exciting class of materials that contain fascinating new physics and have the potential to enable disruptive technologies for devices and in energy applications.

Quantum and nanomaterials have significant potential to deliver a wide range of new technologies. These materials can show drastically different behaviours – such as high temperature super-conductivity, exotic magnetism and high-speed phase transitions – to what is found in the more 'regular' materials that form the backbone of current technologies. However, one of the main challenges in fully exploiting their potential is that there is no clear consensus on why they possess the properties they do and how they can be exploited fully. XFELs have the potential to break this deadlock by providing a transformational improvement in understanding how, and why, quantum and nanomaterials can be manipulated to induce advantageous new properties, shining light on new physics and deepening our understanding of how materials function.

XFELs have the potential to bring about whole new approaches to how we measure materials. To date, Materials Physics has been dominated by the Fourier-domain. Material properties are measured as a function of frequency and momentum. Temporal and spatial dependences are inferred through Fourier inversion. This can be challenging, as most measurements lack the phase information, particularly in the X-ray regime, which generally hinders the inversion process. While this problem is particularly acute for real space imaging, the phase information can be vital for understanding the response of materials, particularly those that are not theoretically well understood.

Short pulse XFELs allow us to make a breakthrough in this direction and measure materials in space and time. The high time-resolution and high-brightness of XFELs allow us to capture fluctuations "in the act". For example, high temperature superconductivity emerges from a "strange metal" phase, where fluctuations between competing phases are believed to play a critical role in the material properties. Basic questions, such as whether these fluctuations compete against each other or enhance each other to determine the materials properties, are still unanswered. A real space and time approach will allow us to see if these fluctuations occur in the same regions of the sample and at the same time, or if they are pinned to specific defects and are essentially different processes – a property which is notoriously difficult to separate from the Fourier domain.

As well as answering existing questions, a time-domain approach will likely yield new opportunities. Most spectroscopic approaches measure two-body correlation functions. Intense and coherent laser-like XFELs may enable higher order correlation functions to be measured, which are vital for understanding spin-entanglement and the quantum properties of partially ordered spin phases. Fluctuations associated with quantum critical points could also be captured in "diffract-and-destroy" types of experiments, where conventional X-ray pulses would result in sample heating, moving the system away from the regime of quantum fluctuations.

In this section, we provide an overview of the major themes and opportunities provided by XFEL science in quantum and nanomaterials, with a summary of key experimental requirements.

5.1 Magnetic materials and control of ultrafast magnetisation

Ultrafast photo-excitation of quantum materials that exhibit intricate coupling between charge, spin and orbital degrees of freedom holds great promise for understanding and controlling the properties of non-equilibrium and hidden states. Here we discuss the state-of- the-art and introduce time-resolved resonant inelastic X-ray scattering (trRIXS) as a means of measuring charge, spin and orbital excitations. These excitations encode the correlations and interactions that determine the detailed properties of the generated states and may advance the technology of, for instance, fast, energy efficient, data storage.

5.1.1 Introduction to magnetic dynamics measured with FELs

Magnetism has fascinated mankind since its discovery over two thousand years ago. Although magnetic fields can be conceptualised using classical physics, the existence of magnetic materials can only be understood in terms of the fundamentally quantum mechanical nature of the world around us. Our ability to manipulate magnetism via ultra-fast laser excitation has therefore attracted considerable excitement within the scientific community. In terms of applications, ultrafast magnetism provides routes to fast switching of electronic devices, which often store information in different magnetic states.[1] From a more fundamental point of view, ultrafast magnetism addresses the questions: what are the fundamental principles governing the interactions of photons with matter?[2] And can we use ultrafast excitations to generate magnetic states that are inaccessible in equilibrium?[3] Magnetic or spin degrees of freedom are also intimately tied to many of the most interesting emergent electronic properties of materials, such as high temperature superconductivity quantum spin liquids, colossal magnetoresistance, etc.[4,5] Understanding quantum magnetism is therefore important to nascent efforts to realise and manipulate such states transiently.

Our current understanding of ultrafast magnetism tends to be based on simple magnetic order parameter ideas, of which the so-called three-temperature model is the most popular.[6] This involves defining effective temperatures for the lattice, electrons and spins, and constructing a phenomenological picture based on rates of energy-exchange between these degrees of freedom. This can, for example, capture the common phenomenology of a magnetic order being suppressed by high-fluence high-energy optical pulses before it recovers slowly. This theoretical approach is rather natural in terms of the common tools for characterising transient magnetism, which are benchtop optical experiments that measure the net ferromagnetic order parameter using the Faraday or magneto-optical Kerr effects. Since most experiments measure simple order parameter dynamics, there is limited information and motivation to develop more sophisticated theories.

Working within this paradigm is, however, very limited, as it is most appropriate for states that are similar to those that are accessible via equilibrium thermal heating. This paradigm excludes many of the most interesting ideas such as magnetic switching,[7] generating transient superconductivity,[8] realising topological lattice or electronic structures[9,10] or rotating spin with terahertz or mid-infrared excitation.[11-13]

5.1.2 State of the art in probing magnetic dynamics

Despite the increasing sophistication of table-top probes of magnetism, the information extracted tends to be held-back by the low energy of the beams. The wavelength of optical light is far longer than the atomic spacing and the length scales usually relevant to magnetism, meaning that a lot of the details of transient magnetic states are inaccessible to such experiments. This is perhaps the primary reason why optical experiments tend to probe the net ferromagnetic order parameters. Using X-rays provides a direct way to access lengthscale-dependent properties and a more complete description. The most obvious way to do so is by studying spatially modulated states such as antiferromagnetism,

orbital order or charge density waves.[14-18] These states have staggered order parameter as a function of position in the crystal lattice, which average to zero in spatially integrating probes.

Standard X-ray scattering with arbitrary X-ray energies interacts primarily via the Thompson cross-section and probes the atomic structure of the material. Resonant X-ray scattering, as illustrated in Figure 5.1 (left) involves tuning the X-ray energy to excite a core hole resonance. This provides a means to couple X-rays to magnetic and orbital degrees of freedom and probe electronic order. The use of resonant diffraction was impressively illustrated in studies of perovskite manganite $Pr_{0.5}Ca_{0.5}MnO_3$, in which the authors probe electronic and structural degrees of freedom after photo-excitation and were able to describe the electronic behaviour of the material in terms of a set of atomic displacements illustrated in **Figure 5.1** (right).[14]

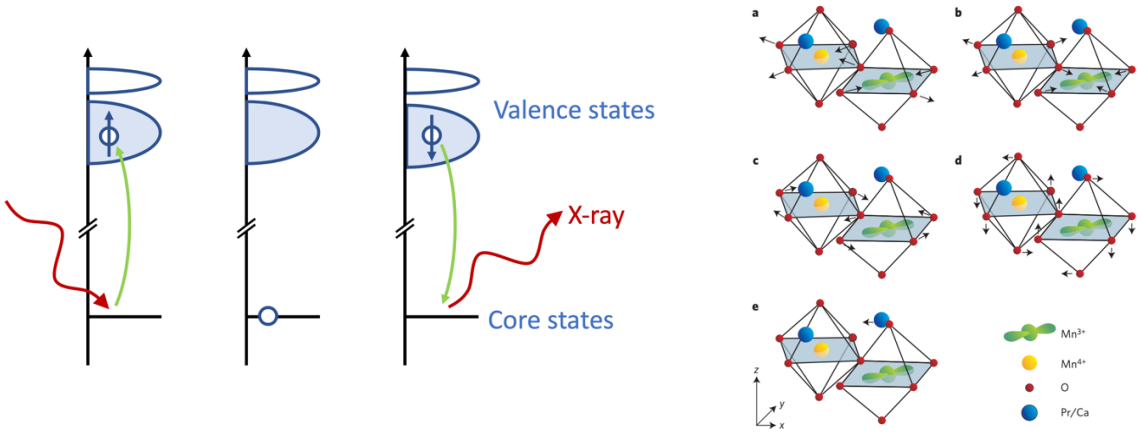

Figure 5.1: Ultrafast resonant diffraction. Left: A schematic of the resonant scattering process. The initial, intermediate, and final states are shown from left to right. Photons are represented as wavy red lines and electronic transitions are shown as green arrows. In this process spin excitations are created and their dispersion can be measured by determining the energy and momentum change of the photon.[19] Right diagram of optical phonon modes related to the different elements of electronic order in $Pr_{0.5}Ca_{0.5}MnO_3$. Taken from.[14]

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Another important class of experiments probe the statistical distribution of magnetism with X-rays.[7,20-22] If one measures a ferromagnet with a characteristic domain size using X-ray resonant magnetic scattering, the diffraction pattern will be azimuthally symmetric, with a peak that reflects the inverse domain size as seen in **Figure 5.2** (left).[7] Previous experiments have applied this approach at XFELs in order to probe magnetism, and have shown unique capabilities for separately probing different magnetic species at different lengthscales .[7,20-22]

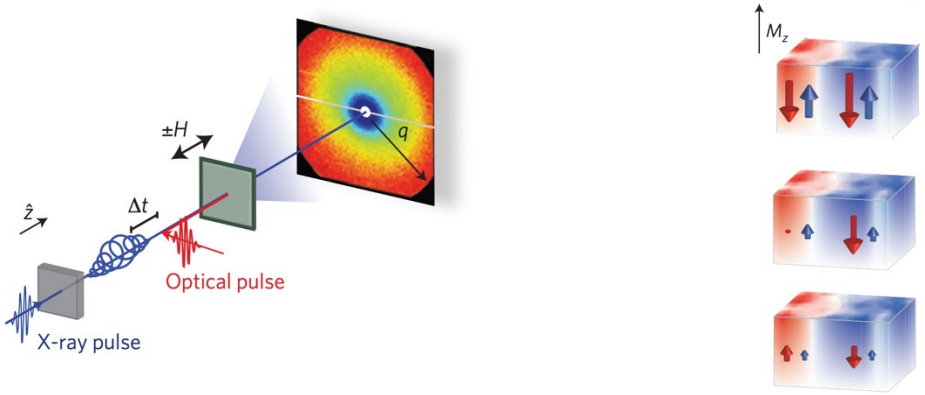

Figure 5.2: Magnetic domain dynamics. Left the experimental setup for magnetic diffraction from domains. Right an illustration of the evolution of iron and gadolinium moments out of equilibrium.[7]

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DOI: 10.1038/nmat3597 Copyright (2013)

5.1.3 Future opportunities in magnetic dynamics

We identify three main categories of new experiments. The first involves more sophisticated and high time-resolution pump schemes, such as THz or mid-infra excitation. This lower energy photo-excitation can couple more directly to magnetism or drive phonon modes in order to realise novel electronic states. Dedicated instrumentation for the pump and probe is highly desirable here, as the X-ray element of the experiment needs to be implemented in a more stable and straightforward way to allow more challenging photo-excitation schemes.

A very appealing, but underexplored, area is performing XFEL experiments in the perturbative regime, in which the ground state is only slightly disturbed and small changes are seen in the magnetic state. In this limit, the sample response can reflect the equilibrium dynamical susceptibility and coupling between different degrees of freedom. This scheme has been compellingly employed to provide parameter-free determination of electron-phonon coupling via the measurement of crystal structure and electronic band-structure after photo-excitation.[23] To the knowledge of the authors, this has not yet been applied to XFEL experiments of magnetism. Experiments involving small changes are especially well-suited to high-repetition-rate XFEL sources, as high average flux is needed to measure small changes in a weak magnetic order parameter signal.

Another area is the prospect of performing spectroscopy of collective excitations in transient states. Collective excitations encode key details about the interactions and short-range correlations in transient states. Time-resolved RIXS, as illustrated in **Figure 5.3**, has recently emerged as a practical means to probe such correlations and has measured magnons in photo-excited iridates.[16,24] Such a spectroscopy could answer some of the most profound questions, such as how can we modify different components of the magnetic exchange on ultra-fast timescales? Or can we soften different components of the magnetic excitation spectra in order to transiently stabilise different magnetic ground states? An XFEL with a dedicated spectrometer for such experiments would provide unique opportunities to help understand transient magnetism.

Looking to the future, the ability of XFELs to deliver multiple, phase-coherent pulses with controllable delay will facilitate new forms of higher-order spectroscopy. This would involve applying two (or more) phase coherent pump pulses prior to the probe pulse and corresponds to measuring a “three-point correlation function”, as distinct from the “two-point correlation function” commonly measured by inelastic neutron scattering, inelastic X-ray scattering or more recently time-domain Fourier transform inelastic X-ray scattering at XFELs.[25] These correlation functions have direct signatures of fractional spin quasiparticles, such as Majorana fermions and fluxes,[26] which hold promise for realising robust quantum computers. This is in contrast to two-point correlation functions, which can only couple to pairs of fractional excitations, leading to a broad continuum in energy. Such innovations have the potential to solve the decades-long quest to discover the quantum-correlations underlying putative spin liquid phases.[27]

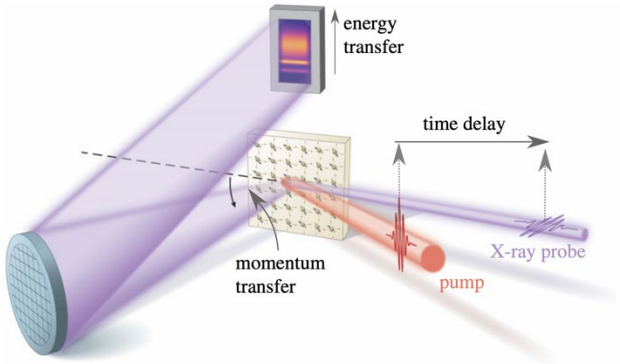


*Figure reproduced from Y. Cao et al. "Ultrafast dynamics of spin and orbital correlations in quantum materials: an energy- and momentum-resolved perspective", Phil. Trans. R. Soc. A. **377** 20170480 (2019) DOI: 10.1098/rsta.2017.0480*

Figure 5.3: Time-resolved RIXS as recently realised in [16,24,25] The momentum transfer is determined by the angle between the incident and scattered X-rays from the sample, along with the wavelength of the X-ray. The energy of the scattered photons is resolved by dispersing the X-rays with a grating or crystal analyser onto a two-dimensional detector. In tr-RIXS, a second pump laser pulse is used which arrives at a controllable time ahead of the incident X-rays.

5.2 Structural dynamics and light induced phases in quantum materials

The transient modification of structure in quantum materials by femtosecond pulses of laser light can induce new properties that do not appear in equilibrium. Coupling with an ultra-fast X-ray probe can provide unprecedented insight into how electrons, phonons and spins interact to determine the properties of materials, such as magnetism, insulator-metal transitions and superconductivity. Here we discuss how light can be used to manipulate these interactions effectively and efficiently, in order to control material properties.

5.2.1 Introduction to the structural dynamics measured with FELs

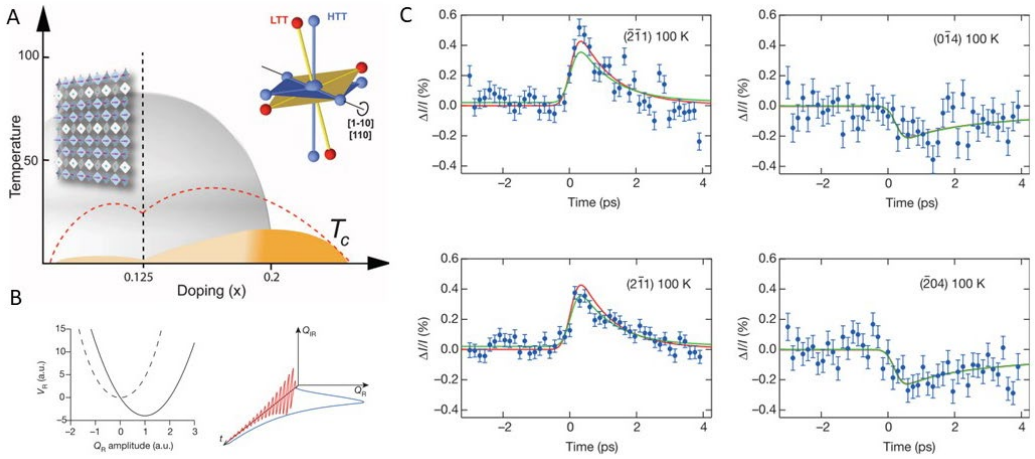
The atomic structure of quantum materials has a profound effect of the material's electronic and magnetic properties. Understanding this connection between the underlying atomic structure and the resulting functionality of the material is one of the key challenges in the physics of quantum materials. In many quantum materials small, picometre, atomic displacements can result in materials with vastly different properties. These displacements are capable of changing a magnetic insulator into a metal or even a superconductor. The sensitivity to distortions represent significant challenges to understand quantum materials, as they intrinsically require highly accurate and precise measurements and theories[29] in order to accurately capture and characterise the subtle structural changes. However, this sensitivity also presents new opportunities for control. As only small atomic displacements are required to induce new electronic and magnetic properties, intense light pulses can distort the crystal structure of the lattice. This has led to a new field with the aim of controlling the properties of quantum materials "on demand".[4]

Several experiments have shown that light can transiently modify the structure of materials to induce new properties that do not appear in equilibrium in the host material. Light tuned to a structural resonance in order to shake specific bonds has been shown to induce insulator-metal,[30] magnetic[31] and superconducting[8] transitions. However, these first experiments have essentially been performed "blind" from a structural point of view. These effects were observed before the first XFELs could look at the atomic structure on the appropriate timescale, and lattice motion that resulted from the optical excitation could only be inferred through indirect methods. FELs are now enabling a step-change in our understanding of lattice dynamics, as they can probe the structural changes directly, capturing snapshots of the atomic configuration as it changes in real time.

Furthermore, FELs allow us to start looking at a new range of questions in quantum materials. Charge density wave instabilities are found in a whole range of quantum materials. The fluctuations of the charge and lattice may compete with, or complement superconductivity, but we have not yet been able to observe these lattice fluctuations in real space. Short pulse coherent diffraction from the lattice may open up new options to image these processes, allowing us to study quantum materials in real space and real time for the first time, while diffract-and-destroy experiments could capture structural distortions and fluctuations that arise from quantum fluctuations at low temperatures that are inaccessible to X-rays at the moment due to beam heating effects.

The new information obtained from FELs will enable completely new insights into both how small atomic displacements alter the functionality of quantum materials, and how light can manipulate these changes, which ultimately could lead to new paradigms in both our theoretical understanding of quantum materials and in future devices that can exploit the dynamic control of the material's phase.

Box 5.1: Light control of material properties



Light resonant to structural modes in quantum materials can be used to control the properties they exhibit. Some quantum materials exhibit high temperature superconductivity, but in others this can be suppressed due to a structural distortion (A). By using light resonant to structural mode, the atomic positions can be controlled though phonon mode coupling (B). Recently, this process has been observed at LCLS using time-resolved X-ray diffraction to provide the first evidence for mode coupling. (part A taken from [8]; B and C from [37]).

***Figure A** reprinted by permission from American Association for the Advancement of Science: D. Fausti et al. Science **331**, 189-191 (2011). DOI: 10.1126/science.1197294 Copyright (2011). **Figures B & C** reprinted by permission from Springer Nature: R. Mankowsky et al. Nature **516**, 71-73 (2014). DOI: 10.1038/nature13875 Copyright (2014)*

5.2.2 Structural dynamics in quantum materials

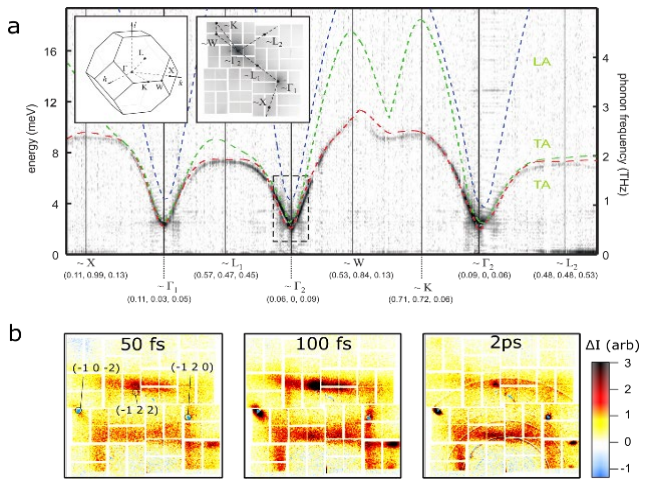


*Figure 5.4: Time-resolved diffuse X-ray scattering. **a** Fourier Transform inelastic X-ray scattering is now able to measure phonon dynamics in Ge throughout the entire Brillouin Zone with sub meV energy resolution.[32] **b** Time-resolved diffuse scattering changes during a structural phase transition in VO_2, showing that lattice disorder dominates at early timescales.[33]*

*Top image reprinted figure with permission from D. Zhu et al. Phys. Rev. B **92**, 054303 (2015), DOI: 10.1103/PhysRevB.92.054303. Copyright (2015) by the American Physical Society*

*Bottom image reproduced from S. Wall et al. "Ultrafast disordering of vanadium dimers in photoexcited VO2", Science **362**, 6414 572-576 (2018) DOI: 10.1126/science.aau3873*

While femtosecond X-ray sources have enabled the study of aspects of light-induced phase transitions in quantum materials for some time,[34] the advent of ultrafast and ultra-bright FEL laser pulses has transformed our understanding of ultrafast structural transitions. Correcting for the intrinsic timing jitter between X-rays and the exciting laser has been key for much of the progress. Real-time jitter correction can time-stamp each measurement with a precision of 6 fs,[35] which is sufficient to observe most structural motion. Initial measurements on light-induced phase transitions focused on exploiting the time-resolution of XFELs to study vibrational coherences induced by optical excitation through Bragg scattering.[36] More recent advances have been driven by combining Bragg scattering with new

methods to control the lattice, specifically mid-IR[37] and THz[38] excitation. By combining state-of-the-art X-ray sources with state-of-the-art laser-based methods to excite the system, new insights into how below-gap light can coherently modify the structures of materials is emerging and enabling new states of materials to form.

In addition to the advances that come from combining advanced pumping techniques with femtosecond X-rays, new techniques are beginning to emerge that can take advantage of the high photon flux. Phonons cause deviations from a perfect lattice by modulating the atomic structure on the length scale set by their wavelength. This transfers some scattered intensity from the 'ideal' Bragg peak into diffuse scattering between the peaks. As the phonon displacements are small, the intensity redistribution is weak, and had been largely inaccessible to time-resolved studies. Ultra-bright XFELs, however, are intense enough to resolve this scattering with ease. Fourier Transform inelastic X-ray scattering[39] is a new technique that exploits this scattering to measure coherent phonon dynamics over the entire Brillouin zone for the first time (see **Figure 5.4 a**).[32] This time-domain approach is excellent for measuring low energy oscillations and sub-meV resolution phonon dynamics have already been reported,[32] making this technique competitive with inelastic X-ray scattering in terms of energy resolution.

Furthermore, this technique can be used to examine how phonon populations change dynamically when the system is rapidly driven through a phase transition. This was performed for the first time on the prototypical quantum material VO_2 (**Figure 5.4 b**),[33] where it was observed that phonons are excited rapidly but incoherently throughout the entire Brillouin zone. This disorder-like process, only visible due to the high brightness and high momentum resolution of the FEL, overturned the previous description, obtained from electron diffraction, that the transition was a coherent-like process resulting from well-defined regular atomic motions.[40]

5.2.3 Future opportunities in structural dynamics

The study of structural dynamics and phase transitions with XFELs is rapidly developing. There are several directions in which future progress can be made, specifically combining state-of-the-art optical pump sources with the new probing techniques that are provided by short and intense X-ray pulses.

XFELs have many properties that make them the leading source for measuring the dynamics of quantum materials. X-rays have significantly higher q-resolution and the pulse durations can be an order of magnitude shorter than electron sources, which is a key competitor. These are key factors for observing small and fast displacements. However, most significantly, X-rays are insensitive to the mechanism used to excite the sample. X-rays are not directly perturbed by the pump pulse and only respond to the resulting changes in the material, whereas electrons are charged and can thus feel the electric field of the pump pulse during transit to the sample. This becomes particularly significant when the pump wavelength is increased, which increases the ponderomotive force applied on the electron beam.

However, there are several technical drawbacks that X-rays face. In order to reconstruct a transient unit cell, i.e. to understand how the atoms re-arrange, at least as many Bragg peaks need to be measured as there are atoms in the unit cell. However, this will only tell you the average motion, and more Bragg peaks are required to determine the Debye-Waller and disorder in the system. Quantum materials typically have 10s of atoms in the unit cell, and thus many peaks need to be measured. MeV electron diffraction, for example, is ideal for this, as the high electron momentum makes it easy to measure 10s – 100s of Bragg peaks in a single geometry.

Currently, with X-rays we have to rotate the sample in order to access a sufficient number of Bragg peaks. While this is not a problem for static measurements, it introduces many challenges for dynamic measurements. Freely rotating samples while cooling and providing optical access has limited most experiments to temperatures above 100 K. In order to match pump and probe penetration depths, experiments must be performed in a near grazing geometry, which results in large spot sizes and limits the field strengths that can be reached. Furthermore, due to the large optical anisotropy of many

quantum materials, rotating samples for X-ray diffraction can result in very different pumping configurations, which makes it challenging to compare results. There is an opportunity for the UK to leverage its expertise in cryogenics to design experimental stations that can access temperatures down to a few kelvin. As low temperature structural transitions are key to understanding quantum materials, this would put a UK machine in a world-leading position.

One way to overcome this limitation is a move to hard X-rays > 20 keV. If high quality free-standing samples can be obtained, a transmission Laue diffraction geometry would enable the measurement of multiple diffraction peaks in a single experimental geometry. These conditions are similar to those required for pair distributions measurements discussed in **Section 5.5**. This would also significantly simplify the experimental setup and cooling requirements, enabling much lower base temperatures to be reached than those achieved to date. Further benefits would arise from a 'normal incident' geometry, specifically high peak electric fields could be generated which would could drive the sample into new regimes, while nanofocusing of the X-ray source could enable direct probing of macroscopic inhomogeneity.

While high repetition would be advantageous for experiments like time-resolved Fourier transform inelastic X-ray scattering, low (kHz-rate) repetition rates can actually be advantageous. Free standing samples have poor thermal recovery and, if samples are in vacuum, repetition rates will have to be limited to kHz frequencies in order for the sample to be able to dissipate the heat. Experiments that aim to capture dynamic fluctuations, such as imaging real space CDW fluctuations, will potentially need to be measuring on a single shot basis.

5.2.4 Conclusions

From a structural point of view, a FEL with X-rays greater than 20 keV is highly desirable, as it would enable new experimental geometries which will generate much cleaner and more detailed information, with an option to access temperature ranges current machines cannot reach. While high repetition rates are always beneficial, they are not strictly necessary from a structural dynamics point of view, and most experiments that are focused on the low temperatures will need to work at reduced repetition rates, while experiments that are focused on imaging fluctuations are likely to work on a single shot basis.

5.3 Imaging dynamics in nanomaterials

The ability to directly image, in three-dimensions, time varying phenomena in nanoscale materials at the surface and in the bulk can greatly increase our understanding of how novel phases develop and how they influence the material properties. Coherent diffractive imaging (CDI) without lenses is a form of microscopy that can permit high resolution imaging, where the use of conventional optics is not feasible. When combined with ultra-fast X-rays, time-resolved Bragg CDI provides a novel and robust means to image ordered material systems with sub-ångstrom sensitivity. Such insight will greatly aid our understanding of nanomaterials and will serve as a platform to develop next-generation materials and devices.

5.3.1 Introduction to nanomaterials imaging with XFELs

Nanomaterials are materials in which the defining characteristics of the material are size dependent. Technologies developed from nanomaterials are the subject of multidisciplinary research stemming from more traditional disciplines that routinely study the physical, chemical, biological, engineering and electronic aspects of materials. Nanomaterials have found use in a wide range of disciplines owing to their unique and often tuneable physical, chemical and biological properties, that often differ widely from the bulk material.[41]

When materials are reduced to the nanoscale, their behaviour is often very different from the bulk material due to quantum confinement effects and the increased surface-to-volume ratio that may result in behaviour that is dominated by surface properties.[42] It is for this reason that our ability to directly image materials in three-dimensions at the surface and in the bulk can greatly increase our understanding of how novel phases develop and influence the material properties. Progress in the study of nanomaterials will require tools to characterise the nanoscale structure in three-dimensions with atomic precision.

The dynamics of nanomaterials are governed by their quantum properties. Strong coupling between lattice, charge, spin and orbital degrees of freedom often gives rise to emergent behaviour and multi-functional properties.[43-46] Such materials are of great interest because the different properties may work together in uniquely different ways and lead to exciting new applications, if we could understand this better. For example, the coupling between magnetic spin and ferroelectric charge ordering can be utilised to develop magnetoelectronic devices where spin transport can be controlled electrically. This is advantageous for technological applications, including novel sensors and ultra-low power memory devices. As a result there is a vibrant effort to understand the underlying mechanisms at work.[47-49]

Nanomaterials where degrees of freedom are strongly correlated can exhibit novel short-lived non-equilibrium phases that occur on the femtosecond timescale. They include light-induced superconductivity, terahertz-induced ferroelectricity and ultra-fast solid-phase structural transformations.[8,50-52] Efforts to shed light on these hidden phases are further compounded by the limited theoretical framework that is able to adequately describe the spontaneous emergence of new phases of materials due to external excitation. In addition, few studies are dedicated to time-resolved measurements due to the limitations of adequate tools. For example, electron microscopes are able to resolve atomic scale features of sufficiently thin materials, but have poor time resolution.[53] In addition, femtosecond laser systems (excluding hard X-ray sources, treated here) have poor spatial resolution and cannot resolve atomic structural changes. The key to deciphering these phenomena lies in measuring time-dependent changes in the materials structure in three-dimensions. The ability to directly image these processes in three-dimensions at the surface and in the bulk will greatly increase our understanding of how the phase is initiated, proliferates and gives rise to emergent properties.

With the advent of fourth-generation XFEL facilities, it has become possible to study ultra-fast structural dynamics in nanoscale materials for the first time.[54,55] This is enabled by the femtosecond coherent X-ray pulses produced by the XFEL. Three-dimensional imaging at the surface and bulk of

structural properties in nanoscale materials is made possible through lens-less imaging techniques, such as coherent X-ray imaging (CDI).[56] The following section provides an overview of the current state-of-the-art in imaging of dynamics in nanomaterials at XFEL facilities. Imaging of biological nano-materials is omitted and is instead treated in **Section 7**.

5.3.2 Ultrafast microscopy of nanomaterials

Traditional non-destructive methods for the study of nanomaterials, such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM) and numerous spectroscopic techniques, can provide detailed information on the surface structure but do not directly probe the structure within its volume as a whole. Coherent diffraction imaging (CDI) is a powerful lens-less imaging technique for probing nanometre-sized crystalline materials with sub-ångstrom sensitivity. It is an attractive alternative to electron microscopy because of the better penetration of the electromagnetic waves in materials of interest, which are often less damaging to the sample than electrons.[56,57] There are a number of important variations on the conventional CDI method. They include forward scattering CDI which is ideally performed on non-periodic structures and Bragg Coherent X-ray diffraction Imaging (BCXDI).[58-61] Forward scattering CDI has found many uses, including serial crystallography and imaging extended objects (See **Sections 7.1** and **3.2**).

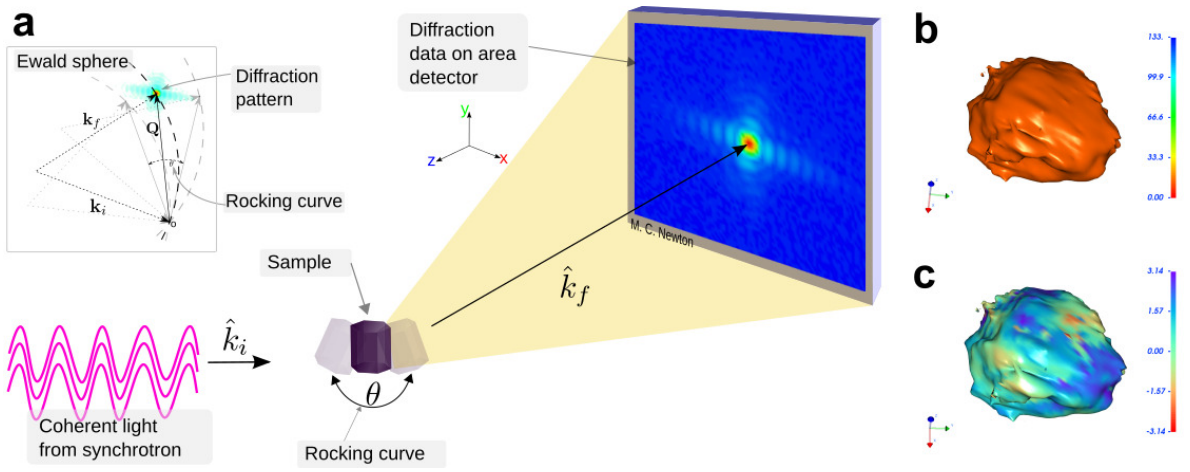


Figure 5.5: Illustration of the BCXDI imaging experiment. ***a****, Schematic of the BCXDI imaging experiment showing coherent X-ray illumination of a single perovskite bismuth ferrite nanocrystal in the Bragg geometry.[52] The inset illustrates Ewald sphere construction of the experimental geometry in reciprocal space.* ***b****, Reconstruction of the electron density amplitude of a single nanocrystal approximately 300 nm in length.* ***c****, Phase information shown at the surface of the nanocrystal in* ***b****.*

BCXDI is the reflection scattering variant of CDI.[57] BCXDI holds great promise for understanding transient phases in correlated nanomaterials (**Figure 5.5**). It is also largely non-destructive and provides structural information at the surface and throughout the bulk of a material. BCXDI was first applied to the study of gold nanocrystals.[58] Later it was shown that BCXDI also offers a means to determine in three-dimensions any structural changes due to strain, most likely to occur for nanocrystals that experience a structural distortion due to defects or external perturbation.[62]

When coupled with an ultra-fast coherent X-ray excitation source, BCXDI can be performed in a stroboscopic mode to provide time-resolved images in three-dimensions with nanometre resolution and ångstrom sensitivity. The spatial coherence of an XFEL beam ensures that BCXDI is feasible. The earliest example of time-resolved three dimensional imaging of nanomaterials was performed on gold nanocrystals at the Linac Coherent Light Source (LCLS).[63] By utilising femtosecond laser pulses to excite the nanomaterial, and femtosecond X-rays to probe in a 'pump-probe' experiment, it was possible to obtain three-dimensional images of the generation and subsequent evolution of coherent acoustic phonons on the picosecond time scale within a single gold nanocrystal, thus providing insights into the

physics of the phenomenon (**Figure 5.6**). Further studies have focused on a broader range of materials systems such ultra-fast processes in complex transition metal-oxides.[52,64,66]

5.3.3 Future opportunities with XFELs

Ultra-short pulses of coherent X-rays beams hold the unique potential to record time-varying three-dimensional images of electronic, magnetic and crystalline structural properties in quantum materials on the nanoscale. The potential to image the inner workings of transient phenomena in and out of equilibrium including (multiferroic) phase-domain structures, dislocations, topological nanocrystals, strong-phase structures and structural phase transitions in three-dimensions will provide a potential route to solving long-standing problems that are driven by strong correlations. There remains a wide range of prototype quantum material systems that are not fully understood and yet lend themselves to XFEL experiments. They include multiferroic perovskite materials (e.g. $BiFeO_3$, $YMnO_3$, La_xCa_{x-1} MnO_3 (LCMO), $La_xSr_{x-1}FeO_3$ (LSFO), $La_xSr_{x-1}MnO_3$ (LSMO) and $PbVO_3$) for electronically mediated spin transport devices, structural phase change materials (e.g. $BaTiO_3$, VO_2) for femto-second ultra-fast all optical switches, and ion diffusion in battery materials such as $LiCoO_2$.[34,52,67-69]

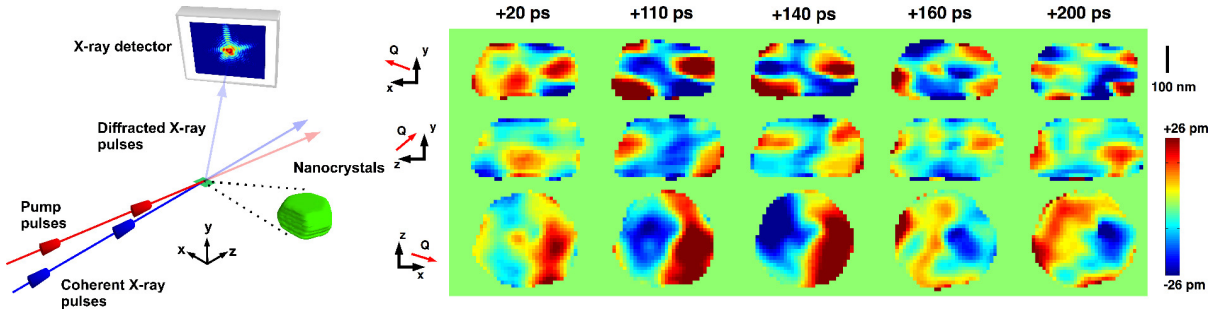


Figure 5.6: Left, Schematic of the setup for ultra-fast time resolved Bragg coherent diffraction imaging. Optical pulses (red) perturb the sample, generating phonons. Coherent X-ray pulses (generated from an XFEL) arrive a short time later where the diffracted pulses are recorded using an area detector. Right, Imaging of acoustic phonons in a nanocrystal. Orthogonal cut planes through the nanocrystal showing the projected displacement as a function of delay time. For each delay time orthogonal slices taken from the centre of the nanocrystal are shown. The direction of the displacement field is given by the Q-vector in red.[63]

*Figure reprinted by permission from American Association for the Advancement of Science: J.N. Clark et al. Science **341**, 56–59 (2013). DOI: 10.1126/science.1236034 Copyright (2013)*

The remaining challenges for imaging quantum nanomaterial systems are two-fold. The first is the difficulty of measuring nanoscale materials using single extremely intense and short X-ray pulses before the onset of radiation damage (diffraction before destruction). For nanomaterials other than simple metals, this can pose a challenge when employed in a pump-probe measurement. The second is related to the ultimate resolution attainable by Bragg X-ray imaging methods, which is ~5 nm at present. Further development of XFEL facilities with increased X-ray brilliance will enable Bragg CDI methods to achieve atomic resolution and realise a long standing dream of an atomic-resolution X-ray microscope.[56,70] This would permit direct comparison of ab-initio simulation with experiments and enable robust materials design with atomic precision.

5.3.4 Summary

The UK has significant strength in theoretical research into quantum materials and nanotechnology. There is also a strong global community in X-ray diffraction imaging techniques. For the UK's X-ray facilities to maintain world-class status, it is essential that important scientific questions are addressed and emerging techniques, such as ultrafast CDI, are continuously developed and utilised. An XFEL that can reveal ultrafast processes that occur on the femtosecond timescale and beyond will prove an invaluable asset for the development of next-generation quantum technologies, and will position the UK as world-leading in ultra-fast imaging of quantum materials.

5.4 Electronic dynamics in quantum materials

Ultrafast photoelectron spectroscopy (PES) is an enabling technique to provide insight into spin, orbital and charge degrees of freedom of chemical bonding characteristics in quantum materials. PES techniques combined with ultrafast X-rays will provide much needed answers to questions related to localised quantum state dynamic behaviour on the femto- and attosecond timescale, capturing electronic behaviour in real time.

5.4.1 Introduction

Correlating the structure and electronic structure of materials lies at the core of our understanding of functional materials. When moving from "regular" to quantum materials, we encounter a significant increase in complexity due to the particular nature and confinement of electronic states, e.g. at surfaces and interfaces. In many technologically relevant device systems, the overall electronic behaviour is dominated solely by interfaces rather than the surrounding extended structures. Even minute changes in the structure of a material can lead to significant differences in its electronic structure and the resulting electronic behaviour, determining whether a material is a metal, semimetal, semiconductor or insulator. The detailed nature of the electronic structure, including band structure, intrinsic and extrinsic charge carriers, and defect and trap states, is of great importance to further develop future device generations.

To date, physical characterisation techniques are predominantly confined to the study of the electronic structure in static, often bulk samples. Dynamic behaviour is often inferred by combining electrical measurements and physical characterisation at specific points, which are "frozen in time". FELs provide an unmatched opportunity to study electronic structure dynamics in energy, space and time, providing a high level of understanding of quantum materials, which is essential to future application developments.

5.4.2 Background including earlier research at XFELs and by other methods

One of the key techniques used to study the electronic structure of matter is photoelectron spectroscopy (PES). Excitation sources from the UV to soft and hard X-rays are used to probe the occupied valence states and, in specific cases, occupied conduction states of materials including gases, liquids and solids. The technique is intrinsically referenced to the Fermi energy of the sample and can not only provide information on the chemical nature of bands in solids, but also their overall alignment. The correlation of changes of the electronic structure of a material with both core level and valence spectra is immensely powerful to study local chemical environments, as well as the electron density and distribution of a system.

Standard PES is performed routinely in laboratories worldwide, but synchrotron sources are necessary for advanced studies. In particular, the probing of low occupation states, often vital to electronic behaviour, necessitates the high flux provided by synchrotrons to enable the detection of such low intensity features. In addition, the energy tunability of synchrotrons enables measurements under resonant conditions, and the associated discrimination between states of different orbital character enables the identification of specific contributions to the overall complex band structure. XFELs are expanding the dimensions PES can explore from energy, space and spin to time, enabling multi-dimensional analysis of electronic structure dynamics.

The most important limitation for PES at FELs is the existence of vacuum space charge effects. The extremely brilliant FEL pulses generate a dense cloud of photoelectrons at the sample surface and the Coulomb repulsion of the electrons leads to a strong distortion of the initial photoelectron energy distribution. This leads to shifting and overall broadening of spectra and therefore a loss in effective energy resolution. Both computational and experimental solutions to this challenge are being proposed and are at the core of current developments.[71-74]

One completely new area that XFELs have opened up is X-ray two-photon photoelectron spectroscopy (XTPPS). This technique exploits the femtosecond timescales provided at XFELs and follows the formation of single or two-site double core hole (ssDCH, tsDCH) states caused by the sequential absorption of two X-ray photons at a timescale matching the lifetime of Auger decay (below 10 fs). The DCH states have been shown to probe the local chemical environment more sensitively compared to single core hole (SCH) states, as they are directly coupled to any changes in valence electron structure of the two core hole atomic sites.[75-77] **Figure 5.7** shows a schematic of the different accessible core hole states. Access to this new regime in PES enables a detailed investigation of both core and valence structure of matter. XTPPS is developing rapidly, but is to date limited to molecular species. Current and future developments towards its application to nano- and condensed matter systems will enable a new window into their electronic structure.

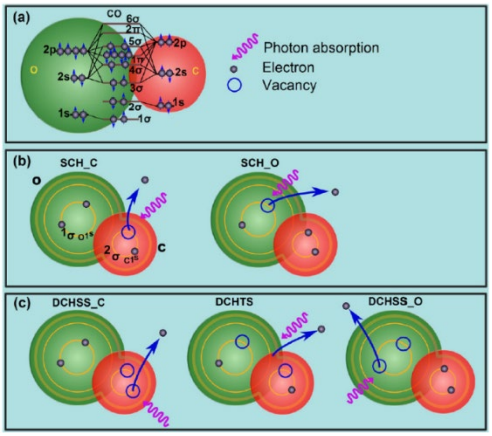


Figure 5.7: Cartoon design of (a) the electronic structure of the CO molecule, (b) the SCH ionization at the C K-edge and the O K-edge, and (c) the ssDCH ionization at the C K-edge, the ssDCH ionization of the O K-edge and the tsDCH ionization.[78]

Figure reprinted from N. Berrah et al. Proc. Natl. Acad. Sci. USA. ***108****(41):16912-16915 (2011) DOI: 10.1073/pnas.1111380108*

Time-resolved PES (trPES) enables access to electronic state dynamics in quantum materials. To date, experiments have been performed using laboratory laser sources and synchrotrons[79,80] as well as XFELs.[71,81] Pioneering work by Hellmann and co-workers focused on understanding metal-insulator transitions, essential for so many electronic devices.[79,81] Their work focused on the Mott insulator 1T-TaS_2 and they successfully employed femtosecond time-resolved core-level photoelectron spectroscopy, as well as time-resolved angle-resolved PES (trARPES) to explore atomic-site specific charge-order dynamics of the charge-density wave and the relative contributions of electron-electron and electron-phonon interactions to electronic order in momentum space. **Figure 5.8** shows time-resolved ARPES spectra of a range of layered compounds.

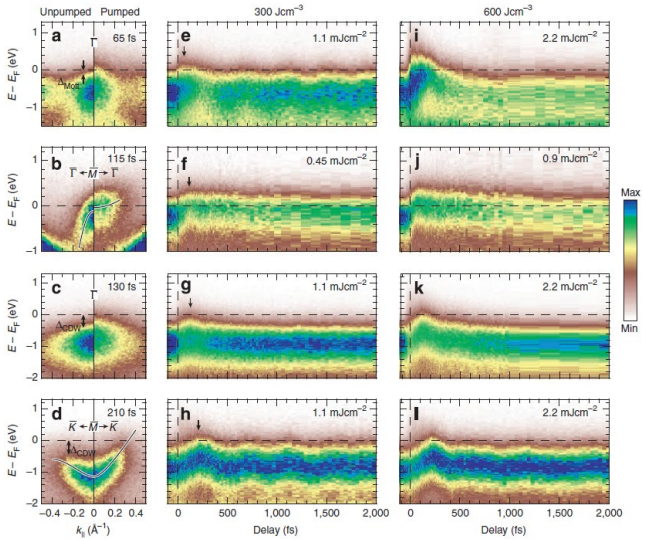


Figure 5.8: Time-resolved momentum-space view of the electronic structure in layered charge-density-wave compounds, including 1T-TaS_2, 1T-$TiSe_2$, and 1T-TaS_2. [79].

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Beyond soft X-ray PES, there has been considerable development of time-resolved hard X-ray PES (trHAXPES) setups and experiments in recent years.[82,83] The main advantage of HAXPES over XPS is the significant increase in probing depth, enabling the exploration of bulk systems and buried layers and interfaces, often crucial to material behaviour in a device context. Oloff and co-workers demonstrated that it is possible to resolve intrinsic charge-carrier recombination dynamics in electron-doped $SrTiO_3$ establishing trHAXPES as a well-placed technique to study intrinsic charge-carrier dynamics on ultrafast timescales.[83]

Recent work by Kutnyakhov and co-workers presents the culmination of current developments for muldimensional PES.[73] They developed a novel setup at FLASH which combined full-field momentum imaging and time-of-flight energy recording. Combined with the photon energies available at FLASH and other FELs, this will enable time-resolved experiments from core level to valence band spectroscopy and photoelectron diffraction exploiting the tunability of the photon energy to access varying probing depths. However, the current limitation to soft X-rays and the available pulse structures severely limits what PES techniques could deliver for complex quantum materials in the future.

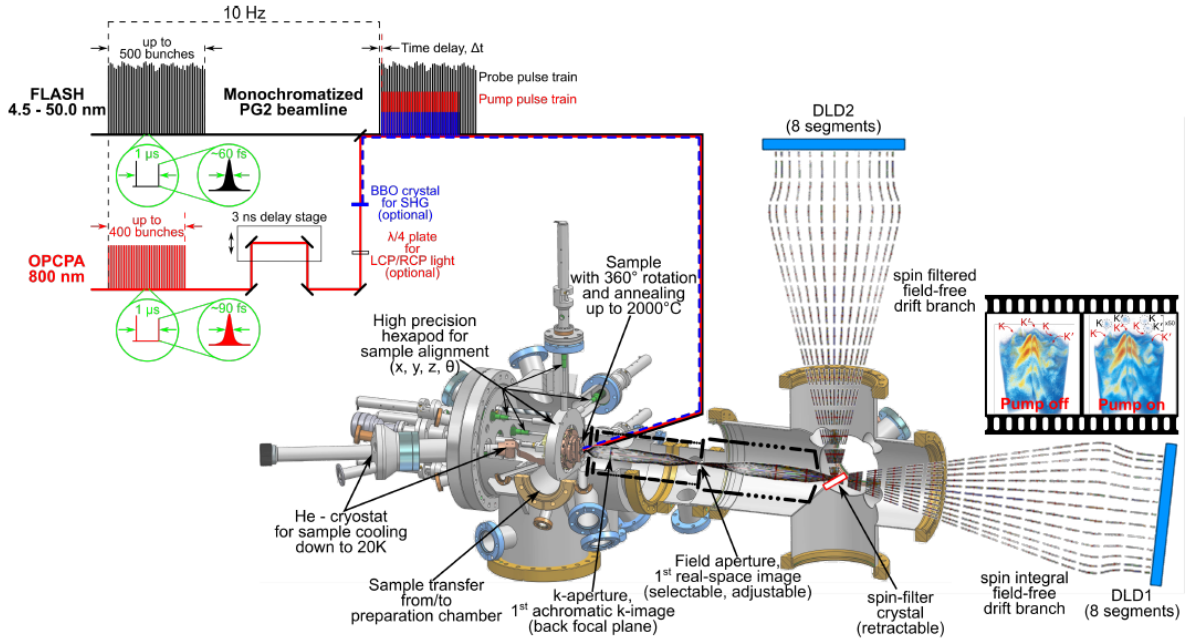

Figure 5.9: Simplified overview of the FLASH pulse structure, the PG2 beamline with synchronized pump laser (top left) and the experimental setup (middle) used to perform time-resolved momentum microscopy and acquire volumetric band-mapping movies (right inset) by means of a multidimensional recording scheme.[73]

Figure reproduced from D. Kutnyakhov et al. Rev. Sci. Inst. ***91****, 013109 (2020). DOI: 10.1063/1.5118777*

5.4.3 Future opportunities with XFELs

XFELs already routinely provide access to femtosecond timescales, and first measurements with attosecond resolution have been reported. This provides access to electronically relevant timescales, allowing the probing of electron dynamics in real time. XFELs will enable going beyond static measurements of electronic structure, towards a full dynamic picture of the electronic behaviour of charge carriers. The ability of advanced PES setups to probe electronic, spin and crystal structure, coupled with the timescales accessible at future XFELs, will enable probing of band and defect populations dynamically and even under operando conditions. This will deliver unprecedented insights into how electronic materials function, providing vital knowledge for the development of future, disruptive device technologies and beyond.

The area of angle-resolved PES has already delivered a wealth of crucial insights into the electronic structure of materials.[84] The prospect to combine further ARPES variants with the time resolution

delivered by an XFEL is promising for the following reasons. Firstly, nanoARPES, which combines the information available from standard ARPES with a nano-focused X-ray beam, could explore a range of crucial questions regarding the electronic structure and dynamics in nanoscale systems.[85,86] Currently, X-ray spot sizes in nanoARPES are on the order of hundreds of nm, but future XFEL and synchrotron sources may enable spot sizes of only 10s of nm to be delivered on the sample. Nanometre scale beams are moving towards matching the length scales of device relevant structures and future in-operando setups, including the ability to bias a sample during measurement, this would enable the exploration of electron dynamics in both space and time e.g. within advanced electronic devices.[87] A second exciting extension of ARPES uses hard X-rays (HARPES) and can be used to explore not just sample surfaces, but also bulk materials.[88] In the future, XFELs may be able to extend this to specific buried layers and interfaces whilst providing the high time resolution necessary to follow electron dynamics at interfaces, which are often crucial to final device behaviour and performance.[89]

Another exciting emerging area of study is multiple ionisation events and their use as chemical and electronic probes in PES, which promise new insights into both core and valence electronic nature of materials. Ongoing research is focusing on the extension of current work on small molecular species to more complex materials in the view to establish this technique for quantum materials.

Several challenges remain when wanting to probe electronic structure both statically and dynamically in quantum materials. One of the biggest practical limitations to date is the difficulty of obtaining useable signals from often small spectral features using short, extremely intense X-ray pulses without acquiring data influenced by radiation damage. Sample delivery and data acquisition systems for nanomaterials, as well as structured multilayer materials, including buried interfaces, will need substantial further development to enable probing of low intensity contributions to e.g. density of states.

As mentioned above, space charge is a fundamental problem for PES, and high repetition rate sources combined with high efficiency electron detectors are necessary to combat its negative effects. Detector developments, e.g. the introduction of single-shot data acquisition systems which can be combined with existing high-resolution hemispherical electron energy analysers, are an integral part of future advances.[90] In parallel, ongoing development of powerful momentum microscope systems for both the soft and hard X-ray regimes is pushing towards three-dimensional data acquisition, collecting electron energies and their distribution in k-space on relevant timescales.[89,91-95]

5.4.4 Summary

The UK has a strong, long-standing record in photoelectron spectroscopy and its application to study the electronic structure of matter. This is complemented by an outstanding theory community, supporting experimental efforts. The continuous development of experimental techniques at X-ray facilities is crucial to the understanding and development of future electronic materials and their applications.

The possibility to investigate ultrafast electron dynamics across a wide range of both chemical and physical systems using time-resolved PES is a game changer in the area of quantum technologies. The simultaneous detection of the electronic, spin, and overall structure of a material on relevant timescales in the femto- and attosecond regime will open up a completely new way to directly probe the interactions between electronic, spin and lattice dynamics in quantum materials enabling the emergence of new technological applications. Existing setups are generally limited to probing only one aspect of a system and can often not reach the attosecond timescales relevant for electron dynamics. This results in experiments only providing a partial view of the complete material system. However, the final behaviour of a material, either isolated or within a device application architecture, is an intricate interplay between electronic, spin, and local structure. Therefore, future XFEL sources that combine energy tunability from the soft to the hard X-ray regime, high repetition rates to overcome space charge limitations, and attosecond time resolution to probe electron dynamics, would enable unprecedented insights into quantum materials for electronic applications and enable the conceptualisation and development of truly novel device concepts.

5.5 Time resolved pair distribution functions

Persistent disorder in quantum materials can appear in various forms, including chemical, electronic, magnetic and geometric. Correlations present within the disorder often give rise to novel phases in the physical and chemical properties of quantum materials. Pair Distribution Function (PDF) measurements are able to probe disorder and, when combined with ultrafast X-rays, provide a potent method to identify the symmetry breaking transitions.

5.5.1 Introduction to pair distribution functions

There is strong community in the UK using total scattering and Pair Distribution Function (PDF) techniques, and exploiting the dedicated X-ray and neutron instrumentation at the Diamond and ISIS facilities. PDF is the Fourier transform of the total scattering intensity, which maps the probabilities of distances between all pairs of atoms.[96] This function can be modelled precisely. We expect there will be significant interest in developing the instrumentation and methodology needed to measure time-resolved X-ray PDFs at the future UK XFEL. Many of the problems of interest to this community will carry over into the time domain with the provision of a pump-probe methodology.

5.5.2 Orbital degeneracy lifting

One immediate application would be to address the important Orbital Degeneracy Lifting (ODL) ideas, widespread in Quantum Materials, particularly those containing transition metal elements with partially filled d-orbitals.[97] The ability to access the femto- and picosecond time domain will enable a completely new dimension of understanding of ODL physics by investigating the speed of its response to an ultrafast laser stimulus. ODL is a local state lacking long-range order, established to lift orbital degeneracies imposed by the high temperature crystal structure. Being electronic in nature and breaking crystal symmetry, it is expected both to fluctuate rapidly and to respond to a driving laser excitation. ODL leads to a subtle kind of local order that is invisible to most other X-ray analytical techniques, but can be clearly seen through the real-space PDF approach. ODL is hard to measure with X-ray Bragg diffraction, because it is a local effect within a crystal that does not change its overall symmetry; it therefore produces broad diffuse scattering in reciprocal space. ODL could be responsible for local the local symmetry-breaking electronic nematicity found in a range of quantum materials, especially complex oxides and chalcogenides.[101,102]

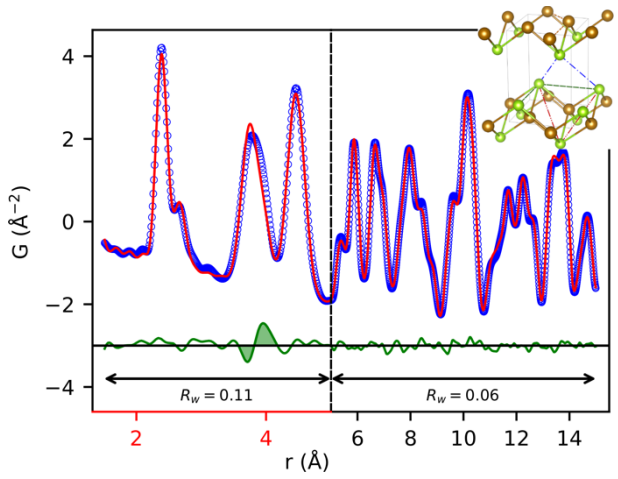

Figure 5.10: X-ray Pair Distribution Function measured from tetragonal FeSe at 300 K, well above its orthorhombic phase transition at 90 K. Local fluctuations are apparent in the second-neighbour peak at 3.9 Å, indicating local symmetry breaking. It is believed this is driven by local fluctuations in the d-orbitals, whose time-dependence could be tracked in a future tr-PDF experiment at the UK XFEL.[103]

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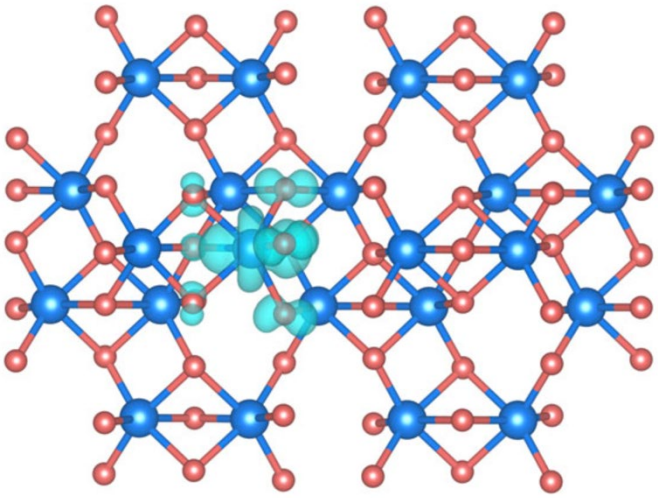
5.5.3 Need for time-resolved Pair Distribution Function capabilities

PDF is a potent method to identify the symmetry breaking which, in extreme cases, leads to crystals with one lattice symmetry at large distances, and a completely different symmetry over the short range distance scale. A simple example of ODL explains the symmetry breaking found in FeSe.[103] PDF

structural analysis of FeSe has revealed the presence of a local orthorhombic distortion (which lifts the degeneracy of d_{xz} and d_{yz} t_{2g} orbitals and which we have identified as an ODL state) with a correlation length of about 4 nm at temperatures where the average symmetry is tetragonal. FeSe is tetragonal above 90 K, with C_4 rotational symmetry about the c axis. The low-temperature orthorhombic structure has C_2 symmetry. **Figure 5.10** shows that the C_4 structure fits the high-temperature PDF data at distances beyond 6 Å, but not below, where the C_2 structure is needed. This large local orthorhombic distortion in FeSe persists over wide ranges of temperatures, including into the nematic state at low temperatures, where the magnitude of the local distortion is much larger than the average crystallographic distortion, suggesting an imperfect long-range ordering of the local state below Ts = 90K. The results point to a model where ODL fluctuations, which persist up to at least 300 K, order at low temperature into the macroscopically orthorhombic phase.

Box 5.2: Bose-Einstein condensation in quantum materials



Proposed small polaron in hematite, α-Fe_2O_3.

The structure of "exotic" excited configurations in condensed matter systems, such as polarons, excitons and possibly Cooper pairs are largely unknown. In each case the structure of the excitation could be detected directly by small-angle scattering or else detected at large Q in a scattering experiment coupling to the small displacement of the atoms in the host crystal. These Bosonic excitations can undergo Bose–Einstein condensation (BEC) leading to a geometric assembly whose structure which could also be probed. For example, CdTe semiconductor microcavities, in which photons are confined and strongly coupled to electronic excitations, can create "exciton polaritons".[98]

The problem is that BEC is destroyed by thermal phonons and so occurs at millikelvin or microkelvin temperatures. A conventional X-ray diffraction experiment would destroy the delicate condensate, opening the opportunity for single-shot "Diffract and destroy" approaches at an XFEL. Pump-probe single-shot methods will be effective for the photo-excited states. The density of excitons in the direct-gap semiconductor Cu_2O is seen to decay on the single ns time scale.[99]

A possible structure of the "small polaron" delocalised electron-hole pair and its associated displacements has been proposed for hematite, a-Fe_2O_3. So long as a sufficient number of these can be generated with a pump laser, the tr-PDF method will be able to probe its role in the entire photocatalysis sequence of this and other solar energy storage technologies.[100]

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The goal of a UK XFEL based time-resolved PDF measurement of FeSe would be to investigate the sequence of events following optical pumping into the valence band, followed by occupation of the Fe d-orbitals relevant to ODL and the subsequent local distortion of the lattice. Ultrafast Electron Diffraction (UED) studies of FeSe have already shown the sort of information that might be learned.[104]

Another class of materials which will be accessible by trPDF are the "relaxor ferroelectrics". This behaviour is typically found in perovskite complex oxide crystals, most famously in lead magnesium niobate, $PbMg_{1/3}Nb_{2/3}O_3$ (PMN), which shows unusual local structure and electrical properties. Conventional ferroelectrics exhibit a sharp first-order phase transition from a high temperature paraelectric state to a spontaneously polarised state at the Curie temperature T_C. The phase transformation at T_C is unambiguously associated with a structural phase transition, which provides vital guidance to the design and scientific development of this class of materials. In comparison, relaxor ferroelectrics have a broader transition and never fully order below T_C, but simply slow down to form a glass-like low-temperature state with the same average crystal symmetry as at high temperature. The low-temperature state is called an ergodic relaxor (ER) state,[105] often explained by nanometre scale regions, called "polar nano regions" (PNRs), which possess randomly oriented dipole moments.

The existence of these PNRs has a dramatic effect on the electrical behaviour and shows a characteristic frequency dependence of the dielectric constant. Unlike the conventional ferroelectrics, which exhibit a Curie-Weiss divergence of ε at T_C, PMN and other relaxors exhibit a rounded peak, which shifts to higher temperatures with frequency. The peak in ε depends very strongly on the measurement frequency, which indicates that there are relaxational dynamics with timescales that freeze out at different temperatures. The origin of this time scale, its dependence on other experimental parameters has been phenomenologically explained by a thermally-activated reconfiguration of the polarisation,[106] but this explanation is not microscopically understood despite extensive neutron[107] and X-ray[108] diffuse scattering studies and X-ray PDF investigation.[108,109]

5.5.4 Summary of tr-PDF Opportunities for the UK-XFEL

To develop the tr-PDF method at the UK-XFEL will present some challenges. First and foremost, high energy X-rays are needed, ideally up to 50 keV. A large area detector sensitive to these high energy X-rays, such as the Rayonix (MAR) MX340-XFEL, will then have to be augmented with a CdTe sensor. The lowest conceivable energy would be about 25 keV. This is needed to obtain a wide enough Q-range, with Q_{max} = 25 $Å^{-1}$ needed to fully resolve the peaks in the PDF in real space, as seen in **Figure 5.10**. New detector geometries, conceivably a wrap-around low-to-high 2θ layout, could be introduced to get to high Q_{max} with lower energy X-rays. PDF structure refinements and simulations can then be obtained with the existing PDFgui program suite[110] or RMCProfile codes.[111]

A general challenge in all pump-probe experiments is to obtain a good laser/X-ray overlap to ensure that every part of the sample responds to the laser pump. For PDF experiments, we could use spin-coating to make thin layer samples of finely ground material on Si_3N_4 membrane windows, aiming for say 10 μm crystals in a close packed single layer. This design would allow every crystal to see the laser at normal incidence. The photo-stimulated electrons generated by the pump laser would traverse the grain quickly in the metallic state to provide overlap everywhere, not just within the electromagnetic skin depth. The X-ray beam will be spread over 100s of microns, even up to 1 mm^2. This helps the powder averaging and spreads the dose so we can stay below the sample damage threshold, but it is important to avoid "shadowing" of grains that would not see the laser.

5.6 Concluding remarks

The UK has a vibrant Quantum Materials community with experience in condensed matter theory, neutron scattering, synchrotron X-ray scattering, photoemission and laser spectroscopy of solid materials. Quantum materials are defined by the interactions of their populations of electrons and spins with the crystal lattice, often described out of equilibrium by using a "3-temperature" model and coupling rate constants. The timescales of the interactions range from femtosecond (electrons and spins) to pico- and nanosecond (acoustic lattice modes). Ultrafast techniques are needed to measure these coupling rates and elaborate the underlying theoretical picture.

Ultrafast excitations over a wide range of frequencies are needed, as well as sample environments to control pressure and temperature. Dedicated instrumentation is then required to measure the X-ray response in a pump-probe sequence. This Section has described a number of advanced methods where the UK has capabilities. Resonant Inelastic X-ray Scattering (RIXS) is used to observe magnons, phonons and excited electronic states. Time resolved measurements of X-ray Diffuse Scattering allow mapping of phonon dispersion curves and population densities. Bragg Coherent Diffraction Imaging (BCDI) can locate the distribution of strain within nanocrystals. Photoemission Spectroscopy (PES) can see the changes in electronic band structure with separated spin states. X-ray Pair Distribution Functions (PDFs) can identify the local symmetry distortion of lattices.

Each of these methods, once developed for users of a future UK XFEL facility, would attract a wide range of material samples important to research enabling the development of quantum devices and energy science applications.

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6. Science Opportunities in the Chemical Sciences and Energy

Virtually any chemical reaction, regardless of the means of its initiation, is enabled and accompanied by simultaneously occurring structural changes. These changes range from the complete dissociation of a chemical bond to subtle fluctuations in local geometries accompanied by changes in electronic structure and spin-state. XFELs give unique and incisive access to these dynamics, which is vital to scientific understanding and myriad applications of chemistry to real-world applications.

The revolutionary impact of the proposed UK XFEL on chemical sciences – as an integral part of all science and technology areas in the age of multi-disciplinary approaches – will be enabled by a combination of key unique capabilities. These include:

- High repetition rate (100 kHz or higher) and high brightness (> 10^{12} photon/pulse) to enable the required sensitivity and signal-to-noise ratio
- A broad coverage of X-ray energies, from soft to hard (200 eV to 20 keV), making it possible to investigate most of the atomic absorption edges across the periodic table
- The flexibility of joining multiple methods of initiation and monitoring by combining X-rays, electron beams, and optical methods.

To bring about a new level of understanding of areas as diverse as chemistry in space and the origin of life on Earth to photocatalysis or information storage, the processes involved need to be followed with atomic precision as they evolve along the multidimensional, multi-parameter landscape. A likely game-changer, ***a combination of high repetition rate X-ray pulses with optical VUV, UV, Vis, IR, THz excitation and detection pulses mixed-and-matched-on-demand,*** is now within reach. Enhanced provision of all these capabilities will be an important feature at a UK XFEL.

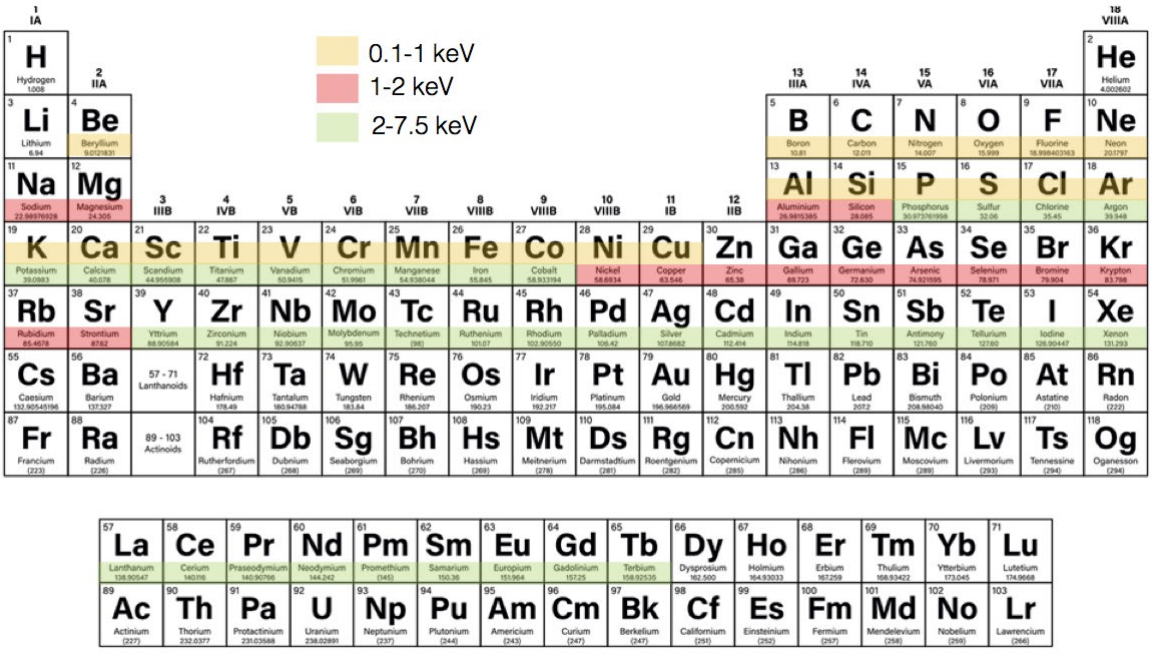

Figure 6.1: The Periodic Table of X-rays

Selected areas discussed in this section include: real-time molecular movies of reactions, transformations and catalysts with atomic precision, on the timescales from femtosecond upwards; the next level of understanding of the interplay of fundamental nuclear, electronic, and spin dynamics underpinning the new 2D-materials, photofunctional materials, materials for energy storage and capture, and catalysis; atmospheric, environmental, and analytical chemistry; chemistry in space; new diagnostics and therapies in medicine.

6.1 Fundamentals of reaction dynamics: Coupling between nuclear, electronic and spin degrees of freedom

Chemical dynamics encompasses the entanglement of phenomena across multiple timescales, from femtoseconds (a vibrational period of a chemical bond) to seconds (full cycle of photosynthesis), involving structural, electronic and spin states evolving together. The UK XFEL source will bring a combination of sufficiently short pulses of photons, with energies tuneable from THz to X-ray, sufficiently high repetition rate of >100 kHz, high spectral purity, and high brightness of 10^{12} photons/pulse, to enable a comprehensive interrogation of chemical reactions, non-equilibrium processes, and transformations, "watching chemistry happen".

6.1.1 Introduction

The last decades saw an explosive development of interrogation of optical phenomena in molecules and materials on ever shorter time-scales, approaching the very act of breaking or formation of a chemical bond and reaching out into the attosecond domain.[1] Key questions that must still be answered include: *Can we possibly ever record a meaningful molecular movie, where the convolved structural, electronic, vibrational, and spin dynamics are simultaneously resolved?*[2] *Can we now establish the role of coherent processes – electronic, vibronic – in charge and energy transport on the nanoscale?*[3] *Can we achieve element-specific imaging of concurrent electronic, spin, and structural changes with femtosecond resolution?*[4-6] Unfortunately, methods based upon the optical region of the electromagnetic spectra cannot measure sub-ångstrom displacement and femtosecond motion in molecules, and therefore alternative and additional methods are urgently needed.

A powerful combination of the diverse femtosecond X-ray methods with optical methods could potentially answer the underlying questions, including:

- How long does it take the atoms to move?
- Where is the motion localised/delocalised within the molecule or material?
- What is the amplitude and the phase of this motion?
- What is the reaction coordinate(s)?
- What is the role of coherence(s) in ultrafast transformations?
- Can we alter the outcome of a chemical reaction at will?

The UK XFEL and associated infrastructure of ultrafast optical methods will bring about a combination of short pulses of photons with energies tuneable from THz to X-ray, high repetition rate of > 100 kHz, high spectral purity and high brightness, to finally enable a comprehensive interrogation of chemical reactions, non-equilibrium processes and transformations, in a real-time molecular movie. By combining multiple means of initiation and interrogation of reactions we will extend our measurement capabilities. As a consequence we will be able, for example, to determine the structure of excited/ transition states with <0.01 Å resolution; follow coherent vibrations in polyatomic molecules; and make direct observation of conical intersections, which are the key part of the mechanism of ultrafast light-driven reactions yet remain elusive experimentally. *The methods of X-ray absorption* that probe structure and unoccupied electronic density of states, *X-ray emission* that probes occupied density of states, *resonant X-ray emission* that enables high resolution experiments,[7] *X-ray Raman*[8] that probes edges of light elements using harder X-rays, and *multiple emerging methods* must be combined. It is also crucial that both light- and heavy-elements can be followed in the same experiment, as illustrated in the *Periodic Table of X-rays* (**Figure 6.1**), to simultaneously interrogate various metal centres and organic ligands, or multiple metal and/or light elements in molecules and materials. Key essential features for chemical sciences include simultaneous delivery of hard- and soft X-rays, and the potential to combine X-ray spectroscopic techniques with X-ray scattering methods, such as Coherent Diffractive Imaging (CDI) and X-ray photon correlation spectroscopy (XPCS). This combined approach is especially important for surface-related processes including heterogeneous catalysis, and for advanced materials

where mapping dynamics, both locally and within heterogeneous domains, on the picosecond and even femtosecond timescale will need to be developed. Such an approach will finally visualise "molecular movies", which will provide vital new insights into mechanisms of reactions and processes in physics, chemistry, and biology, from molecular level upwards.

Since much of chemistry occurs in complex systems, we require the ability to make ultrafast X-ray measurements on systems of varying complexity, ranging from isolated gas phase molecules, nanoscale solvated clusters, and species adsorbed at metal and liquid interfaces, through to large molecular systems in solution. The ability to make ultrafast measurements in such dilute and diverse samples requires both high photon numbers and high repetition rates (> 100 kHz). It is also of critical importance that the trigger and the probe pulses are synchronized or time-stamped to ~5 fs.

It is important to acknowledge that only a small fraction of (bio)chemical reactions can be triggered with (visible) light, and therefore other means of triggering ultrafast reactions need to be coupled with X-ray interrogation techniques, for example T-jump triggered by an ultrafast laser pulse, vibrational (THz, IR) excitation, electron injection or even another X-ray pulse.

Many pioneering contributions of ultrafast X-ray spectroscopies that bring us closer to the "movie" goal have emerged in the last decade, such as ligand dissociation in small metal complexes,[9,10] vibrational wave-packet dynamics in Fe-carbene photosensitizer determined with femtosecond X-ray emission and scattering,[11] the first demonstration of picosecond X-ray absorption spectroscopy to probe ligand binding to heme proteins in physiological media,[12] ultrafast spin-change in spin-crossover materials or single-molecule molecular magnets for new methods of information storage. *Selected areas where such studies can bring transformative change are discussed below.*

6.1.2 Ultrafast spin dynamics in molecules and biomolecules

The importance of deciphering the interplay of electronic and structural dynamics is well-illustrated in spin-crossover (SCO) molecules[13] containing, for example, $Fe^{2+/3+}$ or Co^{2+} which are able to change the spin-state in response to external perturbation, such as light,[14] temperature, or pressure. The change in spin-states is usually ultrafast, sub-100 fs, and accompanied by a dramatic change in properties: magnetic (ortho/para), optical or structural (one well known example is oxygen binding in heme; the bond lengths changes can be several tenths of an ångstrom). The potential for targeted control of properties by external means opens up diverse applications of SCO in materials and devices, such as magnetic switching,[15] all-optical magnetic recording in iron garnet,[16] or photocatalytic CO_2 reduction (**Section 6.4**).

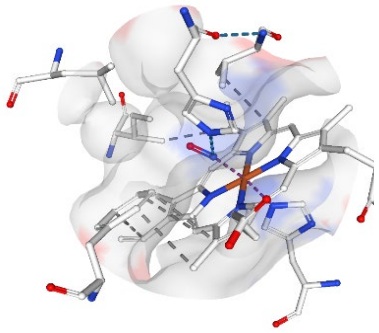

Figure 6.2: Nitrosyl Horse Heart Myoglobin. --- show bonds which reversibly form and break. PDB 2FRJ.

An example of the correlated spin and structural dynamics is the dissociation/recombination of NO from/to Fe-centre in Myoglobin.[12] Here, huge advances have been made in following the structures of the short-lived intermediates by XAS and WAXS; obtaining spin information by XES (K_β, 3p-1s and K_α, 2p-1s) monitoring high spin/low-spin transition. For the next step, we want to follow the formation and breaking of H-bonds (the dashed lines in **Figure 6.2**), and the changes of electron density, not only on and around the Fe centre, but of the ligand/protein itself. This major task calls for higher sensitivity, high repetition rate and, crucially, multiple detection, bringing in correlative XAS and XES methods, and RIXS to follow the changes in the ligand itself.[17]

In materials, the coupling between electronic and structural degrees of freedom is at the origin of the emergence of functions that can be triggered by direct or indirect excitation of various degrees of freedom, such as spin, electron, phonon and lattice. These ultrafast phenomena affect various properties such as conductivity, magnetism and ferroelectricity. Understanding the complex out-of-equilibrium dynamics induced by light in these diverse systems requires both detailed calculations and

molecular model compounds. Polynuclear metal complexes can serve as mimics of materials such as transition metal oxides, two-dimensional dichalcogenides, charge and orbital ordered manganites (anti-to-ferromagnetic phase transitions,[18] cyano-bridged photomagnets,[19] or mixed transition-metal/lanthanides).[20]

The fundamental understanding of the structure-function relationship requires the interplay between the oxidation states, the electron density distribution along the molecule or material, the spin-states, and the geometric changes to be resolved for (ideally) all atoms involved on ultrafast time-scales. The UK XFEL's high repetition rate and brightness will enable optimisation of new non-linear X-ray and optical/X-ray experiments. Together with the tuneability, and the ability to track changes in several metal centres and organic components by simultaneous detection in several spectral regions, this will give new insights principally into charge-transfer/electronic (such as change in oxidation state), structural and spin dynamics, and, ultimately, chemical reactivity.

6.1.3 Ground-state chemistry and solvent-solute interactions

A major challenge across chemical science is to understand molecular reorganisation in complex environments, in terms of both intra-molecular and environment dynamics. The reorganisation of a molecule's environment influences processes by solvation perturbations and outer-sphere molecular co-ordination, and often dictates transition states, chemical outcomes and product state distributions. However, addressing these problems is technologically challenging. One example is the current technological limitations of a powerful method of vibrational spectroscopy. Inter- and intramolecular vibrations underpin *any* chemical reaction, with low-frequency motions of a 10 – 400 cm^{-1} often postulated to be the key reaction coordinate. Current laser technology provides time-resolved IR capability, but with limited spectral coverage; at present, the region below ~800 cm^{-1} is inaccessible. A UK XFEL will enable a fully temporally resolved 4000 – 1 cm^{-1} spectral coverage, which would open up so far impossible studies including: large collective motions of proteins, such as alpha helical stretches; hindered rotations of solvent molecules which influence solvent reorganization dynamics in liquids; the direct probing of metal-carbon and metal-metal atom motions in surface science; and identification of key biologically active radical species during DNA strand breaks.

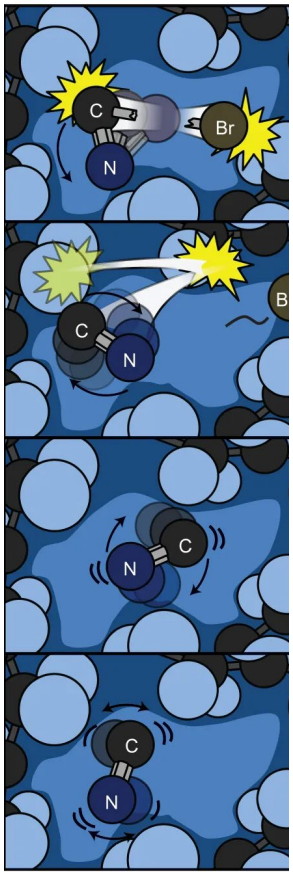

Figure 6.3: Different motions contributing to the solvation of species formed in 220 nm photolysis of BrCN in perfluorohexane.[26]

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The vast majority of chemical transformations are thermally activated, but how can one trigger it in order to resolve structural dynamics? The ability to trigger a reaction in the electronic ground state by, for example, ultrafast T-Jump, a THz or IR pulse, and to follow the accompanying structural, electronic, vibronic and spin changes on the ultrafast timescale *simultaneously* would be of tremendous fundamental and practical importance in understanding chemical reactivity. Ultrafast structural dynamics on the ground state potential energy surface can be investigated following photoexcitation and relaxation to the ground state, as shown by ultrafast X-ray scattering on a dinuclear Pt complex in solution,[21] a deep-UV triggered ground-state ring-opening dynamics of 1,3-cyclohexadiene in gas phase,[22] or a reaction of sulfine in its hot ground state leading to nine different products within < 1 ps.[23] *A UK XFEL with high repetition rate, high brightness and broad spectral coverage, which will enable multiple-detection methods from the same sample, will open up such studies to multiple classes of chemical reactions in all states of matter.*

Photoinduced isomerisation reactions, including ring-opening reactions, are one notable example of reactions with ultrafast structural changes. Recently, time-resolved photoelectron spectroscopy with

a seeded XUV FEL traced the ultrafast ring opening of a thiophene molecule in gas phase after 265 nm excitation, and showed that the initial ring opening and non-adiabatic coupling to the electronic ground state was driven by ballistic Sulfur-Carbon bond extension within 350 fs.[24] These XFEL experiments provide unprecedented insights into both the electronic and the nuclear dynamics of this fundamental class of reactions, and illustrate how a similar approach can be used to follow almost any reaction. More complex systems will need X-ray spectroscopic probing at multiple atomic edges to fully follow and resolve all aspects of their complex and entangled dynamics.

The structure of solute species and the solvent around them is fundamental to the understanding of the multitude of chemical reactions that take place in solution, with various optical spectroscopies providing insight into inter-mode coupling and energy transfer.[25] Resolving contributions from rotational, vibrational, and translational modes into overall solvent-solute interactions (**Figure 6.3**) can also help with understanding of interactions at the interfaces and on surfaces.[26] This important field of fundamental research underpins vast areas of chemistry, biochemistry and medicine. X-ray absorption (EXAFS, XANES) is a particularly powerful technique here, due to its element specificity, its wide-ranging applicability to the characterisation of the local environment of selected atoms in solids, liquids and even gases and its high sensitivity, which makes it applicable to local structural studies from ultra-dilute to pure substances.

The nature of vibrational energy redistribution in molecules and materials following an external perturbation, or within a product of a chemical reaction, is an important fundamental question. 2DIR-spectroscopy is now broadly used to answer this question, by following changes in vibrational frequencies, but it requires specific IR-reporting groups. Use of time-resolved X-ray spectroscopy on the sub-10 ps time-scale to detect directly changes associated with the movements of C, N, and O-atoms, in combination with 2DIR data, will allow “molecular movies” of ground state catalysts or proton transfer reactions to be delivered, or photoisomerisation pathways in proteins to be followed.[27]

6.1.4 Organic reactions, protein dynamics, DNA damage, and photoprotection

Light elements, C, O, N and H, play a key role in all processes around us; in photosynthesis, in free radicals in biology and medicine, in DNA damage and photoprotection, enzyme catalysis or drug-target interactions, and in fundamental organic photochemistry in gas phase and solution-phase.[28] This prevalence of light elements represents one of the major challenges in investigations of ultrafast structural, electronic and spin dynamics, which makes it extremely important to have access to all organic molecules via C, N, and O-edges. We must deliver the “molecular movie” in this area of research without relying on heavy elements, an extremely challenging task which can be solved with the UK-XFEL providing access to the nπ* and ππ* excited states that are present in virtually every organic molecule and building blocks of life.

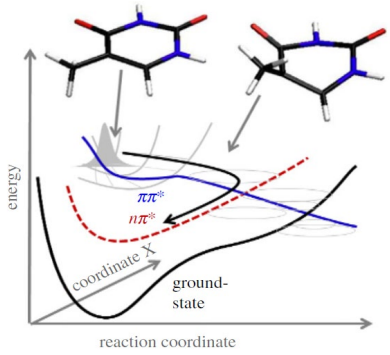

Figure 6.4: Photochemistry of DNA. TR-AES and TR-NEXAFS reveals possible relaxation paths a ππ state of thymine populated by UV-pulse, to the dark nπ* state and to the ground state via conical intersections.[28]*

Figure reproduced from T.J.A. Wolf et al. "Probing ultrafast ππ/nπ* internal conversion in organic chromophores via K-edge resonant absorption". Nat. Commun. 8, 29, (2017), licensed under Creative Commons CC BY 4.0*

An example of ultrafast molecular transformation involving light molecules is the dynamics of -S-S-bridges in proteins that respond to photoexcitation and oxidative stress. How does -S-S-bond cleave? What is the sequence of steps in radical/ion formation, and recombination? Is structural change following the primary photo-chemical event or vice versa? fs-TRXAS studies showed that a model molecule dimethyl-disulfide H_3C-S-S-CH_3 undergoes direct dissociation to two H_3C-S-radicals within 120 fs upon UV-excitation.[29] This pioneering work on small molecules prepared the ground for investigating the dynamics of disulphide bridges in (photocaged) proteins, and under physiological conditions. However, translating this experiment to real biological systems is a big challenge: real systems will have orders of magnitude lower

"concentration" of the -S-S-groups, are delicate, have only limited amounts of samples, and samples need to be interrogated before too much radiation damage occurs. These requirements demand high photon flux and high, 10 – 100 kHz, repetition rate to ensure the necessary sensitivity, and can only be achieved at an XFEL.

High sensitivity and ~1 fs time resolution would enable direct mapping of structural changes as the system evolves through conical intersections, which are postulated but rarely[30] observed experimentally in the majority of reactions, occurring on the ultrafast timescale away from Born-Oppenheimer approximation. Conical intersections (CIs) dominate the pathways and outcomes of virtually all photophysical and photochemical molecular processes. Despite extensive experimental effort, CIs have not yet been directly observed, and the experimental evidence is being inferred from fast reaction rates and some vibrational signatures. Recent theoretical work by Mukamel *et al.* proposes that short X-ray (rather than optical) pulses can directly detect the passage through a CI with adequate temporal and spectral sensitivity.[31] To precisely time the CI and map the energy differences, a molecular system has to pass a CI that is in close vicinity to the Franck-Condon point. The work suggests that Transient redistribution of ultrafast electronic coherences in attosecond Raman signals (TRUECARS), a novel extension of time-domain coherent anti-Stokes Raman spectroscopy (CARS), commonly used to probe vibrational coherence, is an ideal tool to investigate ultrafast, photophysical system dynamics. The experimental parameters required – broadband sub-femtosecond pulses of ~100 eV or more and spectral widths of several eV – could only realised from state of the art XFELs.

Recent pioneering work on organic excited states[32] demonstrated how a combination of time-resolved Auger electronic spectroscopy with TR-NEXAFS resolve structural and electronic changes induced by UV-excitation in the nucleobase thymine (**Figure 6.4**), establishing the elongation of –C–O bond and non-adiabatic transition from $\pi\pi^*$ to the "dark" $n\pi^*$ state. Such direct observation of non-adiabatic dynamics in small molecules is unprecedented, whilst detecting dark states is intrinsically hard in optical spectroscopy. The ultrafast soft X-ray capability at a UK-XFEL will enable the next step of this research – moving from individual nucleobases to DNA, understanding DNA damage. One step further will be real-time imaging of DNA damage/repair in living cells, and watching the action of light-activated therapy, such as PDT (**Figure 6.6**), in real time.

6.1.5 Fundamental dynamics of energy and charge, coherent and optical control of reaction dynamics

The development of new chemical processes relies on the advancement of our mechanistic understanding of chemical change in complex systems. Since chemical change occurs on the timescales of nuclear motion, femtosecond time resolution is a key requirement. Ultrafast chemical reactions are often mediated by the complex non-adiabatic couplings between electronic and nuclear motions that occur when the Born-Oppenheimer approximation breaks down. Combining non-linear methods, multipulse optical and X-ray spectroscopies, on the femtosecond timescale will enable tracking of the evolving structural, electronic, and spin landscape following the trigger.[33]

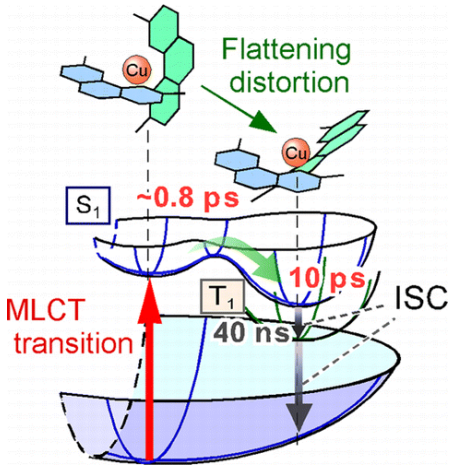

Figure 6.5 Light-triggered distortion in a Cu-complex. Nuclear, electronic, and spin dynamics are convolved on the ultrafast timescale.[35]

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Transition metal complexes, differently to organic entities, often exhibit ultrafast intersystem crossing (ISC) in the excited state, leading to a long-lived excited state which determines their applications in photocatalysis (Re(I) for CO_2 reduction), Phosphorescent Organic Light Emitting Diodes (PhLEDs), or in photodynamic therapies (Pt, Ir, Ru). Ultrafast structural, electronic, spin and vibrational dynamics occur simultaneously. To follow them requires multipulse experiments, where

each parameter can be probed independently following a common trigger. The mechanism of ultrafast ISC is likely to involve spin-vibronic effects, as spin-orbit and vibrational coupling occur on a similar, ultrafast time-scale.[34]

Time-resolved X-ray studies, using a variety of available methods, have been conducted on e.g. Cu-complexes which exhibit huge structural change in the excited state (**Figure 6.5**),[35,36] on dinuclear Pt(II) photocatalysts,[37,38] and on a multitude of Fe complexes (see ***Spin dynamics***, **Section 6.1.2**), all of which demonstrated complex dynamics. It is hoped that ultrafast multipulse X-ray studies with optical triggering, combined with THz, 2DIR and 2DUV spectroscopies, will allow the identification of the reaction coordinates responsible for the ISC in transition metal complexes, as well as in materials. Here, a UK XFEL will bring in element-specific information, for several elements at the same time, and the ability to interrogate the same sample with multiple methods (structural and spectroscopic) simultaneously.

The ability to control chemical reactivity is one of the holy grails of chemistry. Diverse methods have been designed to achieve this goal (some of which are covered in ***Attosecond science***, **Section 3.3**), such as coherent control[33,39] or bond-specific perturbation in molecules undergoing photoinduced electron transfer[40] and in organic PV materials.[41] Various degrees of control of chemical reactivity have been achieved, yet the control mechanisms remain elusive, especially in condensed phase. Ultrafast multipulse and nonlinear structural methods should enable us to resolve vibrational and vibronic coupling in charge and energy transfer reactions, identify reaction coordinates, follow energy transfer from one vibronic mode to another, and visualise where exactly the energy and charge are distributed along the molecules, in space and time, and which reaction pathways are driven by what vibrations. Long-term, it may also bring about rational control and design not only of molecules – for example, single-molecule magnets, molecular conductors – but also of materials, and may bring us one step closer to fulfilling the dream of "reactivity at will".

6.1.6 Conclusions and future vision

Our vision for chemical dynamics is to open up new horizons in science and technology, which rely on currently hidden understanding of chemical change at molecular level on the ångstrom scale with femtosecond precision.

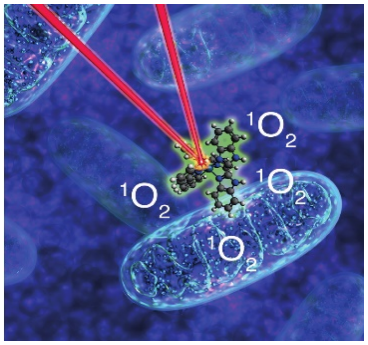


Figure 6.6: NIR two-photon activated killing of cells with a transition metal complex.[42] Could we follow the action of a PDT agent in real time?

Figure reproduced from L.K. McKenzie et al. Chem. Eur. J. 23 (2017) DOI: 10.1002/chem.201780262

The open questions in chemical dynamics range from rare events in gases to energy propagation in condensed media, the intermolecular mechanisms that control DNA damage and organic reactivity, and the drug-protein interactions. Resolving electron-, spin-, and structural dynamics simultaneously is needed to answer these questions. An exciting example of future research, and which is currently science-fiction, is real-time observation of anti-cancer or antibacterial drugs in action at the interface with medicine and structural biology (see **Section 7**). Recent developments of transition metal complexes as anti-cancer Photodynamic Therapy[42] (PDT) and antibacterial agents[43] started the whole new area in photomedicine and antimicrobial sciences. Using Cryo-EM, correlative microscopy or AFM,[44] it has so far been possible to determine the action of such agents only on fixed samples. The ability to track each step, and determine the electronic and structural changes of both the agent and the sub-cellular structures in real time, in live objects, will bring a completely new perspective to our understanding and treatment of disease.

A UK XFEL will also facilitate a step-change in time-resolved ambient pressure photoemission of light elements, most notably including C, N and O, which are the backbone of organic and biological molecular systems. Developing a sustainable economy will rely on deep understanding of their natural genesis and control of chemical and physical transformations to commodities and value-added products. Reaction engineering with homogeneous and heterogeneous catalysis is expected to play an important role here, and XFEL insight to the real-time dynamics in solutions and at interfaces will

facilitate a transformative advance, with research spanning the whole range of Life, Physical and Engineering Sciences. An example of research into high value-added applications of organics is solar energy devices, including hybrid organic/inorganic perovskites and their interfaces with transition metal oxides. Understanding the dynamics of element- and functional group-specific recombination paths is paramount for improving efficiency, i.e. we need to determine the polaron dynamics in the metal oxide[45], as well as electron and hole transport facilitating charge transfer to the electron- and hole collectors.

Another application area is in the broad range of catalytic processes associated with metal-oxide surfaces. Taking photocatalysis as a flagship example, application of ARPES (see **Section 5.4**) to the oxygen evolution reaction on an oxide surface will enable one to follow the decomposition of water and the formation of intermediates on a fs-ps timescale by monitoring the chemical shift of the O 1s ARPES peak. At 4 keV the escape depth of O 1s photoelectrons in water is approximately 9 nm, allowing bulk-like liquid films to be used to study photocatalysis, electrocatalysis, or corrosion. The information from ARPES is complementary to that obtained by X-ray absorption spectroscopy, because it is sensitive to the element specific chemical state near the surface, enabling a complete mechanism of interface processes to be resolved for the first time.

This capability will make a leap from static measurements available at synchrotron facilities, including their recent implementation at Diamond B07. The capability to perform time-resolved ARPES at >3 keV will be unique. Critically it will benefit from the high repetition rate of an XFEL to allow sufficient data rates whilst limiting distortions from space charge. One scenario is to use the 3rd or 5th harmonic of a high-repetition rate seeded XFEL to provide the required high spectral purity, high data rate and moderate pulse energy needed for these measurements.

The key facility features that will enable these breakthroughs include seeded high-repetition-rate operation (>100 kHz), high brightness, broad spectral coverage, THz-IR-Vis-VUV laser sources synchronised to sub-20 fs, and the ability to simultaneously interrogate the process of interest with multiple methods, combining spectroscopic (local information) and structural (scattering) methods. Taken together, these capabilities will allow us to understand and control chemical dynamics and tailor it to our needs.

6.2 Exploring complex energy landscapes through chemical activation

Physical, chemical and biological processes are all governed by interactions across complex potential energy surfaces. Understanding these surfaces is fundamentally important for everything from chemical reactivity and protein folding, through to crystal structure prediction and developing new materials and pharmaceuticals. To understand these surfaces in ever greater detail, across multiple length and time scales, we need new experimental tools that can demonstrate control over the electronic, spin and ionic degrees of freedom of a material, to engineer transient states of matter far from equilibrium, regulate transitions across barriers, and explore new phases and materials with exotic and novel properties.

6.2.1 Introduction

All chemical processes are governed by dynamics that occur across complex energy landscapes. These landscapes need to be understood across multiple length and time scales; in particular, it is often the ultrafast events in nature that control changes on longer timescales, and therefore the understanding on ultrafast timescales is crucial to any chemical understanding. To understand the mechanism behind, for example, chemical reactions, ultrafast magnetization, phonon triggered changes in structure, photon-induced processes within materials and at interfaces, we need to be able to measure these ultrafast changes in real time (~10 fs – 10 ps). The ultrafast X-ray methods that would be enabled by a UK XFEL are perfect tools for this, as they capture all the timescales of motion associated with changes in any complex matter system while providing a probe that is sensitive to both the structural and the electronic change in a system. However, key to these developments at UK XFEL will be the ability to initiate chemical change using a diverse range of synchronized ultrafast pump sources, including optical pump fields from the THz to the XUV, and pulsed radiolysis with electron beams. Of critical importance is that the pump (event trigger) and probe pulses are sufficiently well synchronized to permit temporal resolution approaching the sub-5 fs limit. This in turn would enable complex pulse sequences to be used to build on the more established multidimensional optical techniques[40,46-48] with the inclusion of a single (or multiple) X-ray probe(s) over a range of energies (see **Section 6.1**), which will provide time-resolved structural information that is often only inferred by other measurement techniques. It is essential that any new light source will provide an array of pump-probe and multidimensional capabilities that will collectively resolve the ultrafast structure and dynamics in a wide range of chemical processes.

A number of possible pumping options have been specifically highlighted throughout this Science Case, including THz and IR (**Sections 5.1** and **5.2**), UV (**Sections 6.1**, **6.6** and **7.2**) and X-ray (**Section 3.3**). In this section, we highlight two important options, THz and ultrafast electrons, that provide opportunities for exciting chemical science by providing unique capabilities at a UK XFEL.

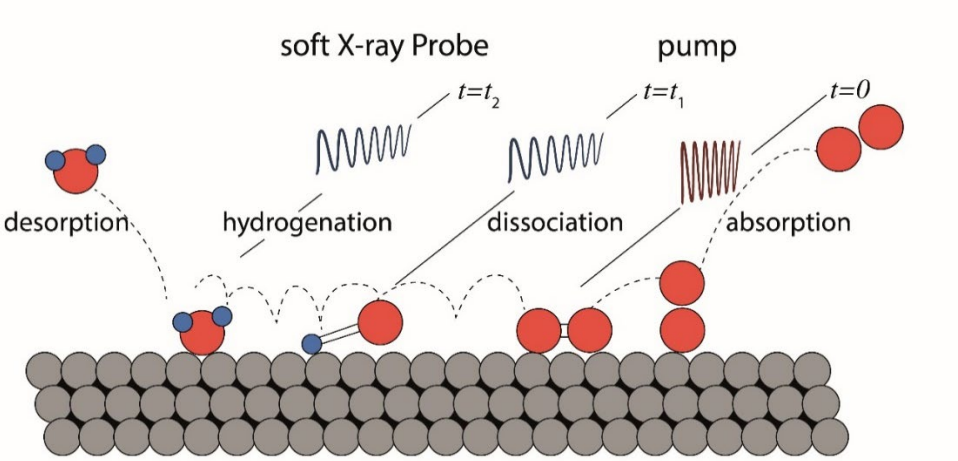
6.2.2 Intense THz excitation combined with ultrafast X-ray measurement techniques

Absorption at THz frequencies (0 – 30 THz) can be complex, and is governed by many different physical mechanisms that are fundamentally important to understand. In simple crystalline materials, the absorption is dominated by strongly coupled phonons,[49-51] while in complex crystalline systems, these are mixed with low-frequency internal motions.[52,53] In amorphous materials,[54,55] a large number of overlapping bands often give rise to a featureless spectral vibrational density of states that is very difficult to interpret — even for apparently simple systems, such as water.[56] THz absorption, however, shows exceptional sensitivity to long-range order and dynamics, whether it be in polymorph formation,[57] structural formation in solutions,[58] or ionic liquids,[59] and sensitivity to enzyme functional dynamics.[60,61]

THz frequency normal modes are particularly interesting because they have been linked to reaction pathways and dynamics in the majority of reactions, with specific examples including the initiation of energetic materials,[54] enzymatic reactions (in particular proton tunnelling[61]), solid-state phase transitions in metal-organic frameworks (MOFs),[62-64] materials that exhibit solid-state phase transitions,[52] and catalytic surface chemistry.[65]

The recent development of a range of methods able to generate intense THz pulses has led to a very dynamic research field to manipulate matter.[66,67] Recent examples relevant to the chemical sciences include the orientation of OCS molecules in the gas phase,[68] and THz-induced crystallisation of carbamazepine and indomethacin from an amorphous phase to different polymorphic phases in comparison to temperature-induced crystallisation.[69] This has obvious implications in the study of the relative stability of pharmaceutical compounds, but has the potential to provide a new insight into the important processes of nucleation and crystallisation, which in turn may provide new perspectives to aid first-principles structure prediction — one of the grand challenges of the chemical sciences which is discussed in relation to industry-relevant research in **Section 8.3**.[70]

Box 6.1: Controlling catalytic reactions with THz excitations



An initial intense THz pump pulse can be used to manipulate a molecule adsorbed to a catalytic surface. This initiates a reaction that is then probed by a series of time-delayed optical and X-ray pulses, which can be used to provide both spectroscopic and structural information of all the active species involved in the entire catalytic reaction pathway, in real time. This is crucial information to aid the design of next-generation efficient and sustainable catalytic materials.[65]

Measurements have also demonstrated that high-field THz pulses can promote specific reaction pathways on a catalytic surface, by strongly interacting with molecules adsorbed on a surface or the electron bath of the catalytic surface; for instance, selectively inducing CO oxidation on a Ru (0001) surface (see the Flagship Research Project in **Box 6.1**, on controlling catalytic reactions).[65,71] There are also a number of studies that show the manipulation of lattice and spin dynamics, including the discovery of novel phases through the direct manipulation of phonons and magnons using high-field THz pulses (**Figure 6.7**).[47,49,50,72]

Recent measurements have used ultrafast X-ray pulses to probe this THz electric-field driven manipulation of dynamics (see **Figure 6.7**). In $BaTiO_3$, the modulations of the ferroelectric polarization[73] were detected, while in $SrTiO_3$ coupling of phonon modes[50] and the identification of a metastable ferroelectric phase has been observed.[49] These studies are, however, limited by the range of accessible Bragg reflections, and by the signal to noise at current XFELs. Extensions to higher energy (> 25 keV), using PDF approaches, or to higher repetition rate (for both XFEL and THz sources), would provide the first direct visualisations of these local atomic-scale motions — a crucial step in making these experimental tools useful for practical exploration of increasingly complex materials.

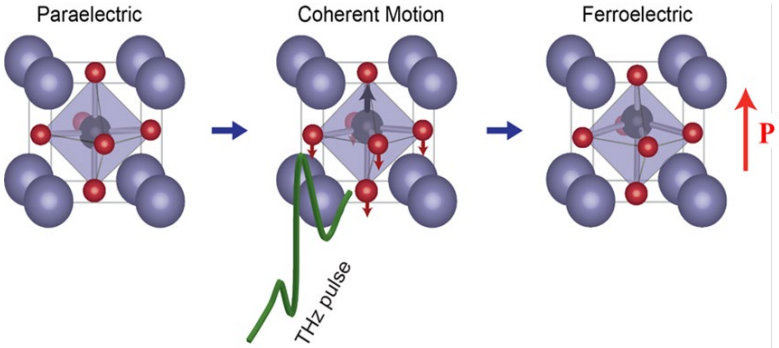


Figure 6.7: A single-cycle THz electric field which moves all the ions it encounters toward their positions in a new ferroelectric crystalline phase. In STO, the initial high-symmetry configuration around each Ti^{4+} ion has no dipole moment and the crystal is paraelectric. The incident field drives the "soft" lattice vibrational mode, moving the ions along the directions indicated into a lower-symmetry geometry with a dipole moment.[49] This ion movement can be probed directly with X-rays.

Figure courtesy of Keith Nelson

What is particularly exciting is that, in all these studies and more, THz pumping has enabled the exploration of the complex energy landscapes that underpin reactivity and dynamics. These systems do not require the chromophores needed for most optical excitation, suggesting that the THz excitation could become a universal pumping source for the majority of materials. Importantly, the low energy of THz radiation, coupled with the high peak electric (< 100 MV cm^{-1}) and magnetic fields (< 33 T) that can be generated, may provide a universal way to manipulate matter without the excess energy associated with optical excitation.[65,71] THz radiation has the ability to manipulate matter on an ultrafast timescale and provides the capability to achieve insight into the fundamental dynamics of processes, which in turn can be used to underpin the future rational design of materials with tailored physical and chemical properties.

6.2.3 Electron-induced radiolysis combined with ultrafast X-ray measurement techniques

An ultrafast pulsed electron beam is a complementary and powerful method for the generation of chemical intermediates, excited states and free radicals. The major difference from laser initiation is that the primary excitation step involves the interaction of electrons with the media, and does not rely on a chromophore to absorb laser light of a particular wavelength. This method therefore opens up the possibility of understanding electron transfer and radiochemical processes that cannot be optically initiated.

Pulse radiolysis as a trigger to accompany soft X-ray probes of structural change will be an exciting and important avenue of research, with a diverse range of applications throughout chemistry, including geochemistry,[74,75] nanoscience,[76] ionic liquids,[77,78] radiation induced corrosion[79] and other radiation-induced processes with applications in understanding how living tissue, and in particular DNA, responds to radiation.[80-83] In particular, it can be used to determine the fundamental radiochemical processes occurring in any media exposed to ionising radiation, through the determination of kinetics in radiation tracks and how they influence the overall radiation chemical processes. A pulsed electron beam is often the method of choice to generate and determine the properties of radical ions, reactive oxygen species and to initiate charge migration and proton transfer processes. The ability to generate charged species will also allow studies of charge mobility in electronic devices and artificial light-harvesting systems.

The coupling of ultrashort (< 20 fs) electron pulses (~ 5 – 15 MeV) as a trigger for chemical change, with X-ray probing techniques to monitor structural change in real time, would represent a unique capability internationally. In particular, compared to existing pulse radiolysis facilities worldwide,[84-86] this would give the UK a leading edge in terms of both structural sensitivity and time resolution. The combination of XUV pulses[87] (from an HHG source, especially in the 10 – 30 eV range) and pulsed

radiolysis at an XFEL will also allow direct comparison of optically-induced dynamics with those of radiolysis, another potential key international defining application of X-ray absorption, emission and scattering for a UK XFEL.

Particular areas of interest include the radiolysis of water[88,89] and other solvents,[90] along with larger molecular systems[91] where the elementary processes associated with ionisation of the material, including initial ionisation, the formation of solvent holes and geminate recombination processes, are fundamental for understanding radiation-matter interactions in chemistry and biology. While water has been heavily studied using a range of pump sources to measure the dynamics of the hydrated electron, only very recent work[88] using an optical pump/ultrafast X-ray probe scheme has provided the first spectral evidence of its partner arising from ionization of liquid water, H_2O^+.

Increased time resolution and signal-to-noise ratios would enable more accurate H_2O^+ lifetime measurements (tentatively assigned to be 46 ± 10 fs) and, at the same, time permit the observation of ultrafast dynamics involving hole alignment, coherences, and nonadiabatic dynamics induced by radiolysis.[88] A comparison of lifetimes measured using electron and optical excitation would be particularly useful. Understanding these processes is fundamentally important in delineating the consequences of radiotherapy, with recent studies showing that ~67 % of DNA radiation damage that occurs during treatment is initiated indirectly via water ionisation – with the reasons for this being very poorly understood.[92] The development of an electron beam instrument with a beam energy of 5 – 15 MeV would also allow increased penetration through thicker samples and, while maintaining a tighter focus inside a sample, provide a facility where more biologically relevant samples, including cells and tissues, could potentially be investigated via radiolysis.

A facility enabling a direct comparison of radiation damage induced by optical, X-ray and electron pulses would be unprecedented. Synergistically, a suitable ultrafast electron pump source would also be ideal for ultrafast electron diffraction (UED).

6.2.4 Conclusion and future vision

While the recent science enabled by the development of new THz/e-beam sources is ground-breaking, the introduction of THz (300 GHz – 30 THz) and e-beam (5 – 15 MeV) accelerator-based sources at high repetition rates (up to 1 MHz), available at the X-ray interaction point (with > 10^{12} X-ray photons per pulse) for complex multi-pulse experiments, is unprecedented anywhere in the world. The THz accelerator in particular would provide unparalleled control of bandwidth, pulse width and field in a spectral region that has been underutilised to date. This, in combination with a range of synchronised laser-driven, optical, infrared, THz and HHG based sources, will be a world-first, enabling a vast amount of new science by exploration of potential energy landscapes for increasingly complex materials using novel experimental tools that combine these pump sources with multiple, in-situ spectroscopic probes, simultaneously. However, the nature of these complex multi-pulses measurements means that the importance of sample environment and delivery should never be underestimated, with some important points discussed further in **Section 9.2**.

One future exciting research direction that a facility of this kind could enable would be the use of intense THz excitation to manipulate biological systems. An example of this approach is the potential disruption of H-bonding in a solvent network surrounding a protein whose structure has already been probed by low-intensity THz radiation.[58,93,94] Another example is through the THz pumping of enzymatic promoting modes[60] which have long been suggested as directly linked to the reaction coordinate in complex enzymatic reactions, particularly where electric field controlled catalytic mechanism[95] are thought to be involved and these high peak THz-fields could be used to resonantly (and non-resonantly) influence the reaction pathway in these complex bio-materials. All of the examples discussed here, and more, require a high-field (> 100 MV/cm), narrowband and tuneable THz pump source that could be used to selectively excite specific modes in a material, combined with a plethora of broadly tuneable XFEL and laser-based sources for providing ultrafast spectroscopic and structural information as the material changes. This would require a tuneable accelerator-based THz source (> 10 µm) combined with laser-based systems for higher wavelengths.

6.3 Energy materials and devices: Solar cells and batteries

Our energy systems are rapidly evolving, driven by the challenges associated with decarbonisation, an ageing infrastructure, and shifts in societal expectations. Achieving a radical shift in how we supply, manage and consume energy calls for new materials and a detailed understanding of how they function. Yet in many energy technologies there remain fundamental processes related to function that we simply do not understand, and this is severely impeding progress. Ultrafast X-ray probing will provide unprecedented insight into the function of materials on the atomic scale of time (femtosecond) and length (ångströms), leading to a greatly improved understanding of structure-property relationships in materials for energy applications.

6.3.1 Introduction

Energy demands are increasing throughout the world (increased by 65% since 1990) and provision is currently being met by a mix of sources, including fossil fuels, nuclear power, hydroelectricity and renewables, such as wind and solar energy. However, many challenges remain and need to be overcome to realise the global energy revolution required to limit the detrimental effects on the planet. Solutions must be found that allow an increase in energy consumption whilst reducing the environmental impact, in order to meet the UK's obligations under the Paris Agreement on Climate Change[96] and the ambition of a net zero emissions energy policy by 2050.[97] This will only be possible by improving all aspects of energy conversion, storage, transmission and low-power device efficiency.

For energy conversion, technologies focus upon the transition from polluting fossil fuels to low-carbon sources, such as wind, tidal and solar power. These technologies are, however, inherently intermittent and consequently must be developed alongside new directions for highly efficient grid and off-grid storage solutions, such as batteries or chemical storage. Crucially, solutions will not be found without new classes of zero-carbon materials that can be produced sustainably and that allow higher efficiency energy conversion with better operational stability than current materials.

The challenge is that materials underpinning many energy conversion/storage processes are complex and poorly understood, especially on the atomic scale. Indeed, they often exhibit functional structural disorder and contain dynamical properties that are needed for their operation, but which are also responsible for energy losses and device instabilities and degradation during decade-long operation under harsh, non-equilibrium conditions. This lack of understanding means that the design of new materials is often focused upon large-scale synthetic programs as epitomised by the extensive literature reporting new potential candidates. Ultimately, few candidate materials make the transition to application in practically useful devices. This *status-quo* leads to incremental progress, stagnation of research fields and makes designing materials costly and time-consuming.

The development and utilisation of ultrafast X-ray methods will play an important role in providing crucial understanding of material properties down to the atomic scale of time (femtosecond) and length (ångströms). One of the key advantages of X-ray methods in the context of materials and devices is that they offer the potential to probe these dynamics under operando conditions, for example, inside an operating battery or at the solid-liquid interfaces of heterogeneous catalysts. Such experiments have the potential to yield unique understanding, that can subsequently be used to control the physics and chemistry of emerging materials for energy conversion/storage, and to guide the design of devices.

By exploiting a broad range of excitation (pump) pulses in the UV, visible, IR or THz region, it will be possible to address a wide range of challenges in energy materials using optical, vibrational and thermal excitations. Probe techniques, such as Resonant X-ray Emission Spectroscopy (RXES), will provide powerful insights into the properties of the materials required to address the above challenges. At present, the repetition rate of XFELs currently available severely limits their ability to acquire RXES spectra, while third generation light sources cannot achieve the temporal resolution for

the required understanding. These techniques will also be combined with complementary techniques, such as X-ray Photoelectron Spectroscopy (XPS), X-ray Scattering, X-ray Magnetic Circular Dichroism and X-ray Raman, to facilitate the study of dynamic process interfaces. Indeed, by exploiting the unique atomic sensitivity, these X-ray techniques can disentangle the coupled motion of the spins, electrons and nuclear dynamics, making them uniquely powerful for studying energy materials. Combined with the X-ray capabilities of a UK XFEL (ultrafast time resolution, transform-limited bandwidth and high repetition rate), these measurements will deliver potentially transformative new approaches to address fundamental and use-inspired questions in energy materials.

6.3.2 Photovoltaics

Approximately 360 W m^{-2} of radiant energy in the form of natural light arrives on earth from the sun, providing around 100 PW of solar energy. The ability to convert this solar radiation into energy is core to attempts to reduce our reliance on unsustainable fuel sources. Crystalline and amorphous silicon photovoltaics (PV) are used owing to their stability and high-power conversion efficiency, but they have distinct drawbacks including, for example, indirect band gap and processing costs. The global PV market is forecast to grow significantly in the coming years, with emerging technologies, including dye-sensitised nanoparticles, organic bulk heterojunctions, thin film semiconductors, such as lead-halide perovskites, predicted to account for 25% of this market.

These emerging technologies are appealing, as they are based around low cost solution processing or vacuum deposition, and are highly scalable. They are, however, currently limited by a number of factors, including efficiency and stability. They rely on sunlight to generate charge carriers (electrons and holes) and, consequently, improvements in performance relies on supporting the desirable processes, such as the creation, separation, transport of photogenerated holes and electrons, while suppressing the undesirable processes, such as trapping and recombination over a wide distribution of time and length scales. These dynamics begin on the ultrafast timescale and therefore require ultrashort pulses to track all of the competing processes. The ultrashort timescales, and the complex interplay of structural and electronic effects, means that many of these processes and various relaxation pathways remain poorly understood.

Recently, time-resolved X-ray spectroscopy has increasingly been used to investigate the fate of charge carriers in these photovoltaic materials.[98] The element-specificity of X-ray spectroscopy can be exploited to directly probe the valence and conduction, to establish a detailed understanding of the interplay between the electronic and nuclear degrees of freedom. This can reduce the complexity of these materials, to provide important insights into the charge carrier dynamics and the effect of morphology, defects and band level alignment.

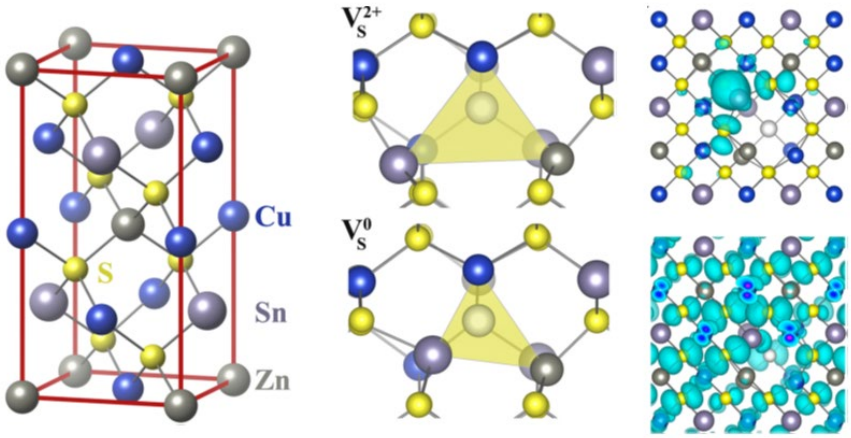


Figure 6.8: Left: The atomic structure of the Kesterite like Cu_2ZnSnS_4 (CZTS) system. Right: Key defects proposed to be responsible for nonradiative electron-hole recombination and charge density associated with them.[99]

*Figure reproduced from S. Kim et al. ACS Energy Lett. **3**, 496-500 (2018) under the terms of the Creative Commons Attribution 4.0 International License. https://doi.org/10.1021/acsenergylett.7b01313*

In this area, there has been a significant research effort in the development of ternary and quaternary semiconductors such as CIGS ($CuIn_xGa_{1-x}Se_2$), kesterite structures (**Figure 6.8**) such as CZTS (Cu_2ZnSnS_4), or halide perovskite structured semiconductors such as methylammonium lead iodide ($CH_3NH_3PbI_3$).[100] Specifically, for the case of the earth abundant solar absorber, CZTS, band gap excitation would excite an electron from the Cu-3d/S-3p state (valence band) to the Sn-5s/S-3p state (conduction band).[101] Time-resolved X-ray absorption and emission spectroscopy can be used to monitor the photocarrier generation, localization and recombination occurring on the femto- and picosecond timescale from the perspective of multiple atomic sites. Through chemical modifications, the effect of the interstitial atoms, vacancies and grain boundary on the excited carrier dynamics can be investigated,[102] while dopants can be introduced to improve photon absorption and shift the energy levels to refine the performance of promising materials. The capability of femtosecond X-ray spectroscopy, and the insights obtained from these measurements, will enable detailed structural understanding of ultrafast charge carrier dynamics and enable us to propose avenues for improving the performance of these materials.

6.3.3 Electrochemical Energy Storage

Many forms of renewable energy, like solar and wind, are intermittent. Consequently, to meet the current worldwide energy demand and control the load exerted on the national grid, a wide variety of energy storage solutions need to be integrated. The development of the Li-ion battery[103] has revolutionised the technology; however, the ever-increasing need for energy storage beyond portable electronics places an increasingly heavy demand on battery capacity and on developing other approaches to electrochemical storage, e.g. redox flow batteries.[104] This calls for further improvements in energy density and a continuous reduction of cost. The need for affordable, large-scale grid storage is urgent and can only be achieved through a detailed understanding of the competing processes occurring in operational batteries.

The operation of all electrochemical storage solutions relies on the movement and/or changes in the chemical state of ions, which is accompanied by solvation and desolvation processes of these ions. The rate of electron transfer involved in the redox process strongly determines the electrochemical activity, and therefore achieving a detailed understanding is essential. The energy and temporal resolution provided by a UK XFEL combined with the high repetition rate will enable X-ray spectroscopy, X-ray Raman, X-ray scattering and photoelectron spectroscopy measurements capable of deeper understanding of the fundamental processes involved in battery performance and degradation. The high time resolution which can be achieved by a UK XFEL will be exploited to probe fundamental charge transfer and solvation dynamics around the ions that occur on the femto- to picosecond timescale.[105] The accessibility to this time domain offers the enticing prospect of directly capturing the phenomena that drive diffusion of electroactive ions in complex electrode materials, to improve the functionality, synthesis and stability of electrochemical energy storage materials.[106]

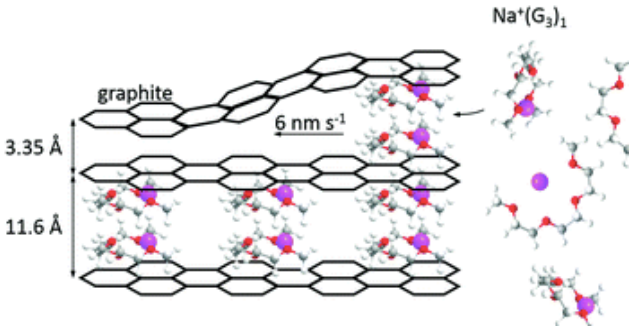


Figure 6.9: A schematic of the solvent assisted Na intercalation mechanism. The size of the Na:solvent complex leads to a ~7 Å increase in the interlayer spacing in Graphite.[109]

*Figure reproduced with permission from L. Seidl et al. "Intercalation of solvated Na-ions into graphite" Energy Environ. Sci. **10**, 1631-1642 (2017), RSC. DOI: 10.1039/C7EE00546F*

Pulse radiolysis pump combined with X-ray probe experiments can be used to enable the study, on the picosecond timescale, of the reaction of the electrons with the ions and the electrolytes,[107] and to reveal the structural dynamics leading to degradation mechanisms. IR-pump / X-ray probe studies will provide structural insights into the solvation dynamics so important to the systems.[108] The increased brightness will concurrently allow the collection of high-quality data of weak signal from in situ studies of systems under operational conditions, such as materials/liquid interfaces in batteries.

An example of where a UK XFEL could contribute a step-change includes providing new insights into the contrasting mechanism for intercalation observed in Li-ion batteries (LIB) and Na-ion batteries (NIBs). Research in the latter has experienced rapid growth in recent years, owing to the elemental abundance of sodium in the earth's crust, which is about three orders of magnitude larger than that if lithium.[109] However, NIBs still exhibit inferior energy, power density and reversibility compared to LIBs. Overcoming these performance limitations requires a fundamental understanding of electrode materials and of the effect of the larger ionic radius of the Na-ion on its intercalation. Despite the large size, it has been shown that Na-ion intercalation only occurs with the solvation shell and, consequently, usually an ether-based electrolyte such as di-glymine is used. Importantly, upon Na:solvent intercalation, the graphite interlayer spacing expands from 3.35 to 10.9 Å,[110] as illustrated schematically in **Figure 6.9**. Given this large expansion, it is astonishing that these systems can be cycled several thousand times without a significant loss in capacity. The UK XFEL, with its ability to probe the absorption edges of all of the constituent atoms, would provide ultrafast insight into the solvation and exchange dynamics of the Na and Li ions, and into how these change upon intercalation.

A combination of X-ray Raman and resonant X-ray emission can be used to investigate the dynamic properties of electrodes during fast charge/discharge process from the perspective of the electrode material, the ions and the solvent. The visualisation of ion dynamics with pico- to femtosecond time resolution will shed new insight into the mechanism responsible for the migration of ions and what drives their diffusion. It will also enable investigations into the reduction of an electrolyte on an anode surface, the initial step towards the formation of an solid-electrolyte interface film: it is challenging to capture the reactions at the electrode/electrolyte interface experimentally, as some of the reactions could occur at the picosecond (ps) timescale.[111] Another example includes atomic scale insight into the crucial electron transfer mechanism between redox couples in redox flow batteries.[100] Besides the time scale for these processes, the high brightness of a UK XFEL will facilitate the collection of high-quality data of photon-in/photon-out spectroscopies in operando, which have previously been shown to provide significant insight into the dynamical mechanism in batteries.

6.3.4 New generation data storage

Magnetism in novel nanoscale materials is a key ingredient in modern information technology. Manipulating magnetic materials is the cornerstone of hard drive technology, where binary digital information is recorded by aligning the direction of the magnetic poles in the hard drive. New technologies are urgently needed because it is estimated that by 2025, up to 20% of the world's energy will be consumed by information technologies, where data centres consume around one-third of this energy. Data storage servers are already emitting as much carbon dioxide as the whole aviation industry. With the ever-increasing use of big data for driverless cars, robots, video surveillance, artificial intelligence etc, there is an urgent need to develop new generation data storage devices.

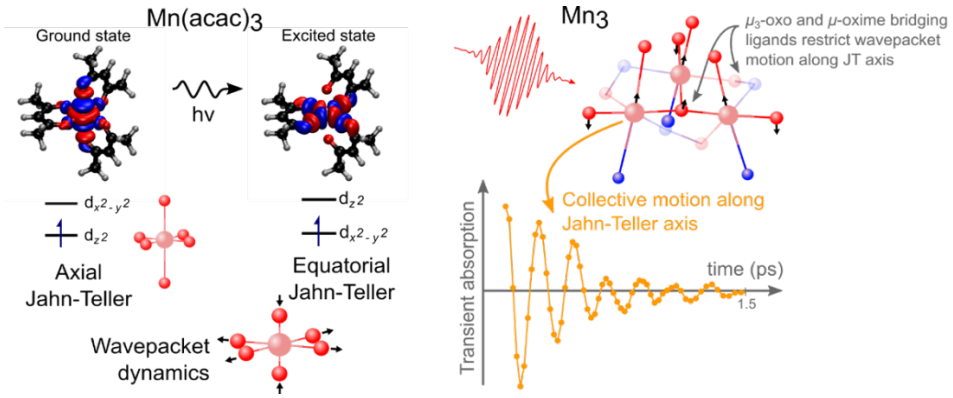


Figure 6.10: Photophysics of Mn^{3+} complexes. The antibonding nature of the e_g orbitals lead to a rapid switch of the JT distortion in the excited state of $Mn(acac)_3$ (left). In Mn_3, the strong bonds in the triangle prevent equatorial expansion and the Mn ion (right).[112]

*Figure reproduced from F. Liedy et al. "Vibrational coherences in manganese single-molecule magnets after ultrafast photoexcitation" Nat. Chem. **12**, 452-458 (2020), Springer Nature. DOI: 10.1038/s41557-020-0431-6*

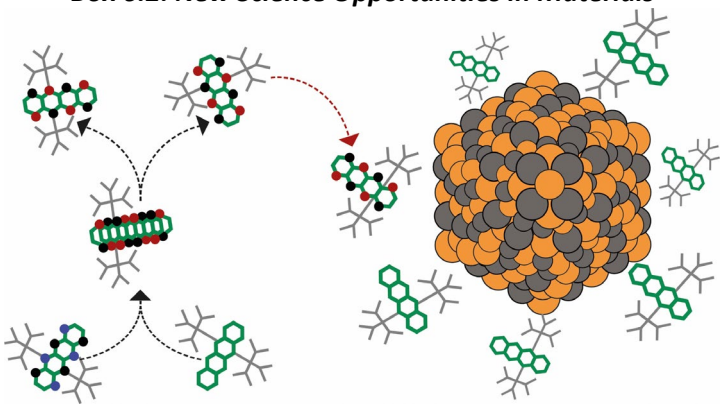
Recent developments in ultrafast magnetism have resulted in photo-magnetic recording in materials which has the distinct advantage of faster sequential switching rates due to the non-thermal mechanism.[113] These experiments make use of specific optical transitions, exciting the electrons from one atomic orbital to another, which in turn changes the magneto-crystalline anisotropy.[113] However, the microscopic mechanisms responsible are difficult to understand because they involve a high density of electronically excited states, vibrational motion, and different spin states, which are all highly coupled (see **Section 6.1**). At present, this lack of detailed understanding is hindering the development of new materials to achieve fast, energy-efficient operation and also miniaturising the magnetic grains towards the nanoscale.

The capability of fs X-ray spectroscopy will facilitate unprecedented new insights into the mechanism of emerging photo-magnetic materials, such as the trinuclear SMM $[Mn^{III}_3O(Et\text{-}sao)_3(\beta\text{-}pic)_3(ClO_4)]$,[112] as performed for light-induced excited spin-state trapping (LIESST) systems.[17,114] In this case, the excitation of a vibrational wavepacket, closely linked to the Jahn-Teller distortion (**Figure 6.10**) was found to be closely linked the magnitude and orientation of the magnetic anisotropy. These results highlight the strong coupling between electronic and nuclear degrees of freedom, and the strong electron correlation between electrons on Mn sites in the polynuclear molecule, important for the photo-magnetic properties. The ability to probe the electronic (XAS, XES), structural (XAS) and spin (XES) dynamics of these complex materials and related analogues on the timescale upon which they operate, i.e. femtoseconds, will enable fine control of the magnetic properties and coherence times of these materials, and provide crucial new insights urgently required to develop to new storage materials.

6.3.5 Conclusion and future vision

In summary, the importance of new tools to disentangle the complex dynamics, and subsequently feed these into design rules for new energy materials, cannot be underestimated. Brute force trial and error approaches to develop new materials do not work, because we cannot test the high number of candidate molecules. The requirement to achieved increased understanding is also crucial to the ongoing digital revolution that is enabling the design process to be increasingly automated, with the potential to rapidly speed-up molecule and materials discovery.

Box 6.2: New Science Opportunities in Materials



Adapted from J. Allerdice et al. J. Am. Chem. Soc. ***141****, 32, 12907-12915 (2019) DOI: 10.1021/jacs.9b06584*

Singlet exciton fission *occurs on sub-100 fs timescales and has the potential to deliver photovoltaic devices which achieve external quantum efficiencies above 100%. However, a grand challenge is to harness singlet fission and to break the Shockley–Queisser limit on the efficiency of single-junction photovoltaics. It has been shown that the triplet states generated by singlet fission can be harvested by inorganic quantum dots, but further work is needed to fully explore triplet energy transfer to inorganic semiconductors and harness it into a device. UK XFEL will make it possible to following the singlet fission and energy transfer processes responsible, providing the new understanding required to achieve high efficiency in photovoltaics.*

Indeed, to take full advantage of these developments, it is essential to achieve an understanding of the important underlying principles and competing processes. This understanding will lead to the definition of descriptors in automated methods and therefore, without careful definition, approaches based upon artificial intelligence are likely to have built in bias and are extremely unlikely to identify step-changing materials.

The UK XFEL will deliver the ability to investigate these fundamental dynamical processes using a range of techniques. In addition, over the next 10 years, the developments in methods such as Coherent Diffractive Imaging (CDI) and X-ray photon correlation spectroscopy (XPCS) will enable the dynamical imaging of structural domains within what are likely to be heterogenous materials into the picosecond and even femtosecond domain. This will complement the local information obtained from techniques such as XAS and XES. Developments required to support this venture include data analysis for heterogenous systems and also the challenges of performing long studies, while ensuring uniformity of conditions and sample integrity.

6.4 Understanding catalysis

Although catalysts are often the key to invaluable chemical and biochemical processes, their complex and elusive nature has by and large defied our current abilities to characterise and understand their microscopic action. This situation has partly arisen from the very fast timescales involved in their role as agents of chemical action, which are faster than conventional characterisation capabilities. The recent developments in femtosecond XFEL technology and instrumentation have finally opened the door on this fascinating research area, and we now have an unprecedented opportunity to capture the behaviour of catalysts in their active state. These developments are now expected to deliver on the long-standing dream of catalyst by design, as opposed to trial and error.

6.4.1 Introduction to catalysis

Catalysis is fundamental for the sustainability of our modern way of life. Most of the products that we use regularly, such as medicines, fuels, fertilisers, perfumes and products designed for the purification of air and water, make use of a catalyst at some point during their manufacture. Catalysts can also be found in nature, where they facilitate critical reactions. It is estimated that 90% of all chemical processes involve the use of a catalyst.[115] From an economic point of view, catalysis generates £50 billion a year for the UK economy through the nation's chemical industry. In 2016, this industry accounted for £12.1 billion of the UK economy's Gross Value Added (GVA)[116] and approximately 100,000 direct jobs.[117]

The discovery of new and improved catalysts is becoming ever more important in order to produce sustainable materials as efficiently as possible. Typical methods that are used in catalyst development are often based on a trial and error approach, where a catalyst is exposed to several types of substrates and analysed, and the process is repeated with adjusted design and operational parameters.[118] Although this approach is often successful, it is heavily resource intensive both in terms of researcher time and of materials, which are often rare and precious metals, whilst still effectively being very narrow in scope. The rational development of catalysts is the alternative approach, but it needs deep understanding of a catalyst's specific functionality and reaction mechanisms. Effective progress by this route can only be achieved by knowing the detailed geometrical structure of the catalyst's atomic and molecular environments, as well as their active electronic structure, and how all these factors change during chemical processes.

Most catalytic studies focus on either the structural characterization of the product outcome or the low energy intermediates formed long after the activation period. However, most catalytic mechanisms require an activation point from where a low energy state material, or pre-catalyst, needs to be 'pumped' to form the true catalyst that exists in a highly reactive state. This true catalyst can then undergo chemistry that either could not otherwise be performed, or with a high selectivity towards the generation of one product type. The characterisation of either the activation route or the properties of the activated species is a challenging prospect, as by its very nature the complex is highly unstable and often short-lived; but in spite of this difficulty, this issue is critical to address as it clearly pre-determines the future catalyst's operational ability. To produce a major shift forwards in the field of catalysis, the focus must therefore shift from the analysis of product distribution and kinetic outlooks, to a direct method of experimental characterisation of the active species paired with advanced computational theory.

XFELs are nowadays capable of providing intense and short X-ray pulses, presenting an exciting opportunity to determine the nature of transient catalytic intermediates and the dynamics with which they are formed, so we can understand, predict and control the resulting chemical processes. X-ray Absorption Near Edge Structure (XANES) spectroscopy, X-ray Emission Spectroscopy (XES), X-ray Scattering (XS) and Resonant Inelastic X-ray Scattering (RIXS) are some of the techniques that have successfully been used in XFELs for the study of catalytic reactions.

6.4.2 Catalysis and XFELs

Photocatalysts are set to become some of the most important materials in terms of sustainability, looking to harness the sun's energy in order to perform high energy transformations, such as water splitting or fuel production.[119,120] Laser pump/X-ray probe studies are proving to be a truly unique characterisation tool for these materials, identifying the highly active species and key excited state chemistry. Many pump-probe studies in catalysis have been performed using the temporal probe capabilities of third-generation synchrotron sources, enabling investigations on timescales of hundreds of picoseconds.[121-124] Although time resolutions below the picosecond have been achieved at synchrotron sources using original timing schemes, such as laser-electron slicing, this has been attained at a significantly reduced flux.[125,126] The emergence of XFEL sources has enabled studies in femtosecond timescales with high flux, that have subsequently allowed the electron and nuclear movements to be followed in real time far from thermal equilibrium, both in the soft and hard X-ray regimes. Here we will review the most significant catalysis studies recently performed at XFEL facilities.

Most of the catalytic system studies on femtosecond timescales in the hard x-ray regime have been focused on understanding the photochemistry of transition metal complexes, as they play essential roles as photosensitisers for hydrogen evolution[127] or for solar energy conversion.[128] Transition metal complexes are widely used for photochemical application due to their ability to absorb light, and subsequently create energetic excited states with holes and electrons that are well separated between the metal centre and the ligands. XANES spectroscopy is ideally suited to investigate the electronic and geometric structure of transition metal centres, taking advantage of the element specificity of the technique to provide access to the d-d electronic transitions in the excited state that cannot be directly detected by optical spectroscopy. The first femtosecond time-resolved XANES (TR-XANES) experiment in the hard X-ray regime was carried out in 2010 at the Linac Coherent Light Source (LCLS)[129] achieving a time-resolution of 500 fs, limited by the instability of the XFEL pulses in arrival time. Since then, the situation has been enormously improved upon, using several technological advances,[130-133] enabling numerous femtosecond XANES investigations.

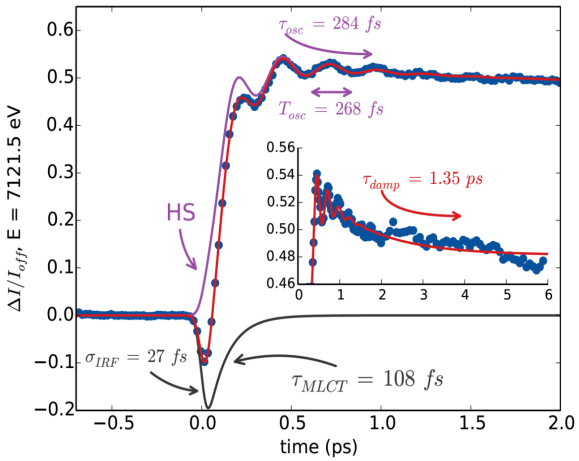


Figure 6.11: Fit to the femtosecond transient XANES of $[Fe(bpy)_3]^{2+}$ measured at 7121.5 eV, showing the contribution of the MLCT and of the oscillating high spin state.[14]

*Figure reproduced from H.T. Lemke et al. "Coherent structural trapping through wave packet dispersion during photoinduced spin state switching". Nat. Commun. **8** (2017), licensed under Creative Commons CC BY 4.0*

One recent example by Lemke *et al*.[14] used TR-XANES to investigate nuclear wavepacket oscillations of the solvate iron (II) bipyridine complex for the first time, extracting valuable information of the Fe-N breathing vibrational mode (**Figure 6.11**). The system was previously studied using the time resolution available at synchrotron sources,[134,135] and although the structural dynamics of the spin crossover was revealed, the molecular breathing was not observed due to the insufficient signal to noise ratio. In a similar experiment, Katayama *et al*.[35] managed to track multiple components of the coherent nuclear wavepacket dynamics in a copper (I) phenanthroline complex, showing that the amplitude of the identified vibration modes can be modified by changing the incident X-ray energy. The increased stability of the XFELs has facilitated the performance of X-ray Absorption Spectroscopy experiments in an extended energy range. Following the publication of the first steady-state Extended X-ray Absorption Fine Structure (EXAFS) spectrum acquired at the LCLS,[136] Britz *et al*.[137] collected a full range time-resolved EXAFS spectrum up to 500 eV above the absorption edge on a Fe(II) polypyridine complex in solution.

While XANES is used to provide information about the empty electronic states of transition metal centres, XES is used to provide information about the occupied density of states projected on the absorbing atom. Although time-resolved XES (TR-XES) has been performed in synchrotron sources to determine the spin state of transition elements with picosecond time resolution,[138] the technique has benefitted greatly from the high pulse intensity and high time resolution of XFEL sources. Many investigations have been performed on the study of the K_α and K_β emission lines of 3d transition metals in molecules, taking advantage of the sensitivity of these emission lines to the oxidation state and the number of unpaired electrons of the transition.[16]

The valence electronic structure of transition metal complexes in solution has also been studied with X-ray spectroscopy in the soft X-ray range with femtosecond time resolution at XFEL sources.[8,139] Time-resolved RIXS (TR-RIXS) at the Fe L_3 edge has been performed to study the ligand exchange dynamics of $Fe(CO)_5$, concluding that the photoinduced removal of CO generates a 16-electron $Fe(CO)_4$ species in an excited singlet state, that either converts to the triplet ground state or combines with a solvent molecule to regenerate a penta-coordinated low spin singlet state Fe species (**Figure 6.12**). It can also recombine with a CO molecule to regenerate the initial state.

Femtosecond soft X-ray pulses have also been used to probe the real-time dynamic evolution of the adsorbate electronic structure of different transient species during chemical reactions using TR-XANES and TR-XES. These studies are important to increase our microscopic understanding of surface reactions, a long-standing goal in heterogeneous catalysis, where chemical reactions occur at the solid surface. In these studies, the optical laser is used to start the reaction, while the XFEL pulse is used to follow the changes in the electronic structure of the adsorbate.[140] Several studies have been focused on the study of the desorption of a CO molecule from a Ru (0001) surface[141,142] at both the O and the C K-edge.[143] Ultrafast X-ray spectroscopy has also been used to identify the short-lived intermediates that are formed during reaction of CO with O_2 on a ruthenium surface.[144] In this study, the optical laser pulse excites motions of CO and O_2 on the surface, allowing the reactants to collide, while new electronic states are shown in the oxygen TR-XANES spectrum.

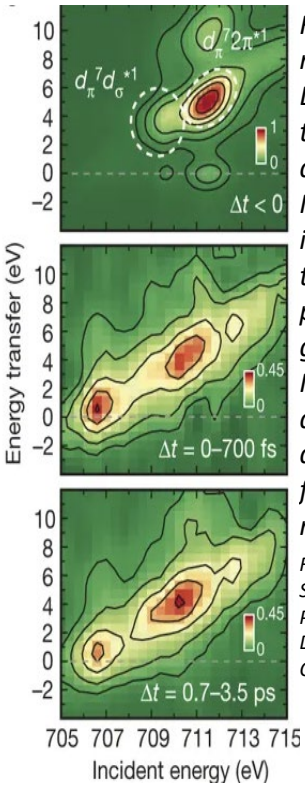


Figure 6.12: Time-resolved RIXS at the Fe L_3 edge sheds light on the ligand exchange dynamics of $Fe(CO)_5$. Measured Fe L3-RIXS intensities versus energy transfer and incident photon energy. Top: ground-state $Fe(CO)_5$. Middle and bottom: difference intensities for delay intervals of 0–700 fs and 0.7–3.5 ps, respectively.[9]

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*P. Wernet et al. Nature **520**, 78*
DOI: 10.1038/nature14296
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The ability to perform time-resolved XS (TR-XS) in solution is also widely used in XFEL sources for the study of catalytically relevant systems, as it provides information on the structural changes in the system under study, including the changes in the solvent cage and the dynamics of the bulk solvent after excitation. TR-XS has been used to extract information of the excited state dynamics in iridium-based dimeric complexes in acetonitrile solution[145] with 100 fs time resolution using a 9.5 keV X-ray pulse. TR-XS has also been used to study the ultrafast structural dynamics of bond formation in $[Au(CN)_2^-]_3$ in solution.[146,147]

As the experimental requirements for TR-XES and in-solution TR-XS are very similar, requiring the use of a fixed incident energy, several investigations have been performed combining both techniques at XFEL sources, illustrating the complementary nature of the techniques: while XES provides information on the changes of the electronic structure, XS provides information on the structural changes. This has been used for the study of photocatalytic dyads,[148] and the study of the solvent-solute interactions that occur simultaneously to the spin transition on aqueous Fe(II) bipyridine.[149]

6.4.3 Future opportunities in catalysis

As seen in the previous section, XFEL sources are now beginning to make a significant impact on the way that we understand chemical processes. The examples demonstrate that the short duration and high flux of XFEL pulses can be used effectively to observe atomic motions and electronic transitions in real time, moving from the scenario where experiments were limited to study only thermally relaxed transient states. The ultimate goal in catalysis is to be able to record movies of chemical processes, where electronic and nuclear structural dynamics are acquired, and XFEL sources are well along the path to delivering this capability. The resulting insights will ultimately bring control of reactions at the electronic and atomic level, when they are initiated by light or other stimuli.

Although spectroscopy and scattering techniques are currently being used with success at XFEL sources to help understand catalytic systems, especially in the field of photocatalysis, most of these studies have so far only been performed on model molecular systems, far from real conditions of concentration. It is expected that, in future, it will become possible for more challenging systems to be studied at XFEL sources under more realistic conditions of concentration and within complicated sample environments, profiting from technological developments that will deliver pulses with higher repetition rates and brightness. The development of spectrometers covering larger solid angles with even higher energy resolution will also contribute to the study of more demanding experiments. Such developments are of considerable interest in catalysis, where often low amounts of the active species are used, and reactions are often performed under harsh conditions of high temperature with toxic and/or flammable gas atmospheres.

It is, however, important to note that the more complicated the system to study, the more difficult it will be to obtain a complete picture of the chemical process with a single structural technique, and the application of multiple techniques simultaneously is going to be necessary to obtain the comprehensive insight required for knowledge guided process optimisation. Chemical studies at synchrotrons reflect this, as multidisciplinary methods under realistic conditions are nowadays routinely used to deliver the full hierarchical characterisation of materials. The study of chemical processes at XFEL sources is not an exception, and many XFEL end-stations now offer the instrumentation needed to perform both spectroscopy and scattering. XES and in-solution XS are frequently used simultaneously, providing complementary information: XES providing information on the electronic configuration dynamics through probing the unoccupied density of states, and in-solution XS providing information on the nuclear motion and changes in the solvent structure. Both methods need a fixed wavelength to be performed and there is no need for scanning the incident beam, and they both profit from the pulse nature of the XFEL source, collecting the entire spectrum in a single acquisition.

XANES is often available together with XES and XS, providing complementary information about the occupied density of states of the absorbing element, traditionally requiring the scanning of the incident energy. One could envisage being able to get information about the occupied density of states using the pulse nature of the XFEL sources using alternative methods such as High Energy Resolution Off-Resonant Spectroscopy (HEROS). This method, when performed using an X-ray spectrometer operating in a dispersive geometry, allows measurements of a scattered X-ray spectrum in a single acquisition using monochromatic incident beam. The feasibility of the method was first demonstrated at the Swiss Light Source (SLS), but due to the extremely weak scattering cross section of the off-resonant signal, it has not been exploited at synchrotron sources.[150] More recently, HEROS has been used at the LCLS to record the static spectra of copper and copper oxide with femtosecond time resolution, taking advantage of the brightness of the XFEL pulses.[151] The next step will be to use this method to study the electronic dynamics of ultrafast chemical processes and combine it with the simultaneous collection of XS data to get structural information, as it is nowadays possible to do when combining XES and XS.

An additional method that will be able to provide complementary spectroscopy information in the hard X-ray regime is X-ray Raman Scattering (XRS). The technique uses hard X-rays for performing XANES spectroscopy of light elements, such as O, C, N, etc. The use of hard X-rays makes this method

a bulk sensitive probe that can be used with a broad range of sample environments, removing the experimental difficulties of working in the soft X-ray regime. Providing access to the study of the electronic structure of low Z materials in the bulk is of significant interest in the study of catalytic reactions, particularly in the field of heterogeneous catalysis, where most systems are composed of an active support that is used for the conversion of small molecules consisting of C, O, N and H (see **Section 6.1**). The Raman cross-section is orders of magnitude smaller than that of the photoelectric absorption, so this method will benefit greatly from the high flux available in XFEL sources, as experiments will be feasible at more realistic concentration conditions than those currently achievable at synchrotron sources. The combination of XRS with other techniques, such as XES and XS, will provide a more complete picture of the catalytic process.

Sometimes in catalysis, the 'one-pot' approach, in which more than one catalyst is used in a single reactor to perform sequential transformations, is used instead of the more traditional stepwise-mediated synthetic approaches. In other cases, the catalytic species contains more than one active site, each catalysing a different step in a chemical process, as is the case of mixed metal photocatalysts. The determination of the electronic and structural dynamics of all the active species involved in the catalytic process is necessary in both scenarios in order to elucidate the reaction mechanism, and to understand how the changes of one active site correlate to the others during the reaction. Element-sensitive techniques, such as X-ray spectroscopies, are an ideal way to acquire this understanding, allowing the disentanglement of the role of the different sites by tuning the energy to the selected element. These sorts of studies have traditionally been performed in a sequential manner, both at synchrotron and XFEL sources, focusing on one active site after another. Very recently, a novel experiment has been performed at the European XFEL in a Fe-Co dyad, where the iron centre acts as the photosensitiser while the cobalt centre catalyses the reaction once the intra-molecular charge transfer has occurred.[152] The experiment used two dispersive emission spectrometers simultaneously, one aligned to collect the emission spectrum of the iron centre, and the other, the Co centre. By measuring the two sites simultaneously, the authors of that study managed to correlate the electronic dynamics of both active sites within the photocatalyst. Although this pioneering experiment represents an important step forwards towards the understanding of the electronic dynamics of mixed metal catalysts, the system was chosen carefully so that the absorption edges of the two active sites were close enough in energy to allow the simultaneous collection of the emission spectra. It is not, however, easy to extend this methodology to other systems where the absorption edges of the elements of interest are at very different energies, but this restriction could be overcome by using two X-ray beams impinging in the sample simultaneously, in a similar fashion to what has been done at Diamond Light Source, where a soft and a hard X-ray beam are used for electron spectroscopy.[153]

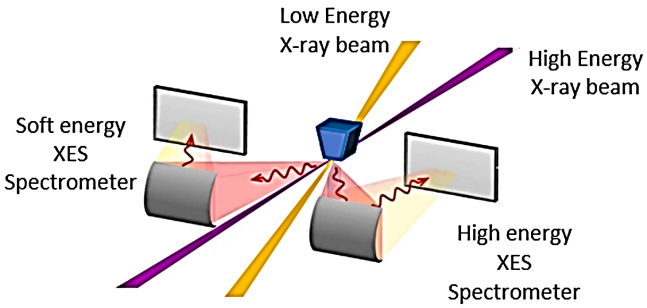


Figure 6.13: Schematic of a XES experiment performed in the soft and the hard X-ray regime simultaneously (adapted from [132]).

*Figure adapted from Y. Kayser et al. Nat. Commun. **10**, 4761 (2019) under the terms of the Creative Commons Attribution 4.0 International License. DOI: 10.1038/s41467-019-12717-1*

Such a development would make the collection of simultaneous XES for more than one element much more generally applicable, including the possibility of studying elements with absorption edges in the hard and soft X-ray energy regimes (**Figure 6.13**). In these cases, not only can mixed catalysts be studied, but also metal transition catalysts with low Z ligands, i.e. the hard X-ray beam will be used to study the electronic dynamics of the transition metal active site, while the soft X-ray beam will be used to study the electronic changes in the ligand donor. This methodology will provide unprecedented insight into electronic movements from two or more atomic sites simultaneously.

6.4.4 Conclusion

Catalysis is critical to all areas of modern life. In order to develop new and improved catalysts to produce materials in a more efficient and sustainable manner, we need a deep understanding of the chemical processes. This information can be obtained by solving the electronic and geometrical structures of the catalytic species and following how these characteristics change during reactions.

XFEL sources are already playing an important role in increasing our understanding of catalytic processes. The high temporal resolution of these sources is opening avenues that allow the study of atomic motions and electronic transitions in real time, recording movies of the chemical reactions, and the simultaneous combination of several structural techniques, such as XANES, XES, RIXS and XS, has often proven essential for fully resolving the subtle but vitally important aspects of catalytic processes.

Higher repetition rates and brightness will enable the study of catalytic reactions under operando conditions, when low concentrations and complicated sample environments are used. Furthermore, the addition of techniques such as HEROS and XRS to the suite of spectroscopy tools available at XFEL sources will have a major impact on our ability to advance our understanding of the field. The long-term goal would be to simultaneously record the electronic and geometrical changes in two centres in the catalyst by using two colour X-ray pulses.

6.5 Chemistry and the environment: Aerosols, atmospheric, space chemistry, combustion, corrosion

The chemistry of complex mixtures inherent in environmental and industrial situations, provides some of the most challenging examples of chemistry to study. The multiscale nature of the problems, combined with random mixing and complex kinetics of multiple competing chemical processes, means that accurate measurements are vital for producing the quantitative models required for material capability studies and process optimisation. Current approaches leave us some way from this point. The capability of a high repetition rate XFEL to provide temporally, spatially and chemically specific maps of reaction mixtures during the process will provide mechanistic detail far beyond current capabilities. The information rich data will provide new perspectives on the chemical and physical properties and processes that control efficiency and material degradation, providing new routes to process optimisation, control and environmental reform.

6.5.1 Chemistry and the environment

Chemistry in the environment covers a broad range of atmospherically and industrially important processes. The key features that links these aspects together is the complex interplay between the chemical changes occurring and the inhomogeneous mixing, driven by complex gas or fluid dynamics.[154] The combined effects lead to localised chemical changes, with almost chaotic spatial and temporal characteristics in some circumstances. This combination of multiscale (in both length and time) characteristics combined with inherent spatial inhomogeneities means accurate measurements remain a significant challenge for conventional light sources. The ability of XFELs to measure spectra in a single laser pulse, that provide chemical specificity (through linear and non-linear X-ray spectroscopies) and particle detection (through diffractive imaging), make XFELs a potentially game changing source for the study of the chemistry of these complex mixtures and materials.

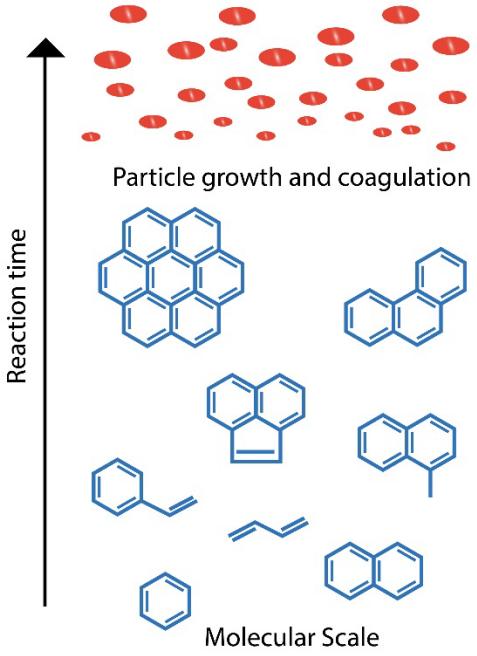
In all cases, the ability to initiate chemistry with a variety of pump sources (IR, UV, VUV, e-Beam) provides routes to studying different reaction types of relevance to various environmental areas. Combined with measurement of ion, electron energy or photon absorption and emission, this provides a multiplexed approach to complex chemical problems that would be impossible to solve with a single technique alone.

6.5.2 Combustion

As well as driving the development of next-generation energy production and storage materials (**Section 6.3**), the UK XFEL can continue to drive efficiency savings in the energy sector through increased understanding of combustion dynamics. Combustible fuels form an integral, and currently irreplaceable, part of our energy portfolio. They provide a high energy density material that is easily stored and transported, making them a key commodity for the foreseeable future. While the UK has committed to banning the sale of new petrol and diesel vehicles from 2035, the use of combustible fuels in other areas is set to continue (e.g. in aviation), such that the challenges associated with driving ever increasing efficiencies should continue to be met. As an example of the impact of efficiency savings, around 80% of energy used within the UK still derives from combustion sources. Despite a growing population leading to an increase in energy demands and the UK's continued reliance on combustible fuels, UK emissions continue to fall and in 2018 were 44% below 1990 levels,[155] in large part driven by increased efficiency. As the UK moves towards the target of net zero emissions by 2050, meeting this will require the combined effect of new technologies and an increase in energy efficiency, both of which are areas where the capabilities of a UK XFEL source can address open questions.

Intelligent routes to increasing the efficiency of combustion sources requires temporally (femto- to microseconds) and spatially resolved, species-specific measurements of the complex chemistry occurring. These data are a prerequisite for the development of predictive models that can direct next-generation system development. For combustion, this means that detailed and accurate

measurements of the dynamic chemical distribution within the flames are required. Optical and fluorescence measurements have limited applicability due to the highly scattering environments and variability in pressure creating spatially-dependent quenching rates, limiting data reliability and availability.[156] Synchrotron based methods can provide time averaged speciation maps through soft X-ray absorption and fluorescence measurements,[157,158] but currently miss the temporal changes in species and how these link to gas dynamics and time dependent local changes in density, pressure and temperature. The unique capabilities of an XFEL in providing high X-ray fluxes at potentially high repetition rates would allow single shot spectral measurements across large spatial areas, providing temporally and spatially resolved species specific maps during the combustion process. Spatially tracking the production, distribution, growth and loss of polycyclic aromatic hydrocarbons (PAHs), for example, will provide details of the early stages of particulate formation and reveal how the local physical characteristics, as well as the chemical environment, either enhances or inhibits their formation (see the *Flagship Project* in **Box 6.3**). This has further links to the chemistry of hot and cold plasmas in planetary atmospheres and to the chemistry of space (**Section 6.5.4**), where PAHs form around 20% of all galactic carbon but question remain over whether their formation is a top down process, deriving from the breakup of soot from carbon stars, or bottom up from small unsaturated chemical species.



Box 6.3: Tracking particle formation in combustion from the molecular level to macroscopic scales

A high intensity optical pump seeds particulate formation through the localised generation of small radical species. By combining X-ray spectroscopies, specifically XANES and XES, with scattering measurements, XFEL probes can map all stages from the molecular growth and formation of PAHs through to particle size distribution via scattering. Extra information on the surface chemistry and structure of the particles can subsequently be obtained through X-ray surface second harmonic generation. The combination of techniques covers time and length scales, from femtoseconds and ångstroms at the molecular level, through to 100s of nm and microseconds for the particulate formation.

This ability becomes increasingly important as we move to higher efficiency engine types, such as those based on Homogeneous Charge Compression Ignition (HCCI). HCCI engines provide much higher fuel efficiency than other internal combustion engines, achieving both CO_2 and NO_x reduction.[159] In HCCI engines, fuel ignition is driven by compression leading to autoignition. The much higher pressure and much lower temperature make the resulting chemistry quite different[160] from a standard engine, and makes measurements challenging. Developing sample environments that create analogous conditions is a challenge. As a first step, mechanical compression provides opportunities to exploit stroboscopic imaging that will utilise the high brightness and high repetition rate of the UK XFEL. Subsequent development in initiating the combustion through pressure waves could lead to robust pump-probe methodologies that allow for a truly molecular scale measurements of these new combustion environments. Both approaches will require the high brightness, ultrashort pulse duration and high-repetition rate of a modern XFEL source for dynamic imaging of the combustion process. By moving beyond state-averaged quantities, such as mixing fractions, to tracking of real time and spatially

resolved chemical changes, fully correlative analysis of the turbulent reaction mixtures can be performed. Optical laser-derived perturbations, e.g. laser filaments, can then drive changes in processes like particle formation,[161] allowing for measurements covering timescales from femto- to micro-seconds. Species-specific probing can be further enhanced through the use of stimulated X-ray Raman probes to monitor changing bonding character in specific reactive intermediates and stable molecules through the flame.[162] The highly detailed and information-rich data will provide detail far beyond the current state of the art, allowing for new insights into the complex interplay of chemistry, fluid dynamics, nucleation and particulate formation that define the fundamental chemical and physical processes that affect energy conversion efficiency.

6.5.3 Corrosion and biofilms

Material suitability and lifetime is often defined by the corrosion processes that degrade material quality over time. Our molecular level understanding of the chemical processes and mechanisms that drive material degradation is limited, which means that our ability to design and manage materials over extended periods is far from optimal. Typical corrosion prevention methods rely on sacrificial layers or the control of diffusion through the use of structured surfaces and coatings. Mechanistic information could lead to a breakthrough technology that impedes the chemistry that drives corrosion, helping to reduce the trillion-pound cost of corrosion to global economies and preserve precious material resources.[163]

To develop these controls requires a molecular level understanding of the degradation pathways and of how the surface level interaction are affected by the coatings and structures currently used. Such studies require detailed structural information of the surface topography and chemical state. Recent developments in operando measurements have utilised synchrotron sources for X-ray diffraction measurements, performed in conjunction with mass spectrometry. The combination of techniques allows for studies of oxidation processes that can be linked to changes on particular facets of complex nanostructures, with a sensitivity to changes on the minutes to hours timeframe.[164] Extending such measurement to localised oxidation state changes, and identification of deposits and corrosion products, requires high sensitivity and rapid spectral data collection. Similar to the combustion studies, the ability to map spatial regions in a single shot removes state averaging and allows for correlative analysis of the changes across all aspects. In electrochemically driven processes, this could include information on the etching and structuring of the surface combined with oxidation state changes and chemical product formation, providing the multivariable analysis required to understand the interplay between physical, chemical and structural effects.

Another pressing concern of material suitability and corrosion surrounds the development of biofilms. Biofilms form due to the collective growth of microorganisms over surfaces. While this presents material opportunities, their growth over implants and in fuel and chemical storage containers causes bacterial infections, corrosion of surfaces and degradation of stored material.[165] Large scale investment into the prevention, detection and management of biofilms is driven by the needs of wide-ranging industries affected by these issues. There are fundamental questions surrounding the composition and dynamics of biofilm growth, and how adaptions to the molecular framework could be used to direct growth and control activity for potentially beneficial applications. For this to become reality, standardised models need to be developed which must be based on detailed experimental data.

Probes that are sensitive to surface properties and reactions are required for both corrosion and biofilm studies. Newly emerging techniques that are only possible at high intensity XFEL facilities are moving non-linear optical probes, developed in the visible and infrared, into the X-ray regime. In recent experiments at the FERMI XFEL, soft X-ray second harmonic generation experiments were performed on graphite surfaces and showed surface level sensitivity with element specificity.[12] These non-linear X-ray techniques will play a key role in understanding these surface driven processes and will have strong links to the catalysis experiments (**Section 6.4**). The increased penetration depth and atom specificity of the X-ray second harmonic generation experiments will detail active site information and

molecule-specific kinetics, even at buried layers and interfaces.[166] Moreover, by simultaneously following biofilm growth, the activity of bacteriophages at controlling and removing biofilms can be integrated at the molecular level, impacting on the boundary between chemistry, life sciences and industry.

6.5.4 Atmospheric and space sciences

Atmospheric science shares many of the experimental challenges associated with studies of low temperature combustion. The generation of radical and reactive species through exothermic reactions leads to local heating and pressure changes that redistribute the reactive species, setting off chains of chemical reactions that depend on the local chemical composition. With the ever-increasing range and complexity of chemicals in the atmosphere creating challenges in the measurement and characterisation,[167] it is from this starting point that wide and varied chemistries can occur leading to reactions with trace pollutants, aerosol or particulate formation, or termination through recombination. The relevance of these effects will, of course, bridge across all planetary atmospheres, impacting on our understanding of the development and chemistry of other planetary atmospheres where detailed measurements of systems both within our solar system (e.g. Titan, Jupiter, etc) and outside (exoplanets) are increasing in number and relevance.

Almost all these processes proceed through complex, multi-welled potential energy surfaces. The formation of bound intermediates leads to indirect reactions, multiple branching points and complex kinetics.[160] Identifying key intermediates of the many possibilities requires highly sensitive probes that can identify small changes in bonding and structure. The complexity is highlighted in **Figure 6.14**, which outlines the currently identified reactions of isoprene.[168] Isoprene is a naturally occurring volatile organic compound (VOC) that forms a trace chemical species found in green spaces. From this single molecule, the molecular branching space is huge such that tracing these species, and their reactivity with atmospheric oxidants, plays a major role in understanding our environment. Other important examples include the reactions of alkenes with ozone and the formation of Criegee intermediates.[169-171] The ozonolysis of alkenes contain a similarly complex series of reactions and side reactions, meaning that their kinetics and mechanisms of reaction are poorly understood. The ability of a high repetition rate XFEL to monitor the dynamics associated with complex formation and reaction, in both time and spatially resolved modes through sheet or line imaging of X-ray absorption or emission, will provide detailed mechanistic information and kinetic profiles that can be fed into improved atmospheric models, while mechanistic details can be obtained from XFEL probes combined with photoelectron and photo-ion coincidence detection methods.

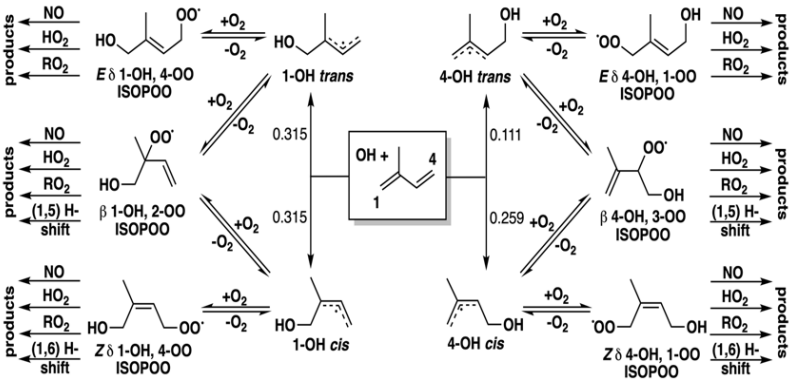


Figure 6.14: Reaction scheme for isoprene highlighting the complex branching space and kinetics required in understanding atmospheric composition and chemistry.[167]

Figure reproduced from K.H. Bates et al. Atmos. Chem. Phys. ***19****, 9613–9640 (2019), licensed under Creative Commons CC BY 4.0*

Additionally, atmospheric aerosol and particulate concentrations have a major impact on human health and climate change.[172,173] Reduction in particulates forms a major component of the UK's clean air strategy due to the particularly strong impacts of breathing in small particulates in polluted atmospheres, while the effects of atmospheric aerosols and particulates on climate change models have large uncertainties, limiting reliability.[174] Part of the problem associated with controls and climate models results from fundamental questions about the production and characteristics of formation. In atmospheric science, as in combustion, the process by which aerosols and particulates form is unclear.

The uncertainty lies not only in the nucleation and growth processes (see also **Section 8.2**), but also in the chemical composition, arrangement and surface activity of the resulting aerosols and particulates as they grow. This can affect removal processes, reactivity and atmospheric lifetime, all of which feed into climate models.

X-ray probes from an XFEL can provide information on particle growth, size and morphology through hard X-ray scattering, and on composition and functionality through linear and non-linear soft and hard X-ray spectroscopies such as XANES, XES and XCARS (**Section 3.5**), with surface sensitivity possible through recently demonstrated techniques, such as X-ray second harmonic generation, which only become viable with the high flux and high intensity available at XFEL facilities.

Another key region of the environment is the interfacial layer, where the oceans and the atmosphere form a coupled system, exchanging heat, momentum and water, and a large variety of chemical species at the air–sea interface. These exchanges exert a considerable and complex influence on the climate system, as well as having more local effects on regional air quality and marine biological productivity. The emission and deposition of trace chemical species at the air–sea interface has important environmental implications, hence the chemical and physical processes involved need to be far better understood. Key to this is an understanding of the structure, composition and chemistry of the sea-surface microlayer (SSM) that defines the uppermost tens to hundreds of microns of the ocean, its equilibrium and interaction with the atmosphere.

The chemical and biological complexity of the SSM (enriched concentrations of amphiphiles, colloids, aggregates, halogenated VOCs, and phytoplankton) mean the important interactions bridge across biology, chemistry, physics and oceanography, and have the potential to impact the environment at almost all scales. Experiments with high flux XFEL sources on laboratory analogues of the SSM provide opportunities to monitor the coupled reactions involved in environmentally important processes (such as the production and subsequent reaction of molecular iodine) as a function of controlled parameters (e.g. temperature, humidity, pH, sea-salt concentrations, ozone levels, nature of microalgae). Important experiments would cover the full range potentially available at the UK XFEL. X-rays from XFEL radiation would be used for spectroscopy in liquid microjet experiments to monitor reactants, reaction intermediates and products with time and spatial resolution. To gain full information gas phase studies using X-ray photoelectron spectroscopy, and photoelectron-photoion coincidence spectroscopy (PEPICO), would be combined with methods that take advantage of the highly penetrating nature of hard X-rays to probe processes deeper in the solution with atom and oxidation state specificity.

The surface sensitivity and potentially broad energy range available from the XFEL and supporting sources also allows for measurements of relevance to space chemistry. Many of the reactions of relevance to the interstellar medium occur on ice grain boundaries and can lead to much more complex chemicals than may otherwise be expected.[175] Large numbers of chemical systems are being identified, with the data from space-based observing platforms tuned to the mid- and far-IR regions (James Webb Space Telescope) and tasked with the observation of star forming regions through observations of icy dust (IceAge Project[176]), and to identifying small molecular coolants (small hydrides, water etc.) as well as more chemically complex systems. The UK XFEL provides opportunities to study the mechanism of formation through the use of synchronized THz to XUV ultrafast light sources with ultrafast X-ray probes. The use of high energy pump sources creates the short-lived radicals involved, while THz or X-ray probes provide chemical identification and track changes in bonding and structure. Combining this with non-linear X-ray probes that provide site-specific detail of the chemical changes promises to provide the most detailed insight into how the molecules of life (e.g. peptides)[177] are formed, and through the use of X-ray probes of chirality (**Section 3.1.3**) we can investigate the fundamental origins of their formation in such inhospitable environments.

6.5.5 Conclusion and future vision

The proposed measurements will provide new insight into a wide variety of complex, multiscale dynamics, leading to the development of new computational models that provide understanding and drive the innovative design of future systems. A key challenge to the successful implementation will be the production of stable and reproducible sample environments, equivalent to the real gas reactors, fuel injectors, liquid jets, droplets, interstellar ice surfaces etc. Such development will require innovation and attention during the design and development stages of any future UK XFEL. These are challenging technical problems but, once solved, the promise of a highly stable, high repetition rate XFEL facility to make fully correlative measurements of key criteria offers unprecedented advantages over current methodologies. In particular, the combination of X-ray spectroscopies that offer atomic and/or molecular sensitivity in isolated systems (XANES, XES, XCARS, etc) and on surfaces (X-ray second harmonic generation), combined with information on particle growth, size, morphology and the rare events (**Section 3.4**) that drive growth and formation, obtained through hard X-ray scattering and CDI measurements, will allow for detailed comparisons across systems and environments.

6.6 Conclusions and vision: XFEL and chemical sciences

Chemical science at XFELs covers a broad subject range, from the fundamental science associated with photochemical reactions and catalysis, through to the device and material properties of batteries and photovoltaics, and further into biochemistry and medicine. Due to the ultrafast timescales of XFEL measurements combined with molecule and atom-specific probes, a state-of-the-art UK XFEL facility could revolutionise our understanding of chemical processes across all these areas. A UK XFEL can open up new horizons in chemical sciences and at the interface with materials, physics, biology and medicine, by bringing about an unprecedented degree of scrutiny of reactions happening in the gas phase, liquids and solids; yielding with atomic precision and femtosecond resolution, real time molecular movies; and paving the way for new photoactive materials. Examples of real-world impact may include photoactive materials for harnessing solar energy and magnetic information storage, light-driven Earth-abundant catalysts for conversion of CO_2 into value-added chemicals, anticancer drugs, and antimicrobial compounds which can help bringing clean water to all.

The unique ability of a high repetition rate of over 100 kHz, high brightness XFEL with $>10^{12}$ photons to measure chemically-specific, and even atom-specific maps, on the intrinsic time (towards attoseconds) and length scale (ångstroms) of molecular processes, will offer unprecedented detail into the molecular-scale changes that enable molecular- or macroscopic function, and control efficiency across many orders of magnitude, from molecular level to whole-organism or device. Crucially, the new technological advances of the UK XFEL will also have the potential to capture the rare events that initiate chemical change, thus providing routes to understanding and controlling material degradation and fouling. Knowledge of the molecular level processes that control chemical and material properties will provide new understanding and real-world impacts that will inspire and deliver next-generation technology.

Such a broad and bold vision also demands a significant provision of diverse auxiliary sources to act as pump and/or probe. These sources should cover the *VUV, UV, Vis, IR,* and *THz* regimes to allow for interrogation of the complex energy landscapes across systems where different modes of activation are required. Synchronisation (sub 20-fs) of multiple pump-probe sources, and the ability to interrogate the same sample by a multitude of X-ray spectroscopic (XES, XAS) and scattering methods (CDI, XPCS) simultaneously is another key requirement of the proposed X-ray-LEGO approach. Active development of novel sample delivery methods will be essential to take full advantage of the XFEL capabilities; particularly where materials are potentially delicate (e.g. batteries and solar cells), contain complex, sometime heterogeneous, mixtures and structures (e.g. combustion), or are both delicate and extremely precious (e.g. cells, proteins, or DNA). Achieving these challenging targets will provide the routes to increased impact across industrial sectors, enable sustainability targets to be met, guide environmental reform and drive innovation for a prosperous and resilient society.

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7. Science Opportunities in the Life Sciences

The strongest current cases of XFEL use in the life sciences include serial femtosecond crystallography (SFX), time-resolved SFX and time-resolved single particle imaging. These methods exploit slurries of nano- to micro-crystalline samples, at near-physiological temperature and pressure, to generate atomic resolution models and probe authentic function from the same sample. Reaction cycles for time-resolved SFX are initiated by light or mixing strategies, and many are generalisable across all of biology. Thus, dynamic structural biology and molecular movies of macromolecular function will become routine. In many cases, especially with metal-dependent systems, complementary spectroscopic information can also be collected from the same samples and X-ray pulses, providing even more detailed mechanistic insights. Structure-functional results will translate into better drugs and treatments impacting human health, and better catalysis for clean energy and agriculture. A frontier opportunity is to extend single particle imaging methods of biomolecules in solution, so that nearly all dynamic processes in biology can be studied with high temporal and spatial resolution.

Sixty years ago, at the dawn of structural biology, Nobel laureate Max Perutz attempted to measure the structural impact of O_2 binding to haemoglobin crystals. His large crystals did not survive O_2 exposure, because it triggered significant and functionally relevant conformational changes in each protein within the crystal lattice.[1,2] When Perutz conducted his experiments, he used a weak, lab-based X-ray source that required large crystals to collect as much diffraction data as possible from a small number of samples at room temperature. One hypothesis is that the crystal lattice, which is held together by weak interactions, builds up strain across a large crystal and breaks into smaller and smaller fragments – essentially dissolving. Importantly, the lattice also did not prevent the dynamic and functional consequences of O_2 binding; although considering the instrumentation at the time, there was nothing useful left for structural analysis.

XFELs offer new opportunities in structural biology, especially for samples at near-physiological conditions and for time-resolved studies that link together the analysis of structure and function with the same samples.[3-8] The unparalleled XFEL intensity reduces the crystal size requirements, such that even submicron crystals can yield high quality diffraction data collected at room temperature.[9,10] The fs pulse duration also provides sharp temporal resolution, without sufficient time for radiation-induced alterations in most cases. These characteristics prompted the following statement from Tetsuya Ishikawa, (Director, RIEKEN SPring-8 Center, Sayo, Hyoga, Japan) at SLAC National Accelerator Laboratory, Menlo Park CA USA on 02 May 2014:

> *The basis of science is observation. The most fundamental way of observation is by light. X-rays are a form of light that can probe atoms and molecules. X-ray lasers can probe atoms and molecules on their fundamental time scales, femtoseconds. X-ray lasers are therefore one of the fundamentally most powerful tools for science.*

More than 99% of all organisms that have ever lived on the Earth are now extinct; and yet the current diversity of life is still staggering.[11] With life spans that range from hours to dozens of millennia, organisms tolerate temperatures from about -15°C to 125°C, pressures from the vacuum of space to up to 1,100 atmospheres, pH values between 0 and 12.5, visible light conditions ranging from full sun to 5 x 10^6 fold attenuation, UV and/or ionising radiation up to ≥1,000 J m^{-2} or 50 Gy/hr (12,000 Gy in an acute dose).[12] Despite these taxonomic characteristics, modern biology today is often defined and underpinned by genomic analyses (**Figure 7.1**).

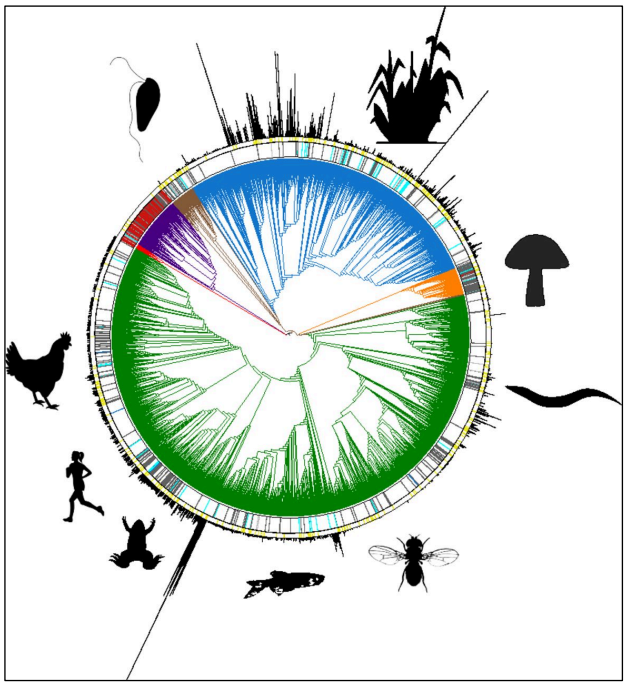

*Figure reproduced from H.A. Lewin et al. Proc. Natl. Acad. Sci. USA **115**, 4325-4333. Copyright (2018) National Academy of Sciences DOI: 10.1073/pnas.1720115115*

Figure 7.1: Current status of the sequencing of life.
Open Tree of Life (opentreeoflife.org) synthesis of phylogeny for all of life with resolution to the genus level, and showing phylogenetic information for Archaea (red), Bacteria (purple), Fungi (orange), Plantae (blue), Protista (brown), and Animalia (green). The current state of genomic information available from NCBI's GenBank is shown in the inner circle, with complete genomes colored in red, chromosome level in blue, scaffolds in dark gray, and contigs in light gray. The second circle shows the transcriptomes from the NCBI Transcriptome Shotgun Assembly Sequence Database (www.ncbi.nlm.nih.gov/genbank/tsa/). Genome size as C value is displayed in bars around the outer circle. Data for animals is from the Animal Genome Size Database (www.genomesize.com/), data for plants is from the Royal Botanic Gardens, Kew (cvalues.science.kew.org/), and data for fungi is from the Fungal Genome Size Database (www.zbi.ee/fungal-genomesize/).

Indeed, the impact of the human genome project is enormous as suggested by the statement from Battelle (Columbus, Ohio) and the United for Medical Research[1] coalition:[13,14]

> *The reference human genome is to biology what the periodic table is to chemistry: a fundamental platform for understanding and advancing science for generations.*

Genomes derive from "individuals," whereas in contrast, metagenomic analyses help reveal complex relationships amongst organisms and their environments.[15-18] As of May 2020, the Kyoto Encyclopedia of Genes and Genomes (KEGG) database lists complete genomes from 541 Eukaryotes, 5683 Bacteria, 318 Archaea, and 341 viruses, as well as metagenomes from 477 environmental and 712 organismal samples.[19-22] Table 7.1 indicates millions of genes that exhibit massive diversity and cover all macromolecular and enzyme classes. About half of the gene products have also been mapped or linked to metabolic or signalling pathways, or many other important biological functions. **Interactions between organisms range from benign to symbiotic to pathogenic; deciphering the fundamental principles that dictate the scale, scope, and consequence(s) of these interactions remains a grand challenge in biology.** Answering this challenge will have profound implications to human health, renewable energy sources and climate change, species extinction versus survival, and food production for a human population expected to reach 11.2 billion by the end of the century.[23]

The answers will not come exclusively from genomic analyses, but rather are greatly influenced by structural biology and many complementary methods (Figure 7.2, see also **Appendix 2**). X-ray macromolecular crystallography (MX)[3,4,6,8,24-26] and cryo-Electron Microscopy (cryo-EM)[27-33] are essential and well established tools for structural biologists worldwide. The impact is highlighted by ten Nobel Prizes awarded in the past decade with a component linked to structural biology. Synchrotron X-ray sources or cryo-EM were vital to the R&D efforts in each of the Nobel laureates' laboratories. Synchrotron facilities also serve the entire structural biology community, who now leverage these capabilities on a daily basis.[24,25] As a result, more than 160,000 atomic models are

[1] The coalition consists of the American Association for Cancer Research, American Cancer Society Cancer Action Network, American Diabetes Association, American Heart Association, Association of American Universities, Association of Public and Land Grant Universities, BD, Biotechnology Industry Organization, Boston University, Corning, FasterCures, Harvard University, Johns Hopkins University, Life Technologies, Massachusetts Institute of Technology, Melanoma Research Alliance, Northwestern University, Pancreatic Cancer Action Network, Partners Healthcare, PhRMA, Research!America, Stanford University, The Endocrine Society, Thermo Fisher Scientific, University of Pennsylvania, University of Southern California, Vanderbilt University, and Washington University in St. Louis.

currently curated by the Protein Data Bank (PDB), with an estimated economic value of more than $16B.[34-36] Furthermore, structural biology was critical to more than 90% of all drugs approved by the US FDA since 2010.[37-40]

Table 7.1: KEGG GENES Annotation Statistics (as of 17 May 2020) [a]

Category	Protein-based genes		RNA-based genes		Pathway linked genes	Enzyme genes with EC numbers
	All genes	KO assigned genes [b]	All genes	KO assigned genes [b]		
KEGG organisms	30,224,913	15,635,407	628,182	347,049	8,700,385	6,750,695
Brassica napus	96,972	31,875	65	64	17,171	13,133
Homo sapiens	19,855	14,264	2,641	336	8,039	3,363
Saccharomyces cerevisiae	6,002	3,793	415	394	2,399	1,311
Escherichia coli	4,240	3,169	179	152	1,697	1,302
Viruses	367,122	10,122	5,500	24	N/A	5,235
Addendum	3,973	3,881	N/A	N/A	N/A	3,064

[a] Source: www.genome.jp/kegg/docs/genes_statistics.html
[b] Annotated with the KEGG Orthology (KO) system; the basis for cross-species annotation in KEGG. The set of genes in the genome that can be mapped to KEGG reference pathways and BRITE reference hierarchies to generate organism-specific pathways and hierarchies.

The PDB has released 145,680 atomic models linked to X-ray crystallography, 12,983 to NMR spectroscopy, and 5015 to cryo-EM (compiled on 15 May 2020).[41] Despite these impressive results, and the important biological insights derived from them, the known genes summarised in **Table 7.1** are tallied in the tens of millions with the number of genes per organism ranging from a few thousand for microbes to about 20,000 for humans to over 100,000 for some plants. Although there are more than six million annotated enzyme genes listed in the KEGG databases, enzymes typically account for about 20% of the genes in most organisms. Because enzymes "do the work" of life, it's the overall level of homology and structural/functional differences that account for the diversity we observe in life today. Thus, one might conclude that we are incredibly ignorant with respect to an atomic level understanding of biology on a global scale, and that there is a tremendous amount of new information still to be discovered. To these ends, structural biology results via any and all experimental methods are critical to our comprehensive understanding of life (**Table 7.1**, Figure 7.1 and Figure 7.2). High resolution structures – mainly obtained to date by X-ray crystallography, NMR spectroscopy and cryo-EM – are also complemented by electron diffraction from micron to submicron-size crystals,[42-48] neutron diffraction and small angle scattering,[49-52] macromolecular structure prediction,[53-56] small and wide angle X-ray scattering of biomolecules in solution,[57-61] super resolution fluorescence microscopy,[62] optogenetics,[63,64] DNA and RNA sequencing and multimodal data analysis technologies applied to single cells,[65,66] cryo-electron tomography,[67-69] X-ray microscopy, tomography and ptychography,[70-75] and a variety of methods to establish interaction networks between biomolecules.[76] As a result, most biologists analyse integrated structural, functional and dynamic data from different techniques, samples and conditions. This applies to macromolecules in pure states, to increasing complexity of heterogenous samples, and ultimately to physiological conditions such as within whole cells or tissues.

The vast majority of the MX datasets are collected from one to a few crystal(s) measuring ~ 10s - 100s μm^3, held at 100 K in a cryostream and rotated about one or more axis during data collection.[77] Similarly, nearly all of the cryo-EM atomic models are collected from samples at ~ 100 K. But life is dynamic and function is not compatible with the cryogenic conditions. Indeed, dynamics and timescales in biology (Figure 7.2) range from fs for electronic transitions and bond vibrations, to ps for light-induced charge separation, photoisomerization and amino acid side chain rotation, to µs for domain motion and ion transport and fast enzyme reactions, to ms for most enzyme reaction rates and fast protein folding, to seconds for protein synthesis and DNA or RNA replication/synthesis.

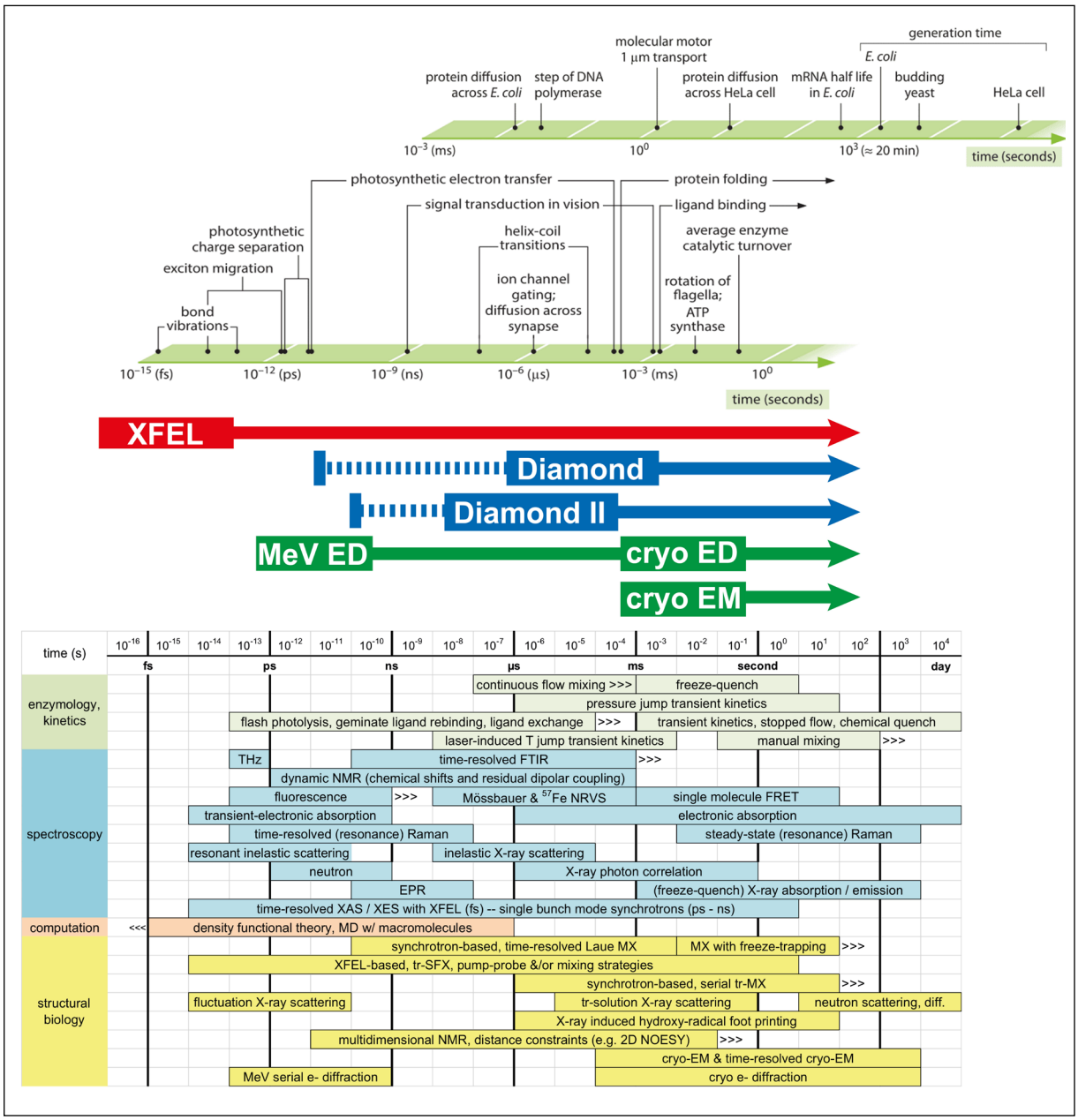

Figure 7.2: A comparison of X-ray sources and types of phenomena they are used to study
Biochemical processes span orders of magnitude in time (top). The X-ray dose and time required to elicit a spectroscopic change and an X-ray diffraction pattern to high resolution at a modern synchrotron or XFELs range from μs to fs at synchrotrons and XFELs, respectively. For comparison, examples of complementary methods are shown along the bottom. Biologists will often use many of these methods in their research.

Top figure reproduced from "Cell Biology by the Numbers", by Ron Milo, Rob Phillips. Copyright 2015, Taylor and Francis Group LLC

We are experiencing a step-change in macromolecular crystallography. This derives from serial MX and time-resolved functional studies that are directly linked to XFELs and the use of micron-size samples.[3,4,6,8] One important hypothesis is that micron-sized crystals minimise or eliminate barriers to relieving strain that builds up when conformational changes propagate across molecules and unit cells. A dramatic case in point is an aptamer of messenger RNA, a riboswitch that binds adenosine and undergoes a large conformational change that ultimately regulates gene expression.[78-80] Using a slurry of micron-size RNA crystals and mix-and-inject methods, Stagno *et al.* reported time-resolved SFX results that demonstrate ligand binding-induced conformational changes so significant that the crystals changed symmetry, but they did not shatter.[81,82] This remarkable result has also recently been observed via atomic force microscopy wherein the probe-tip is scanned across the outer layers of microcrystals. These experiments demand the intensity and tight focus of the XFEL beam; without either, these experiments would not be feasible.

7.1 Serial femtosecond crystallography enabled by XFELs - a new era in structural biology

Serial crystallography presents a revolutionary opportunity to solve structures from slurries of nano- to micron-size crystals. The high brightness and tight focus of the XFEL beam enables a diffract-before-destroy methodology that rapidly reveals structures from samples at physiological conditions.

7.1.1 Introduction

Crystallographers frequently observe microcrystal showers, measuring only a few microns on a side, that arise from initial sparse matrix screens used early in most projects. These conditions are then "optimised" to yield large single crystals typically measuring ~ 25 - 100s µm or more on at least two sides. During typical data collection at 100 K, the X-ray dose is distributed throughout the entire crystal volume, by combinations of rotation and translation.[83-90] And so, although microcrystals are ubiquitous, they are frequently overlooked because they can be difficult to use and/or perceived to be inappropriate for structural analysis. However, the characteristics of XFELs change the sample requirements for MX. Showers of microcrystals are ideal for XFELs that deliver hard X-rays with high flux density in a very well-focused fs-long pulse. Microcrystals of membrane proteins – an under-represented class in the Protein Data Bank (PDB) – are often produced and well-suited for serial femtosecond crystallography (SFX) methods.[91-96] Moreover, SFX strategies have translated to analogous serial MX methods at synchrotrons around the world including Diamond, and are anticipated for Diamond-II.

SFX is a new technique developed to exploit the fs pulses from XFELs and to use thousands of micron-size crystals or smaller.[3,4,6,8] It is the dominant method in life sciences at all five XFELs since it was first reported in 2011 by Chapman and colleagues at the LCLS.[97,98] The impact of SFX is summarised in **Table 7.2**, wherein atomic models released by the PDB are a measure of impact. These atomic models are almost always accompanied by a primary citation. It is noteworthy that 60% of the primary citations since 2011 were in high profile publications such as *Science*, *Nature* or *Cell*, etc. These results often highlight the unique characteristics of SFX methods afforded by XFEL facilities. This includes an almost complete lack of radiation-induced alterations in the atomic models, exploitation of micron to sub-micron size crystals, and exquisitely sharp temporal resolution in time-resolved studies. These are impressive advances in only a few years of operations, and the biology community is very eager for more XFEL access to expand the experimental use cases.

Table 7.2: Macromolecular atomic models linked to data collected at an XFEL released by the PDB [a]

LCLS (USA, 2011 to date; CXI, XPP, MFX beamlines) • 223 atomic models released • 85 primary citations • 62 high profile citations [b]
SACLA (Japan, 2014 to date; BL2, BL3 beamlines) • 109 atomic models released • 36 primary citations • 11 high profile citations [b]
European XFEL (Germany, 2018 to date; SPB/SFX instrument) • 19 atomic models released • 4 primary citations • 4 high profile citations [b]
PAL-XFEL (South Korea, 2019 to date; NCI - SFX beamline) • 8 atomic models released • 2 primary citations • 0 high profile citations [b]
SwissFEL (Switzerland, 2019 to date; Aramis, Bernina beamlines) • 1 atomic model released • 0 primary citations • 0 high profile citations [b]

[a] Compiled on 16 May 2020

[b] Primary citation appeared in either *Science*, *Nature*, *Cell*, *Proc Nat Acad Sci USA, Nature Methods, Nature Communications, Nature Chemistry,* or *Structure*

7.1.2 Sample delivery and efficiency

SFX studies are very often conducted at room temperature, from which one still diffraction pattern is recorded from each microcrystal in a random orientation. XFEL beams are typically well-focused to deliver submicron or 1 - 3 µm spot size at the sample, and are about nine orders of magnitude brighter than synchrotrons like Diamond Light Source. Because so much energy is deposited into the sample, it explodes.[99] Consequently, SFX methods require a unique sample for each diffraction pattern and the whole dataset

is merged from thousands of still images. To this end, sample delivery methods for serial MX is a very active R&D effort in the field. The aim is to rapidly and efficiently deliver samples, without wasting precious material, at a rate that matches the XFEL pulse frequency and/or the detector characteristics.

A variety of methods have been developed to deliver a slurry of microcrystals into the XFEL interaction region, which include liquid flow-focusing gas dynamic virtual nozzles (ff-GDVN) or viscous media jets and extruders,[95,97,100-106] a concentric-flow electrokinetic injector,[10,107,108] on-demand micro-droplets that may be coupled to a conveyor belt transport system,[109-117] fixed targets that raster a sample array through the X-ray beam,[114,118-127] and goniometer-based methods.[128-132] Many of these methods are readily adaptable to time-resolve studies in which the reaction is triggered by either light or mixing, as discussed below.

SFX data collection times are driven by a combination of the X-ray pulse frequency, the detector capabilities, and the hit ratio defined as the number of indexed lattice(s) divided by the total number of X-ray pulses delivered. Crystal hit ratios range from much less than 1% to greater than 100% in some fixed target systems with more than one crystal in a fraction of the wells. Ideally each crystal lattice will be in a random orientation and thus, the whole SFX dataset is built up in a stochastic process. **Table 9.1** in **Section 9.2.4** compares the typical data collection times required at different XFEL facilities in operation now and anticipated at those currently under construction. It illustrates that a 25,000 indexed lattice dataset can take significantly more than a 12-hour shift with a low hit ratio and a slow detector or pulse frequency. In contrast, only a few seconds are needed under conditions that yield a high indexing ratio with a fast detector. It is important to point out that in the fastest cases to date, the detector becomes a limiting factor rather than the X-ray pulse frequency. Moreover, in every case, the scientists must evaluate each SFX dataset in as near to real time as possible. This is clearly more challenging with faster data collection, larger image files, and larger unit cells with many more reflections that must be merged. Consequently, highly parallelised algorithms will be critical as well as access to large clusters and/or supercomputer centres for the most intensive calculations.[133-138]

Although SFX was first demonstrated in 2011 at the LCLS,[97,98] serial MX methods are now also available at nearly all major synchrotron facility around the world.[25,139-144] Moreover, beamlines dedicated to serial MX are often identified as a flagship capability at facilities undergoing upgrades to diffraction-limited lattice configurations, including Diamond-II (see **Appendix 2**).[145-147] Thus, room-temperature, serial MX methods that couple dynamics and functional studies with structural analysis will become routine around the world. This trend will continue to expand and impact all of life sciences.

7.1.3 Membrane proteins

About 30% of the human genome codes for membrane proteins.[92,148-150] Because they are located and function at the interface between cells or organelles, they are critical mediators/sensors of environmental conditions, nutrient transport, and cell communication and signalling. Not surprisingly then, membrane proteins are targets for more than 50% of all drugs available worldwide.[151,152] The PDB currently curates more than 17,700 membrane protein atomic models, of which more than 15,300 were determined by X-ray diffraction and more than 1250 by cryo-EM. Furthermore, SFX methods at three XFELs facilities have been used for more than 85 of the recently released atomic models. Because membrane proteins are hard to crystallise and often only yield microcrystals, they are ideally suited to structural analysis at XFELs.[92,93,150,153]

Significant progress has been made crystallising membrane proteins using lipidic cubic phase (LCP) methods.[91,96,154] In addition, viscous media and LCP extruders (see **Section 8.6** and **Figure 8.12**) are highly efficient methods for delivering membrane protein crystals into the X-ray interaction region.[95,155,156] The high viscosity of LCP makes it unsuitable for mix-inject style time-resolved studies. However, LCP is amenable to ligand exchange under equilibrium conditions, which is an emerging strategy for drug discovery, especially in the G Protein-coupled Receptor (GPCR) family.[92,93,157,158] To date approved drugs that target GPCRs impact to the central nervous, cardiovascular, immune, metabolic, and reproductive systems, as well as many human cancers. The importance of GPCRs was

the recognised by the 2012 Nobel Prize in Chemistry to Lefkowitz and Kobilka "for studies of G-protein-coupled receptors."

7.1.4 Future directions

Serial MX will continue to expand at synchrotrons and XFELs around the world. This will benefit from hard X-rays with tight focus and XFEL pulse frequencies from kHz to MHz. Data collection from samples at near-physiological conditions, especially compared to cryogenic conditions, will provide new strategies for drug discovery (see **Section 8.6**). Membrane proteins, including a wide range of important GPCR family members, will be a strong use case for academic and industrial XFEL users in the coming decades. In biology, samples are often scarce and, therefore, on-demand sample delivery methods will always be important to the community. Some of the current methods for on-demand sample delivery can operate at up to 50 kHz, but further developments are needed to achieve 0.5 MHz or faster. For MHz pulse frequencies, fast GDVN-type jets are likely to be essential (see **Section 7.3** below). It is also clear that future SFX experiments will tax computational resources by generating very large datasets, that may require varying degrees of image triage, and will need merging as fast as possible so that scientists can make the most effective use of XFEL beamtime.

Light source characteristics that include essentially CW high repetition rate and increased stability parameters will allow the further development of the accuracy of stationary serial MX. Post-refinement is being developed to improve the quality of the retrieved amplitudes.[159-167] With the necessary increased frame rate of area detectors, orders of magnitude improvement in data collection rates relative to current 'warm Linac' hard X-ray FELs will be achieved (see also **Section 9.2.4** and **Table 9.1**). For example, the European XFEL fields AGPIDs[168-170] and JUNGFRAU[171,172] detectors, wherein the former can collect 3520 data frames per second overall, out of the 27,000 pulses per second delivered in 4.5 MHz trains lasting no more than 600 μs; compared to warm Linac machines that deliver pulses at up to 120 Hz. In addition, increased stability will allow a more accurate X-ray geometry determination to improve post-refinement methods, for further enhancements of the structure factor amplitude determination. A discussion of the crystallographic signal-to-noise and the new molecular physics that may be probed in such a regime has been presented.[173] These include the detection and analysis of vibrational coherence dynamics, in addition to resolving reactive mode displacements on ultrafast timescale.

7.2 Dynamic structural biology: Photosensitive systems

A remaining frontier challenge of structural biology is to determine time-resolved structures at atomic resolution directly from systems engaged in function, at physiological temperatures and pressures. XFEL methods coupled with pump-probe strategies are making important advances towards this goal.

7.2.1 Introduction

Time-resolved serial MX naturally blends functional and structural analyses into the same sample and experiment. This is sometimes described as *Dynamic Structural Biology.* It exploits slurries of microcrystals at room temperature and is increasingly prevalent at XFELs and synchrotrons. Light-activated systems are relatively rare in biology, but are easier to initiate and many have the potential to probe isomerisation rates from fs and slower. General time-resolved structural biology is separated from ultrafast applications by fundamental time scales of decoherence, which is typically completed within few picoseconds. Coherent dynamics are separately discussed in **Section 7.3**, while pure population dynamics at slower timescales are the focus of biochemistry applications discussed here.

Heretofore the *status quo* in structural biology has been to use many separate samples, from which different types of data are collected under different conditions. Some of the experimental conditions may be very far from physiological. For example, traditional MX or cryo-EM methods usually provide insightful atomic models of a particular ground state or a trapped intermediate state molecule from a sample held at 100 K. In contrast, most functional studies are conducted in solution, at room temperature, and often include binding, conformational changes, and/or other types of dynamics.

7.2.2 Time-resolved studies of light-sensitive proteins

Ultrafast time-resolved spectroscopic experiments performed on photo-active proteins in solution have provided many important insights into the very early events after absorbing a photon. Because XFELs are still new, analogous time-resolved SFX experiments are still emerging. In most reports, authors compare time-resolved SFX and spectroscopic results; although they may have used similar pump-probe delay times, the comparisons frequently do not yield one-to-one correlations. One possible explanation is that the crystal versus solution conditions are sufficiently different that ultrafast spectroscopic experiments have not been performed at, for example, the same pH, viscosity, or ionic strength, among many other potential variables that were present in the SFX experiments. Furthermore, the desire of structural biologists to observe and maximise illumination-dependent differences in electron density maps has often pushed experimental conditions into the multi-photon regime. Recently it has become clear that visible light power dependence studies are critically important to nearly all light-activated time-resolved SFX experiments. Unfortunately, in part because beamtime is so rare, scientists may underprioritise these “control” experiments, and as a result these types of data may be sacrificed under time-pressure situations.

Examples of XFEL experiments involving light-activated systems include photosystem I [98,174-178], photosystem II,[107,109,111,112,130,179-190] photoactive yellow protein,[191-193] human rhodopsin,[155,194] bacteriorhodopsins,[103,195-201] jumping spider rhodopsin[202,203] light-activated ion channels[204], fluorescent proteins,[205-208] several phytochromes,[111,209,210] DNA photolyase, and photo-dissociation studies of myoglobin-CO [211] or cytochrome c oxidase-CO.[212,213] Of these systems, photosystems I and II have evolved mechanisms to diffuse the excess energy absorbed in multiphoton events through the network of internal chromophores, and are therefore less susceptible to the impact of single versus multiphoton time-resolved SFX studies. The photo-dissociation of CO from metalloproteins can be considered outside their normal function and less constrained by illumination conditions. The remaining systems evolved to react to visible photons, and single photon methods are likely to be most physiological. Moreover, many of these systems experience photo-driven conformational changes that are often linked to photoisomerization of the chromophore. Such events are often very fast and require timing tools to help coordinate the pump-probe experiment.[214-217]

Optogenetics refers to the ability to control a biological outcome through illumination with light.[64,218-224] The field has grown with our understanding of how various organisms sense and respond to ambient light through the action of one or more photoreceptors. These types of proteins evolved to absorb visible light photons, which drives photoisomerization event(s), that consequently trigger conformational change(s) and ultimately elicit an output response most likely though signalling cascades or a change in pH or ion concentration. Thus, optogenetics combines biophysics, structural biology, genetics and cell biology. But it all starts with a fundamental, atomic level understanding of structure, function, and dynamics of photosensor proteins — of which there are many. Their function relies upon chromophores that often exhibit extreme radiation sensitivity.

An illustrative example is the phytochrome superfamily of proteins that are generally divided into two functional regions (Figure 7.3).[225-227] For instance, an N-terminal photosensory module houses a covalently-bound bilin, or bilin-derived chromophore within a central domain, followed by a C-terminal output module that usually contains one or more protein kinase domains that transfers the signal to various downstream phosphorylation signalling cascades. Typically, phytochromes act as red/far-red photoswitches that are activated/deactivated by absorption of red or far-red light, respectively, by means of a covalently bound bilin chromophore. However, using a similar bilin cofactor but different protein-ligand covalent linkages, these proteins photoswitch between other colours of light, e.g. blue/green for Te-PixJ. Moreover, the spectroscopic analysis of the photoconversion reaction typically identify several intermediates formed with kinetic rate constants ranging from fs - ps - µs - ms - seconds. The photoisomerization effects are the fastest events, and the slowest events relate to larger conformational changes propagating throughout the protein that have the largest biological impact. The structural basis and dynamics for these proteins is still poorly understood and several groups are perusing time-resolved SFX programmes and synchrotron-based studies with various pump-probe strategies.[111,209,210,228-240]

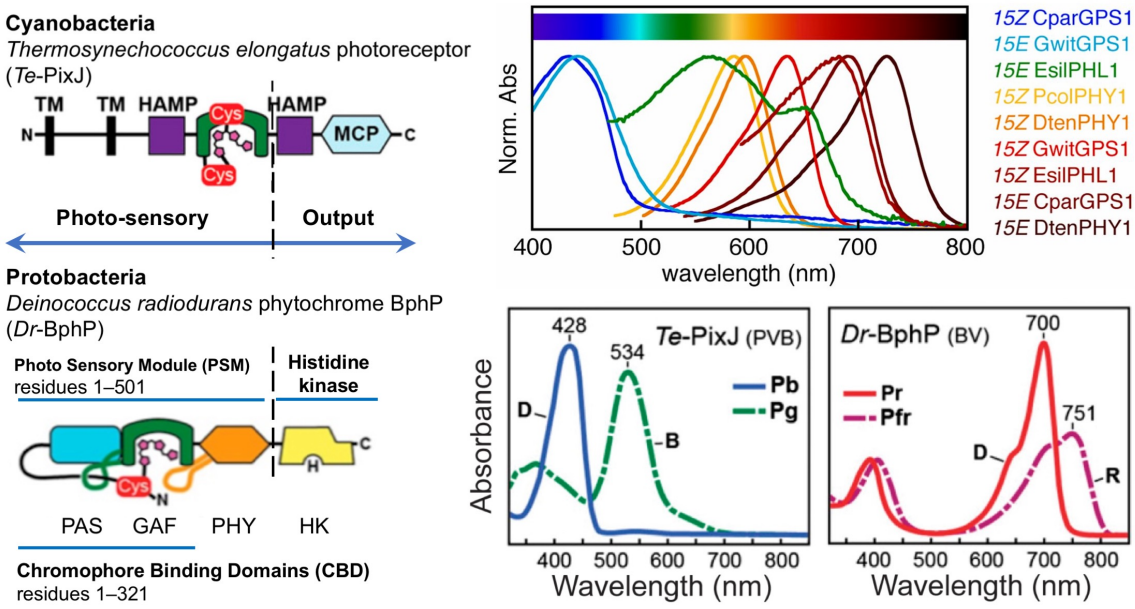

Figure 7.3: Protein domain organisation and spectral properties of two phytochrome photosensors
(top, right) Normalised absorption peaks for several algal phytochromes. (bottom, right) Absorption spectra of the dark-adapted (D) and photoactivated states after blue (B) or red (R) illumination of Te-*PixJ or* Dr-*BphP. (left) The domain architecture of two phytochromes; abbreviations are: TM, predicted transmembrane region; HAMP, histidine kinase/adenylyl cyclase/methyl binding protein/phosphatase; MCP methyl-accepting chemotaxis protein; PAS, Period/Arnt/Single-Minded; GAF, cGMP phosphodiesterase / adenylyl cyclase / FhlA doain with chromophore binding residues; PHY, phytochrome-specific region; HK, histidine kinase.*

*Left and lower right figures adapted with permission from E.S. Burgie and R.D. Vierstra, The Plant Cell **26** (12) 4568-4583 (2014) DOI: 10.1105/tpc.114.131623; Upper right figure reproduced from N.C. Rockwell et al. Proc. Natl. Acad. Sci. USA **111**, 3871-3876 Copyright (2018) National Academy of Sciences DOI: 10.1073/pnas.1401871111*

7.2.3 Photosystem II is a benchmark system

Photosystem II (PS-II) is a high-value, benchmark system for time-resolved SFX studies with results coming principally from three international teams of researchers in the USA, Asia, and Europe.[109,175,179-181,183-185,187,188] The enzyme is responsible for the "great oxidation event" approximately 2.4 billion years ago, that transformed the earth from an anaerobic reducing atmosphere to the O_2 rich and oxidising atmosphere today. PS-II is a large integral membrane protein expressed in all plant and most photosynthetic microorganisms. The protein uses four photons to catalyse the four electron oxidation of two water molecules that form one O_2 molecule plus four H^+ that help establish a proton gradient used for ATP generation by ATP synthase. The PS-II reaction is driven by visible light photons that initiate very rapid charge separation events (fs – ps), and much slower electron-transfer events (hundreds of ms) to reduce the quinone pool.

Thus, PS-II is an ideal system for time-resolved SFX studies; but the entire reaction cycle spans more than 12 orders of magnitude in time, which creates experimental challenges. A large collaborative group developed an on-demand, acoustic droplet ejection onto tape system (**Figure 7.4**).[109,111,113,114,185,189,190,241] It transports discrete nL droplets across a laser illumination platform before they reach the X-ray interaction region. This allows for multiple illumination/equilibration perturbations to advance the reaction cycle for time-resolved SFX experiments. An added benefit of the design is that the region between the droplet ejection and the X-ray interaction region can also be fitted with either an O_2 reaction chamber or a second pL droplet ejector system, both of which enable a wide range of mixing based time-resolved reactions.

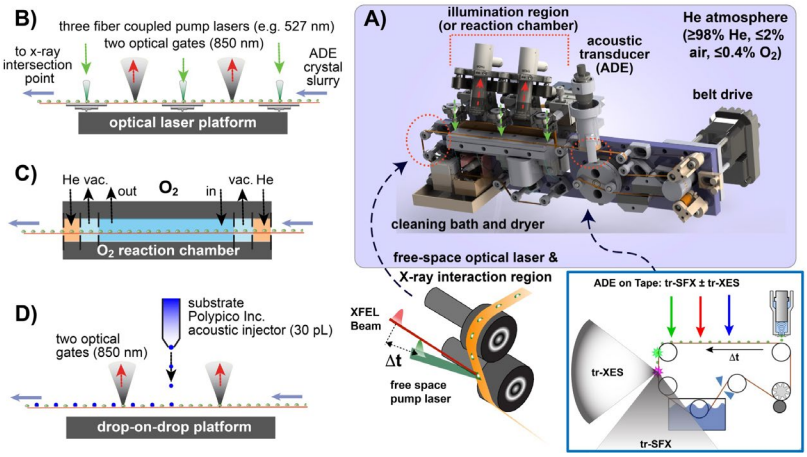

*Figure 7.4: Acoustic tape drive system for pump-probe time-resolved SFX and XES measurements of PS-II (A & B) and options for O_2 dependent reactions (C) or drop-on-drop ligand additions (D). See also Fuller et al (2017) Nature Methods **14**, 443-449.*

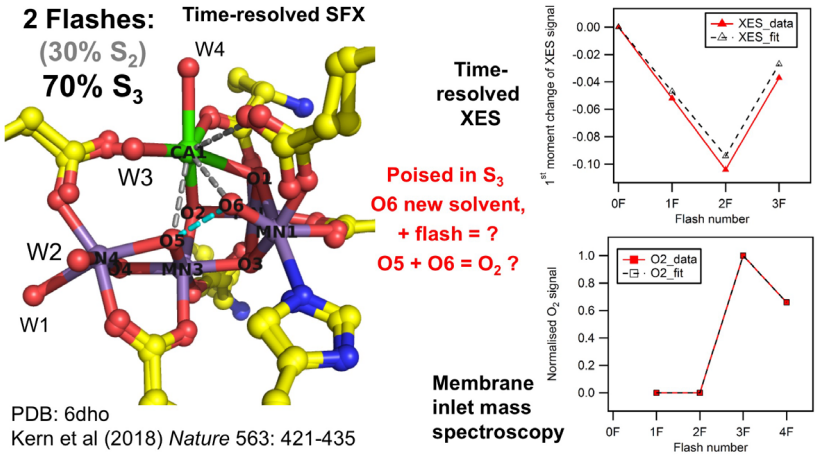

Figure 7.5: Correlated time-resolved SFX and XEX results from PS-II. (left) the 2.09 Å resolution atomic model for S3. (right, top) The first moment change of the Mn Kβ1,3 XES spectra from PS-II crystals obtained in situ simultaneously with SFX. (right, bottom) Flash-induced O_2 yield in crystal slurry as a function of flash number.

*Right top and bottom reproduced from J. Kern et al. "Structures of the intermediates of Kok's photosynthetic water oxidation clock", Nature **563**, 421–425 (2018), Springer Nature. DOI: 10.1038/s41586-018-0681-2*

O_2 bond formation within PS-II is catalysed by the oxygen evolving complex (OEC) that include a Mn_4O_5Ca cluster (**Figure 7.5**).[242,243] When a photon is absorbed by the P680 chromophore, it results in charge separation and electron transfer to the quinone site. The oxidised P680 is then reduced by the OEC, which advances one oxidation state with each photon absorption event. In the Kok cycle, the first photon promotes the S_1 to S_2 transition, the second photon S_2 to S_3, and the third photon from S_3 to S_4. The S_4 state catalyses the conversion of two water molecules into O_2 resulting in the S_0 state of the OEC. Absorption of a fourth photon produces the stable S_1 starting state.

The Mn atoms within the cluster act as a redox "buffer" and each oxidation state has a unique $K\beta_{1,3}$ X-ray emission spectrum (XES). Consequently, time-resolved XES collected simultaneously with time-resolved SFX provides complementary data on the electronic and atomic structures of the catalytic centre.[109,185,187-190,244] Groups working principally at the LCLS and LBNL developed methods to simultaneously collect time-resolved SFX data in the forward direction and time-resolved X-ray emission spectroscopy (XES) at 90°, from each sample and each X-ray pulse.[109,111, 112 ,185,186,188-190,244-246] Some of the results for PS-II are shown in **Figure 7.5** for the OEC poised in the S_3 state where µs time-resolved structures demonstrate motion of the Mn atoms and entry of a new solvent atom (label O6 in the image).[109] The atomic model is correlated with oxidation of the Mn atoms within the OEC and the O_2 generation assays from crystal slurries. Details for the time-resolved reaction that forms the O_2 molecule remain ill-defined; however, the deepest mechanistic insights will likely depend upon correlated studies and benefit from XFEL sources.

7.2.4 Caged compound and proteins

Light-driven strategies to initiate catalysis in systems that are not naturally light sensitive include: a) caged compounds, b) caged proteins, c) ligand exchange, or d) temperature jump methods.[182,247-263] Each of these must satisfy the requirements of high selectivity, high quantum yield and temporal resolution. To these ends, *o*-nitrobenzyl moieties are among the most common photocaging groups for substrates and amino acids, but their decaging photochemistry may not be as fast nor as clean as *p*-hydroxyphenacyl or coumarylmethyl derivatives. Caged substrates are either co-crystallised with the target macromollecule, or soaked into slurries of microcrystals. Incorporation of non-natural amino acids that convert a given protein into a caged protein is more difficult (e.g. **Figure 7.6**). Consequently, caged protein approaches typically include a computational evaluation stage, followed by protein translation using *amber* TAG codon-suppression methods, or post-translational modification strategies. The photo-active moiety is most often linked to thio, amino, carboxy or hydroxy groups of proteins or substrate ligands, and is then cleaved by irradiation with UV to visible light. Photo-cleavage of the caging group varies in rate (ps - µs) and quantum yield (<0.2 - 1), which then generates: *i)* authentic substrate in the active site vicinity, *ii)* a rapid pH shift, *iii)* a temperature jump, *iv)* removes an active site barrier and enables substrate binding, or *v)* eliminates a dynamic or conformational restraint required for catalysis. Ligand exchange methods include photolabile metal-CO or NO complexes that mimic a metal-O_2 intermediates in a reaction cycle. Photodissociation of the blocking diatomic molecules then allows for O_2 binding and the ensuing reaction. All of these methods are experiencing a resurgence of R&D activity and provide important opportunities for time-resolved structural biology at XFELs. Some of these techniques will require careful coordination of the timing between the visible light pump laser and the XFEL probe pulse.

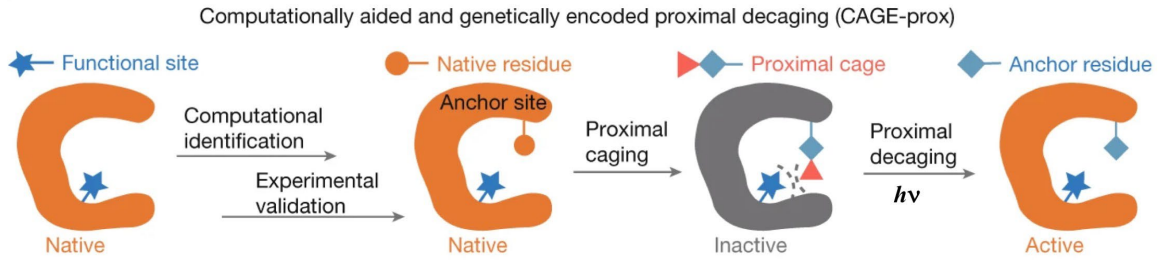

Figure 7.6: Schematic concept of the CAGE-prox strategy.
A proximal cage can be genetically incorporated at an anchor site in close proximity to the protein functional site for temporal blockage of its activity. Proximal decaging can lead to rapid rescue of protein functions, as long as the decaged anchor residue has negligible influence on protein activity.
Reprinted by permission from Springer Nature: J. Wang et al. Nature 569, 509–513. Copyright (2019) DOI: 10.1038/s41586-019-1188-1

7.2.5 Future directions

Time-resolved serial MX studies of light-activated proteins will continue to expand at synchrotrons and XFELs around the world. This R&D effort will benefit from hard X-rays with tight focus and XFEL pulse frequencies from kHz to MHz. A variety of illumination schemes must be well integrated into the sample delivery and data collection strategies. For instance, some systems will need fs time resolution, whereas other more complex dynamic process may require seconds to evolve. Moreover, short pulse duration visible laser illumination schemes should be complemented with longer exposure strategies, potentially from CW lasers and/or diodes with triggering. Since many chromophore containing proteins are radiation sensitive, XFELs offer clear advantages for obtaining diffraction data before deleterious effects destroy the samples. Data processing to provide near-to-real time analysis is critical and will burden computational resources.

A second opportunity for data analysis of stationary diffraction is the explicit retrieval of ultrafast population information through application of optical crystallography theory.[173,264] This is an important example that provides one of several strong cases for high-repetition rate and increased sensitivity of time resolved SFX.

Specifically, for all crystal classes of uniaxial and biaxial symmetries (trigonal, tetragonal, hexagonal, triclinic, monoclinic and ortho-rhrombic crystal classes) the resulting birefringence connects the orientation dependence of electric field decomposition to the explicit analysis of power density dependent population transfer. Inversion of an indexing matrix for a stationary diffraction image from time-resolved SFX data will allow a calculation of orthogonal field directions in the X-ray crystallo-graphic coordinate frame from solving Maxwell's polarised wave equations in anisotropic media (**Figure 7.7**). While this requires explicit knowledge of the intrinsic birefringence value and wavelength dependence depending on the point group symmetry, opportunities for

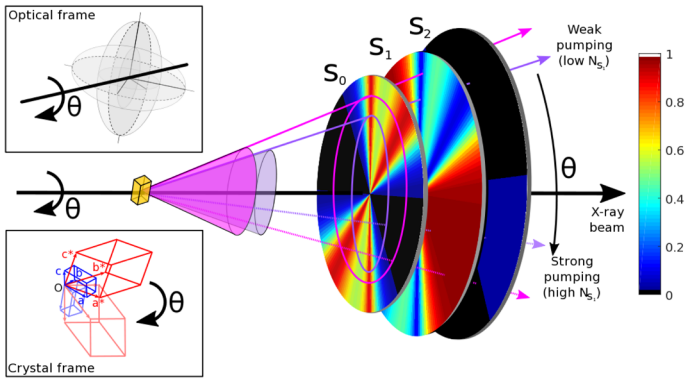

Figure 7.7: Illustration of the analysis of orientation dependence of photoinduced populations with reference to both the optical orientation and the X-ray crystallographic orientation.
Tracing a Debye-Scherrer ring in revolution, the polarisation directions are modified according to the solutions to Maxwell's polarized wave equations. Therefore, population transfer may be analysed radially in the detector plane, as illustrated with a physical calculation example for a uniaxial case.
*Figure reproduced with permission from C.D.M. Hutchison and J.J. van Thor, Phil. Trans. R. Soc. A. **377** 20170474 DOI: 10.1098/rsta.2017.0474*

population analysis specifically exploit the high repetition rate regime. With knowledge of linear and non-linear optical cross sections, the time-resolved SFX data can be separated in data bins according to the calculated photoselection of linear and non-linear population under intense femtosecond optical excitation. With currently available signal-to-noise and crystallographic statistics, time-resolved studies effectively average the full Debye-Scherrer range of individual reflections, while high repetition rate studies will separate the population difference that exist within (**Figure 7.7**). This provides additional compelling motivation for the development of high repetition rate, increased stability and high accuracy crystallography. It is evident that such applications will be possible and successful with the availability of many more stationary diffraction observations. A second compelling motivation for increased sensitivity is the control and observation of small amplitude coherent motion, discussed in **Section 7.4**.

7.3 Dynamic structural biology: Molecular movies of enzyme catalysis

Dynamic structural biology is as much a philosophy as a set of tools to collect as much data as possible, from every sample and every X-ray pulse, at physiological temperature and pressure, with an aim to create time-resolved molecular movies of macromolecules engaged in function. Time-resolved SFX studies exploiting mixing methods are generalisable and have significant potential for revealing the dynamics of enzyme catalysis in broad context across biology.

7.3.1 Introduction

The concept of dynamic structural biology is illustrated in **Figure 7.8** and links reaction dynamics with sample preparation, reaction triggering and data collection. Diffusion-triggered methods for time-resolved crystallography experiments were proposed in 2000 by the LCLS Scientific Advisory Committee, in 'First Scientific Experiments for LCLS' (http://www.slac.stanford.edu/pubs/slacreports/reports03/slac-r-611.pdf). [265]

> *Time-resolved structural studies on diffusive processes in crystalline enzymes are difficult due to problems with mixing enzyme and reactant in the crystal. With submicron-sized samples, the vast majority of solution techniques and methodologies will suddenly become available for time-resolved structural investigations at the LCLS.*

Macromolecular crystals are typically about 50% protein and 50% solvent, which is similar to the 65% fraction of water within human cells. Analyzing more than 36,000 enzymes listed in the *BRENDA* database reveals that *a)* the median turnover time for catalysis in solution is about 70 ms, *b)* more than 60% exhibiting a k_{cat} value between 1 – 100 s^{-1}, and *c)* enzymes catalyzing reactions related to secondary metabolism are typically 30-fold slower than those of central metabolism.[266-270] Dynamics play important but often ill-defined roles in enzyme catalysis.[269-278] A driving hypothesis for time-resolved serial MX is that because small molecule substrates diffuse relatively fast (*e.g.* molecules in water at 310 K: O_2 (32 g/mol) = 2 $\mu m^2/ms$; glycine (75 g/mole) = 1 $\mu m^2/ms$; glucose (180 g/mole) = 0.6 $\mu m^2/ms$; sucrose (342 g/mole) = 0.52 $\mu m^2/ms$), enzyme microcrystals will equilibrate with substrates faster than catalytic turnover.[174,279-287] This implies that time-resolved structural biology methods are generalisable when exploiting micron-size crystals or smaller. With 6,029,364 enzyme genes and tens of thousands of enzyme types listed in the KEGG databases (**Table 7.1**), there is an enormous reaction landscape to be explored. However, due to the very limited availability of XFEL beamtime, relatively few time-resolved SFX experiments exploiting mixing strategies have been conducted at fully commissioned XFEL facilities.[8,81,111,286,288-294]

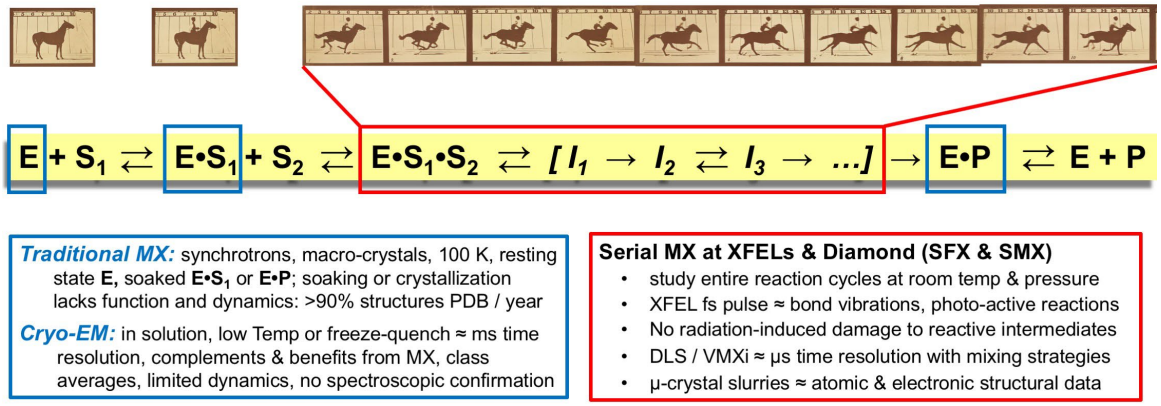

Figure 7.8: Concepts of time-resolved structural biology.
Snap-shots of data inspired by Muybridge's "horse in motion" photographs (Palo Alto CA, June 1878, 500 µs shutter speed). Stable, ground-state complexes are studied by traditional MX and cryo-EM methods, most often at 100 K. Time-resolved cryo-EM methods use freeze-quench techniques, typically with ms time resolution. Serial MX methods with microcrystals and monochromatic X-rays at synchrotrons or XFELs collect still diffraction images at room temperature with µs - fs exposures, respectively, at different Δt intervals after optical laser flash(es) or ligand mixing.

7.3.2 Mix-inject sample delivery for time-resolved SFX

To date, most time-resolved SFX studies that exploit mixing methods used liquid gas dynamic virtual nozzle (GDVN) style jets or microfluidic devices that have been developed by several groups.[81,82,101,102,174,286,288-297] For the majority of cases, GDVNs typically achieve sample injection speeds of 10 – 30 m s^{-1} and are suitable for 10 – 120 Hz repetition rate XFEL sources. Many of these mixing-injectors are slow and need on the order of seconds to fully mix substrate with crystals. Other types of devices mix on the ms time scale, but require high-dilution ratios to infuse substrate into the crystal slurry stream. These types consume large amounts of substrate or ligand and dilute the crystal concentration, which also reduces the overall SFX data collection rates. All of the GDVN nozzle methods are prone to clogging or freezing when used in vacuum chambers and benefit from cleaning between samples.

For MHz sources, sample injection speeds need to be on the order of 50 – 100 m s^{-1} so that fresh material is presented to each XFEL pulse.[99,176,298-301] Mixing injectors that produce such high jet velocities must have very small orifices and therefore can only accommodate microcrystals. This matches the desire to use less than ~3 µm crystals and is consistent with rapid equilibration of ligands throughout the crystal. These constraints also impact GDVN nozzle fabrication. For instance, a recent example developed for MHz data collection at the European XFEL used a high-end 3D printer (Nanoscribe GmbH) and two-photon stereolithography methods to achieve free-form geometries with submicron precision.[101] Devices like those illustrated in **Figure 7.9** produce 50 – 225 µm jet lengths, diameters as low as 536 ± 35 nm with a liquid flow rate of 2.4 ± 0.12 µl min^{-1} and a gas flow rate of 22.5 ± 0.2 mg min^{-1}. At the SPB/SFX instrument at the European XFEL, a similar design with a gas and liquid orifice size of 60 and 50 µm diameter, respectively, was used to inject microcrystals of up to 6 to 8 µm in size at velocities of up to 100 m s^{-1}.[300,301] The delay timepoint(s) achievable for high velocity mix-inject jets is principally a function of the flow rate and the distance the sample-ligand mixture travels to the nozzle exit; the time of flight to the beam will only be ~ 1 – 3 µs and thus very short compared to most enzyme reaction times (average turnover time of ~ 70 ms).

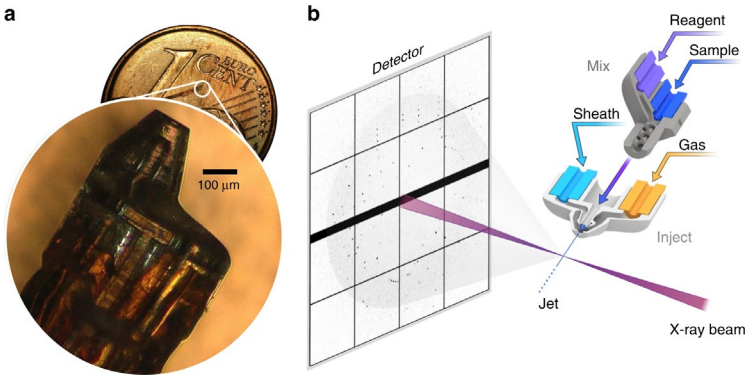

Figure 7.9: A microfluidic device for time-resolved SFX. ***a)*** *Through micro-3D-printing Knoška et al fabricate microfluidic devices of a few 100 µm in size. Magnified view of a nozzle placed on a 1 cent coin for scale reference.* ***b)*** *This technique can realise integrated nozzle assemblies to jet protein crystal suspension into the X-ray interaction region for diffractive imaging.*

Figure reproduced from J. Knoska et al. Nat. Comms. ***11****, 657 (2020) under the terms of the Creative Commons Attribution 4.0 International License.*

7.3.3 '*Multimessenger techniques*' help reduce ambiguity in time-resolved SFX experiments

Time-resolved SFX that is correlated with time-resolved XES has been used extensively to study PS-II.[109,111,185-190,246] This strategy provides data relevant to the electronic and atomic structures of metal centres. For these types of experiment, it is important to evaluate the impact of the XEFL pulse intensity and duration upon the metal centre since the measurement itself will alter the electronic structure of the centre. Under some circumstances non-linear excitation processes may disturb the spectroscopic signature of the metalloenzyme without significantly altering the recorded diffraction pattern.

The acoustic tape drive system described above can also be used for mixing-based studies from metalloenzyme reactions, including those that react with O_2 (see **Figure 7.4**). For example, iron-dependent enzymes are ubiquitous in biology, but it is difficult to study oxygen-Fe intermediates by traditional, synchrotron-based MX methods, because their reactivity also makes them very sensitive to photoreduction by the X-ray beam. In many cases an Fe(IV)=O intermediate is produced in the reaction cycle; therefore, it is also important to include X-ray emission spectroscopy to help differentiate it from Fe(II)–OH_2, and Fe(III)–OH species. The electron density maps for these three moieties are nearly identical except at extraordinarily high resolution. These types of compound are also very sensitive to X-ray radiation-induced artifacts, but the spectroscopic signatures are very different. This strategy provides critical correlations between atomic and electronic structures (especially first row transition metal centres) from the same sample and X-ray pulse. For instance, this also represents an opportunity to include time-resolved XES measurements into the time-resolved SFX data processing pipelines so that only diffraction patterns that also exhibit the appropriate spectroscopic signature are merged together into a timepoint dataset. Such a strategy will provide more confidence in the electron density map interpretation and in the resulting atomic models deposited to the PDB that are released to the whole structural biology community.

The electronic structure of a metal centre is an essential factor in reactivity and is profoundly influenced by its first and second shell coordination geometry, as well as the local electrostatic environment.[302-305] X-ray absorption spectroscopy (XAS) techniques complement crystallography, especially the analysis of the X-ray absorption near-edge structure (XANES) and the extended X-ray absorption fine structure (EXAFS) regions of the spectrum. The XANES portion provides insights into the oxidation state and coordination geometry, whereas XAFS region provides accurate measurements of metal-metal and metal-ligand distances. Indeed, the metric parameters that come from fits to the XAFS spectral region are often far more accurate than the errors in crystallographic methods will allow.

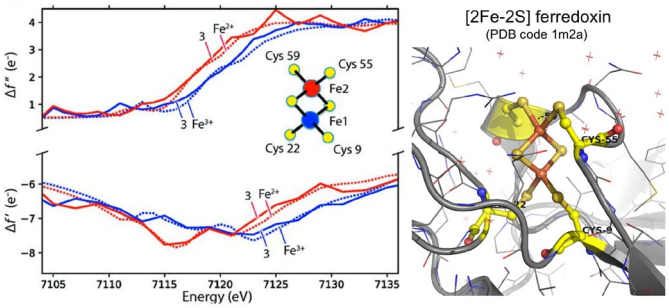

Figure 7.10: Spatially resolved anomalous dispersion (SPREAD) and crystal structure enable redox assignment to metal ions.

(left) Simulated anomalous scattering curves for the two iron centres converge to the ground truth showing that the oxidation state difference between Fe^{2+} and Fe^{3+} is clearly revealed by the refined 3-macrocycle models. (right) The 1.5 Å resolution crystal structure of the [2Fe-2S] ferredoxin from Aquifex aeolicus reveals the atomic position, but not the redox status of the metal atoms.

*Left-hand figure reproduced from N.K. Sauter et al. Acta Cryst. D **76**, 176-192 (2020) under the terms of the Creative Commons Attribution (CC-BY) License. DOI: 10.1107/S2059798320000418*

Nearly all types of spectroscopic measurement, including XES and XAS, record a signal from all of the particular metal atoms in the sample, whether they are ordered in the crystal lattice and/or enzyme active site (likely catalytically relevant) or disordered in the surrounding mother liquor (probably not mechanistically important). Thus, spectral overlap can be a challenge and is particularly difficult for enzymes that contain multinuclear metal clusters wherein each metal atom may have a discreet redox and electronic structure (**Figure 7.10**). An emerging method to resolve this ambiguity is to measure the XAS edge in the crystallographic diffraction data; a technique referred to as **spatially-resolved anomalous dispersion (SPREAD)**.[306-309] The method typically includes a series of complete diffraction datasets collected at several monochromatic energies across the K-absorption edge of the particular metal of interest. The electronic structure is then assigned to each individual metal centre by refining the wavelength-dependent anomalous correction parameters in the datasets. This data collection strategy has been attempted at LCLS beamtime using seeded beam and SASE mode; and the preliminary results suggest that it is possible. In the meantime, recent theoretical calculations using 50,000 – 100,000 simulated diffraction patterns with *nanoBragg* demonstrate that SASE-based XFEL pulses with a 30 eV bandpass are suitable for analysis by SPREAD analysis of the [2Fe:2S] reduced ferredoxin containing an Fe(III)-Fe(II) centre.[306] The simulations also indicate that the incident spectrum for each XFEL pulse must also be included in the analysis.[310] Furthermore, radial streaks are observed in Bragg reflections collected with a long crystal to detector distance and derive from the combined effects of the broad XFEL bandpass, crystal mosaicity, and energy-dependent structure factors.[311]

In parallel and complementary to XFEL efforts, time-resolved MX methods are also under development at synchrotron facilities, especially those that provide pink-beam and microfocus capabilites.[141,142,144,312] At XFEL or synchrotron facilities, the reactions in crystals must be synchronised throughout all unit cells in order to observe high resolution diffraction from reaction cycle intermediates. For mixing strategies this will depend upon viscosity and the size of the substrate molecules traversing channels within the crystal lattice and macromolecules themselves.[313-315] Therefore, best practices dictate that when possible scientists should measure reactivity in the solid state and from more than one space group with different lattice packing. The homogeneity of the microcrystal slurry is also an important optimisation parameter for mixing-based time-resolved SFX experiments.[316,317]

7.3.4 Future directions

Time-resolved serial MX using nano- to micro-crystals and triggered with substrate diffusion is potentially generalisable across all of biochemistry. Therefore, it will continue to expand at synchrotrons and XFELs around the world. This effort will benefit from hard X-rays with tight focus and XFEL pulse frequencies from kHz to MHz. The quality and homogeneity of the crystal slurry with respect to size and morphology impact diffusion of substrate(s) into the crystal lattice and enzyme active sites – this is an active area of R&D by several groups. Datasets with two or more complementary types of information will continue to yield deeper mechanistic insights on more

metalloenzyme systems. Spatially-resolved anomalous dispersion (SPREAD) analysis shows promise for assigning redox status to individual metal atoms from highly-redundant SFX datasets collected with SASE mode,[306] and should be further evaluated with seeded and monochromatic XFEL methods. Data processing to provide near-to-real time analysis is critical and will burden computational resources.

Electron diffraction (ED) also generates high resolution atomic models from slurries of microcrystals (see **Appendix 2**); however, the crystal thickness is restricted to several hundred nanometres because electrons interact with matter more strongly than X-rays.[43,44,46,47] Sub-micron size samples reduce problems associated with inelastic scatter, multiple scattering events, or simply diminishing returns of information. A pulsed electron source, coupled with sub-micron size crystals that are injected into the interaction regions, is a perfect match for time-resolved dynamic structural biology; provided that various challenges are overcome.[318-320] Many of these issues are synergistic with time-resolved SFX at XFELs, and include sample delivery with mixing strategies and data processing pipelines with near-real time feedback.

7.4 Controlling and measuring nuclear and electronic coherence within biological systems

Some photo-induced biochemical processes are so fast that nuclear and electronic quantum coherence are believed to have a role. XFELs are offering a new incisive window into this behaviour.

7.4.1 Introduction

The current and future abilities for ultrafast protein X-ray crystallography hold great potential for the development of methods and new approaches to interrogate protein dynamics. The field of ultrafast spectroscopy has traditionally used indirect methods for observation of structural dynamics, such as spectral shift analysis. Direct ultrafast crystal structure determination and electron density dynamics will allow many advances in structural dynamics that are not directly possible with spectroscopy. The development of time-resolved SFX at XFEL facilities has enabled the detection of nuclear coherent motions with application of ultrafast pump-probe techniques. For such applications, access to the ultrafast time scale is necessary and needs the ability to combine a femtosecond optical laser excitation pump with an X-ray probe from an XFEL pulse at ångstrom wavelength, femtosecond duration and delay time(s), and high X-ray photon flux.

A number of successful time-resolved protein X-ray crystallography experiments have been reported which included delays in the sub-picosecond timescale that includes vibrational coherence dynamics.[192,197,211] For time-resolved macromolecular crystallography, the combination of large unit cell dimensions, light atoms having small cross-section, and often small isomorphous differences, dictate the X-ray source requirements.[97,98,175,179,301,321,322] The photoinduced differences for protein crystals are analysed in real space from the electron density differences obtained by inverse Fourier transform, rather than on the level of $\Delta I/I$ of individual Bragg diffraction spots.[323] This requires strict isomorphism, which is maintained on ultrafast timescale in protein crystals.

Because the atomic cross-section, which dominates the valence electron density contribution, determines the measurements of protein structural dynamics by X-ray crystallography, it is rapidly dominated by displacements and order-disorder transitions through the analysis of isomorphous differences. It is well established from the ultrafast vibrational spectroscopy field that the typical dephasing timescale measured for protein samples is on the order of $\sim 1-2$ ps depending on the system of interest.[324-328] The ultrafast time-resolved SFX of proteins thus must include contributions from coherent vibrational dynamics.[173,323] This is a relatively new experimental ability that has been demonstrated in recent years, but has opened up a new field of application. Electronic coherence properties may not be readily available from X-ray crystallography, but a new type of application can be proposed to apply phase-locked two-pulse femtosecond excitation for time-resolved SFX experiments that would in principle provide a frequency correlation measurement from the coherence time alteration. [173]

7.4.2 'Blending' ultrafast spectroscopy and ultrafast time-resolved SFX

The emerging area of ultrafast time-resolved SFX can exploit and build on decades of ultrafast vibrational spectroscopy research and coherence theory.[173,323] A close analogy can be made between the technique of impulsive Raman spectroscopy, which is an ultrafast time-domain technique, and the ultrafast time-resolved SFX observation.[324,326] The comparison additionally identifies clear and obvious opportunities for future development of time-resolved SFX, particularly with emphasis of growing the experimental bandwidth and improving the signal-to-noise ratio. Impulsive Raman spectroscopy can achieve observation of vibrational wavepacket motion at frequencies exceeding 3000 cm^{-1} employing few-femtosecond laser pulses.[329] The detection in transmission resolves the four-wave mixing signals which modulate the population dynamics signals with typically very small amplitudes, from the transition probability modification of coherent motion in the ground and excited state. In the pump-probe time-resolved SFX experiment the creation of ground and excited state wavepackets are

population and displacement driven, respectively, and result from the field-dipole interaction with rank of two, which is sufficient to create interstate coherence.[173,330] Their properties have been evaluated on the basis of theoretical considerations.[173] In the case of protein crystallography, which lacks the atomic and subatomic information, charge density analysis is typically not available and detection of electron density differences are primarily caused by atomic displacements. This places limits on the frequency range of nuclear coherence that can be expected to contribute to the measurements, judged from the calculation of displacements and reduced masses for harmonic frequency calculations of proteins.[323] In addition, the Huang-Rhys factors, as well as anharmonicities, must be evaluated in order to analyse their real-space displacements. Therefore, currently the explicit measurement of fingerprint modes in the ~800 – 1800 cm^{-1} frequency range, which have few pm characteristic displacements, are currently not accessible. Similarly, high frequency hydrogen stretching modes (3000 – 3500 cm^{-1}) are not accessible for reasons of small displacement and experimental bandwidth, and additionally from the small cross-section of hydrogen.

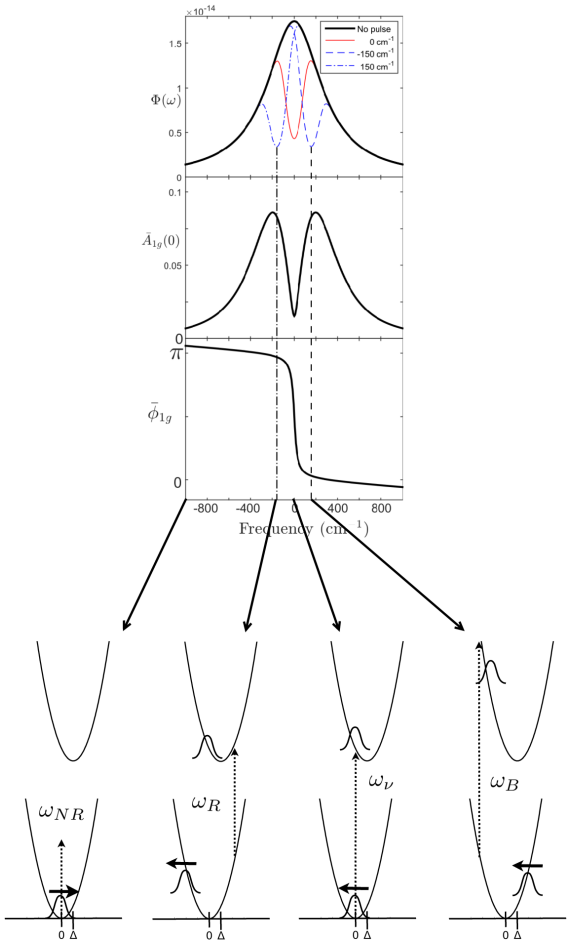

Figure 7.11: Illustration of the lineshape theory treatment of ground and excited state vibrational coherence calculation using additional wavepacket representations.
Laser excitation of a homogeneously broadened line $\Phi(\omega)$ with carrier frequency below (ω_R), on (ω_v), or above (ω_B) resonance creates a total impulsive ground state coherence A_{1g} with phase φ_{1g}. The resulting ground coherence is shown for the high temperature case (300 K).

*Figure reproduced from J.J. van Thor, Struct. Dyn. **6**, 050901 (2019) under the terms of the Creative Commons Attribution (CC-BY) License. DOI: 10.1063/1.5110685*

The Raman spectroscopy literature includes ample evidence that the study of fingerprint modes is particularly desirable for the functional analysis of protein dynamics. In contrast, current time-resolved SFX capabilities include measurements that can only be strongly dominated by low frequency modes (below few-hundred wavenumbers) which have large displacement as the result of significant associated reduced mass.[326,329] An additional reason that the frequency range is limited to low frequency modes is a physical limit to the crystallographic signal-to-noise that arises from the current sub-KHz repetition rate and source and detector capabilities. In this regime it is shown that very intense femtosecond optical excitation is a requirement, or otherwise no light induced differences will be resolved. Practically, this requires the stretching of optical pulses in the range of 100 – 200 fs. A detailed discussion of non-linear optical transformation in this regime has been presented previously.[2,173, 323,331,332]

7.4.3 Future directions

The case for development of increased experimental bandwidth and signal-to-noise is particularly compelling. Since the experimental bandwidth for pump-probe application of SFX is currently dominated by the optical pulse rather than the XFEL pulse duration, increased sensitivity of the pump-induced difference measurements will allow improvement of the time resolution. This would be achieved through increased repetition rate of a hard X-ray FEL light source, as well as the area detector frame-rate to achieve orders of magnitude improvement in data rate. In addition, the improvement

of source stability will significantly contribute. The latter includes pulse intensity, carrier frequency, spectral distribution and bandwidth stabilisation on a shot-to-shot basis. Such future capabilities will increase the ability to resolve ground and excited state coherent vibrational motion at frequencies higher than the current $\sim$300 cm^{-1} limit, by time-resolved SFX from crystallographic coordinates directly (**Figure 7.11**). The novel capabilities will significantly develop results from decades of ultrafast Raman spectroscopy methods and theory.

For ultrafast diffraction studies, a compelling case is made for precise control of XFEL pulse parameters and stability. Time-resolved crystallography studies require highly accurate determination of structure factor amplitudes and their temporal differences.[173,216,264,323] Beyond the formal limit of the time resolution in pump-probe applications, a proposal for chirped-pulse experiments has evaluated an alternative for extracting and analysing ultrafast dynamics.[333] A broadband energy-chirped hard X-ray pulse has been demonstrated at the SwissFEL with up to 4% bandwidth.[334-336] Characteristic parameters for analysing the time dependence of stationary protein diffraction with energy-chirped pulses have been reported.[333] Depending on crystal mosaic spread, convergence and recordable resolution, individual reflections are expected to spend at least $\approx$ 50 attoseconds and up to $\approx$ 8 femtoseconds in reflecting condition. The maximum theoretical time resolution achievable to be on the order of 50 – 200 as from the instantaneous bandwidth of a chirped SASE pulse. High repetition rate XFEL experiments with high flux will maximise the achievable time resolution and potentially allow an optical excitation shorter than the sweep of a chirped XFEL pulse, and coinciding within its temporal envelope, such that internal 'dark' structure factor referencing can be extracted.[333] This demonstrates very promising experimental approaches for dynamical studies using energy-chirped XFEL diffraction. Since the high resolution information is associated with the highest time resolution, small molecule experiments that allow recording of sub-atomic resolution, providing transition charge density information[173] are of particular interest, in addition to protein dynamics studies.

7.5 Capturing biological function in single molecules

If enough diffraction patterns from single particles at random orientations can be collected with a sufficient signal-to-noise ratio, then the ab initio three-dimensional electron density for the molecule can be calculated. Current theoretical calculations and experiments suggest that high repetition rate XFELs and efficient sample delivery methods will generate the > 100,000 images needed to produce approximately 3 Å resolution models. Thus, the potential for near atomic resolution of macromolecular dynamics under physiological conditions remains a driver for XFEL-based coherent diffraction imaging of single particles.

7.5.1 Introduction

Among the important science drivers for the development of the LCLS was the potential to observe structures of macromolecules from close to physiological conditions, without requiring crystals.[265] The concepts of single particle imaging (SPI) were supported by timely theoretical considerations by Hadju and Neutze *et al*.[279,337,338] However, as discussed in the sections above, SFX methods succeed "easily" because they depend upon collecting Bragg reflections from nano- to micron-size crystals; in essence a strongly diffracting sample with data originating from a strong, well-focused X-ray beam. In a way, Gati *et al.* and Tetreau *et al.* approached the SPI goal by using extremely small crystals that consist of only few thousand unit cells.[9,10] Based upon their analysis, Gati *et al.* conclude, "It should be possible, under ideal experimental conditions, to obtain data from protein crystals with only 100 unit cells in volume [and] that single-molecule imaging of individual biomolecules could almost be within reach."

These SPI efforts are complementary to fluctuation X-ray scattering (FXS), an emerging experimental technique in which X-ray solution scattering data are collected from particles in solution using XFELs.[61] Traditional synchrotron-based solution scattering methods, such as SAXS/WAXS, suffer from a very low data-to-parameter ratio because the exposure time is much longer the particle rotation rate. This produces an angularly isotropic scattering signal. In contrast, each SAXS/WAXS measurement at an XFEL is collected much faster than the particle rotational diffusion times. As a result, the signal contains authentic angular fluctuations and consequently orders of magnitude more information when extracted by calculating the angular correlations in the dataset. With brighter and faster XFEL facilities, it will be possible to collect much larger volumes of higher-quality correlation data outside the water window, thereby extending the resolution of the data, and allowing high-throughput studies on smaller biomolecules at sub-nanometre resolution.

7.5.2 The single particle imaging (SPI) initiative

Single particle imaging, in contrast to SFX, demands that one measure a weak signal from a strong beam that is further complicated or obscured by any and all other scattering structures in the beam. Experience and recent theoretical calculations demonstrate that more images of high quality are always better.[339] Moreover, newly emerging manifold-based machine learning algorithms when applied to large datasets are able to reveal the rare events and dynamic changes exercised by the sample.[340]

Some recent progress in SPI has exploited the high repetition rate of the European XFEL[341,342]. For example, gold nanoparticles in two morphologies and sizes (octahedra of 30 and 40 nm sizes; cubes of 42 and 17 nm sizes) were used to generate SPI datasets with more than 564,000 images to more than 1,430,000 images[343]. These were derived from "good" hits of the X-ray beam on the different high-Z particles and of sufficient quality to reproduce models to between 21 to 53 Å resolution. Sample delivery remains a critically important challenge for low-Z particles in biology, wherein aerosol injectors inspired by mass spectroscopy show promise.[344-346] Nevertheless, as the European XFEL delivers 3520 pulses per second with images collected with the AGIPD and assuming a 1% hit ratio, then scientists should anticipate more than 1.5 million images in a single 12-hour shift. Even more data will come faster at MHz XFELs with 10 – 20 kHz detectors.

The challenges have been extreme and originating from many perspectives, ranging from sample delivery all the way through to data processing. To address the challenges, an international collaboration, the SPI initiative,[347,348] formed to coordinate activities amongst groups. For SPI experiments, the typical LCLS pulse energy is about 2 - 5 mJ, which at the CXI instrument equals about 1.78 to 4.46 x 10^{12} photons/pulse at 7.0 keV, and at the AMO instrument equals 7.80 x 10^{12} to 1.95 x 10^{13} photons/pulse at 1.6 keV. To date, at the LCLS they have achieved about 6 Å resolution with hard X-rays at the CXI instrument, and about 10 Å resolution with soft X-rays at the AMO instrument. Thus, the potential to study macromolecular dynamics in near-physiological conditions, and to capture (ultrafast) biological, chemical and physical processes remains a grand challenge for XFEL facilities.

As alluded to in **Appendix 2**, cryo-EM has overtaken single particle X-ray imaging as the dominant method for macromolecular structure determination from non-crystalline, frozen hydrated samples. Nevertheless, Chapman states:[3]

> *The promise of more photons per atom recorded in a diffraction pattern than electrons per atom contributing to an electron micrograph may enable diffraction measurements of single molecules, although challenges remain.*

Some of the challenges include:

- developing methods to introduce homogenous macromolecules into the interaction region, with high and sustainable overlap between sample stream and X-ray pulses
- delivering high enough X-ray intensity in a tightly focused beam (need > 10^{14} photons μm^{-2} of 4 – 10 keV photons focused into tens of nm^{-2} size)
- eliminating background scattering, or limiting it to no more than about 100 photon counts per diffraction pattern
- delivering a stream of reproducible and uncontaminated particles (perhaps at variable delay time(s) after initiating a reaction via mixing or pump-probe strategies)
- acquiring tens of thousands to millions of patterns per dataset
- interpreting the noisy diffraction data.

In **Section 3.4** it was pointed out that the density of the data sampling must be high enough that the rarely occupied high-energy states of the system are present within the dataset. Moreover, the exposure time must be short enough to capture the various stages of these conformational changes without time averaging, scrambling or blurring. If these criteria are met, then the data techniques can in principle retrieve the structural dynamics of these critical events at high atomic and temporal resolution.

Thus, XFEL facility repetition rate and detector frame rate both impact the quality and quantity of SPI data that can be collected in a given time (**Table 7.3**). To date, the main limitation has been achieving adequate and sustainable sample hit rates. However, to realise higher resolution single particle imaging, the field needs faster detectors with lower noise such that it is easier to differentiate single scattered photons from the sample compared to those from the various sources of background noise.

		AMO / LCLS	CXI / LCLS	TXI / LCLS-II	SPB/SFX / Eu.XFEL	BL2 / SACLA	SwissFEL
Detector		pnCCD	CSPAD [b]	ePix10k	AGIPD [d]	MPCCD	JUNGFRAU [f]
Pixel Size (μm^{-2})		75 x 75	110 x 110	100 x 100	200 x 200	50 x 50	75 x 75
Single Photon Sensitivity		yes	yes	yes	yes	yes [e]	yes
Quantum Efficiency		> 80% @ 0.3~12 keV	~97% @ 8 keV	~85% @ 5 keV	> 80% @ 0.3~25 keV	~ 85% @ 5.5 keV	Up to 85% @ 12 keV
Dynamic Range		10^3 @ 2 keV	3.5 x 10^2 @ 8 keV	~ 10^4 @ 8 keV	> 10^4 @ 12.5 keV	1.2 x 10^3 @ 6 keV	>10^4 @ 12 keV
Noise (e^-)		20 / 2 [a]	300	120	265	300	100
Pulse Rate (kHz)		0.12	0.12	0.48 / 2~4 / 10~20 [c]	4500	0.06	0.1~2.4

Taken from Sun, Z.B., Fan, J.D., Li, H.Y., and Jiang, H.D. (2018) Current Status of Single Particle Imaging with X-ray Lasers, *Appl Sci-Basel 8* doi: ARTN 132; 10.3390/app8010132.

[a] For pnCCD, the readout noise is 20 e^- for low gain, 2 e^- for high gain.

[b] The dynamic range and ASIC noise for CSPAD under high gain mode are 350 photons @ 8 keV and 300 e^- r.m.s. For low gain mode, they're 2700 photons @ 8 keV and 1000 e^- r.m.s.

[c] The current version is about 480 Hz. For digital domain multiplexing, the frame rate will be 2~4 kHz. For fast ADCs, the frame rate will be 10~20 kHz.

[d] See D. Greiffenberg, *J. Instrum.* 2012, **7**, C0110 and A. Allahgholi, et al *J. Instrum.* 2015, **10**, C01023 for information.

[e] Keeping the single photon detection capability for X-ray photon energy higher than 6 keV.

[f] See J.H. Jungmann-Smith, et al *J. Synchrotron Radiat.* 2016, **23**, 385–394 for detailed information.

Table 7.3: Main detector characteristics used at several XFEL facilities

Thus, a faster X-ray source does not necessarily translate into a faster detector. Indeed, a 100 kHz detector is a distant R&D objective, and yet MHz sources are available now.

7.5.3 Future directions

Significant challenges still need to be overcome, but solutions to many of these are on the horizon. The overall quality of the SPI reconstruction depends heavily upon the number of diffraction patterns in the dataset. Assuming realistic conditions for a) experimental sample delivery conditions, b) X-ray fluences in a well-focused beam at 4 – 10 keV, c) MHz repetition rate sources with at least kHz or faster detectors, then scientists anticipate collecting tens of millions of snapshots during a single productive shift. Theoretical calculations estimate that at least 66,000 to > 500,000 images are needed to generate an electron density map to about 3 Å resolution.[339]

7.6 Conclusion and summary

Biology is a large and high-impact area at all synchrotron and XFEL facilities. About 50% of the total user community at Diamond focuses on life sciences; although they frequently rely upon highly automated data collection strategies and use a smaller overall fraction of Diamond beamlines. The number of important biological targets is staggering, as illustrated by the KEGG databases statistics listed in **Table 7.1**. Moreover, new and novel threats to human health are always emerging. For example, proteins from the COVID-19 virus were recently used for cryo-EM structures and MX-based ligand screening at the XChem facility at Diamond Light Source.[349-358] Those are prime examples of high-throughput data collection and analysis that is enabled by mature and optimised facilities.

Structure-based drug discovery and fragment-based screening are major strategies used by all pharmaceutical companies to bring new drugs to market. And yet, most new drugs fail because they lack efficacy. These strategies often rely upon ground-state crystal structures determined at 100 K. An emerging alternative, that de-risks new therapeutic avenues, is to study the whole dynamic reaction cycle, which will reveal and mediate changes that are focused upon particular function. Indeed, XChem is very likely to expand capabilities to room-temperature complexes or reaction cycles inspired by serial MX approaches.

To meet these challenges, there is strong consensus in the UK, and the wider life science community, that anything that can be done to improve XFEL access and training would be very useful. To these ends, there is a need in the intermediate term to widen the applications of XFELs in life sciences especially by:

- Making SFX and time-resolved SFX methods more accessible to smaller groups through automation in sample delivery and data processing
- Coordinating training of expertise, building capacity, and engagement with the XFEL Hub at Diamond by the UK community, to make best use of the five existing XFEL facilities
- Establishing a XFEL Doctoral Training Centre for studying biological dynamics should be a *Priority Theme* for EPSRC/BBSRC, as well as providing short-term training courses
- Increasing industry involvement – dynamics of enzymes and protein-ligand interactions will have major implications in drug discovery.

High impact life science is being generated by XFELs. The current situation has been reached after only 10 years of operation, with most of that time being restricted to a couple of low repetition rate facilities. Over the next 10 years we must anticipate further advances in capability, understanding and techniques that may open new doors to go far beyond the opportunities outlined above. The impact of a UK XFEL facility optimised for high repetition rate data collection would present a very significant future capability and capacity increase, that would doubtless be of substantial benefit to the UK life sciences community.

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8. Opportunities for UK Industry, Society and Defence

Measurement of processes at their essential length and time scales is immensely important to advancing technology, as well as science. Key sectors of industry and manufacturing, such as engineering, advanced materials, chemicals, medicines/pharmaceuticals, consumer/household products, food, automotive, energy, agriculture and electronics, will substantially benefit from these advances, with societal impact in healthcare, environment, transport and defence.

The case presented so far has focused on science opportunities, but there are strong connections to technology and the broader application of the methods and knowledge afforded by XFEL science. As discussed in **Section 2**, the capability to measure matter at the quantum scales of both *time* and *space* inevitably connects to advanced technologies and manufacturing. Another example is the Chemicals sector, which has an annual UK turnover of £60 billion, and generates a £5 billion trade surplus. The entire UK manufacturing sector relies on chemistry to generate £600 billion of annual aggregate sales to the economy. The chemistry-using industries' growth strategy[1] aims to increase their gross value-added (GVA) contribution from £195 billion to £300 billion by 2030, building on £200 billion of market opportunities.[2] Just the subset of consumer products, chemical and pharmaceutical manufacturing represents an annual GVA over £65 billion.[3] Any deep understanding of materials and matter, including their genesis, transformations and performance under conditions of applications, opens up new innovation routes to high value-added products.

In this section we will explicitly address some of the opportunities we foresee for UK Industry, Society and Defence. This survey is not complete, as we anticipate myriad industrial and societal impacts, but the ones we highlight are hopefully illustrative of the broad potential. We start by discussing the impact of a UK XFEL in the context of the Grand Challenges identified in the UK government's Industrial Strategy, and connect also to the emerging UKRI themes. We then examine a sample of areas we see as having highest potential impact: shocked materials, crystallisation and nucleation in soft materials, dynamic processes in advanced manufacturing, nuclear materials and nuclear security using gamma ray probes, and life sciences in pharma and bio-tech. So the cases we explore include:

- The behaviour of shocked materials relevant to diverse applications, ranging from turbines to explosives, and feeding into UK engineering and defence
- The fundamental understanding and measurement capabilities to track the formation of solid phases from liquids, which is relevant to situations ranging from food processing to lubrication of engines to drug discovery and medicines manufacturing
- Development of a quantitative understanding of mechanisms in advanced manufacturing in order to optimise processes such as friction welding, additive manufacturing and laser processing, and even to develop new concepts in X-ray lithography for beyond the next generation chip manufacture
- Harnessing gamma rays for applications to the UK nuclear industry and nuclear security
- Building on SFX structural biology and time-resolved methods to use insights from life sciences to address the most pressing questions in drug discovery, human health and agriculture.

We briefly highlight the importance to society of having the full range of science tools in our armoury with two examples (that are discussed further in this case), for (a) rapid deployment in a crisis such as the current one caused by the COVID-19 virus, and for (b) a large-scale, long-term challenge like achieving net zero carbon emissions.

Finally, we present a broad-brush economic impact analysis, which should be seen as the starting point for a fuller Business Case analysis if the project moves to the next stage.

8.1 Addressing national strategic priorities

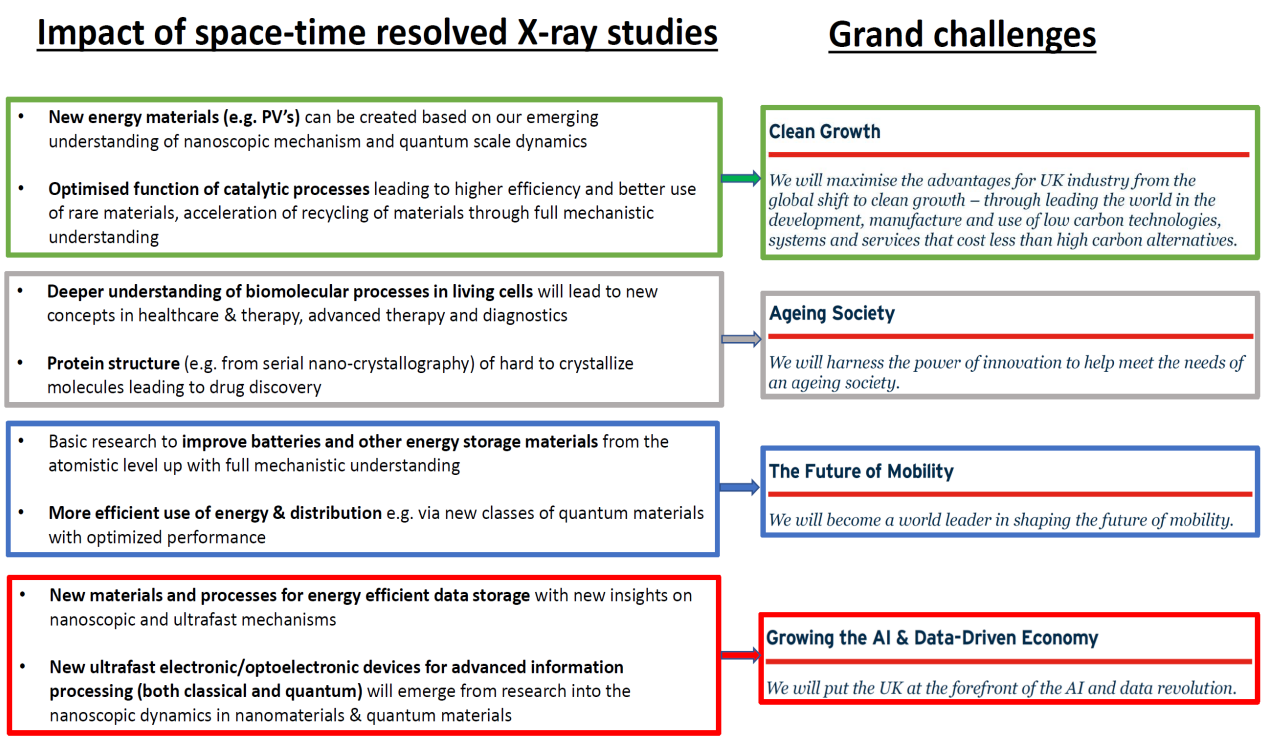
A UK XFEL will impact science across all disciplines and be an underpinning resource for future technologies in vital sectors, such as healthcare, defence and green energy. It is thus in a prime position to address UK government strategic priorities. It will boost skills training in essential areas and cultivate STEM subjects across the nation.

8.1.1 Mapping to scientific and technological strategic priorities

It is clear that the scientific, technological and economic impact of a UK XFEL will be broad, far-reaching and directly resonant with the ambitions of the UK government's Industrial Strategy. The evidence for this comes from the analysis already conducted in this science case (see **Sections 3 - 7** and especially **Sections 8.2 - 8.6**), and from the experience of the five major FEL facilities already operating, where national strategic priorities were implicitly part of their justification. Within UKRI it will enable developments across the science portfolio and is well matched to the key UKRI priorities, for example:

- *Advancing Technology* – through quantum scale structural dynamics
- *Healthcare* – through structural biology and conformational mapping
- *Frontiers of Knowledge* – through access to brightest ultrafast X-ray pulses
- *Net Zero Growth* – through unravelling photo-chemical/catalytic cycles
- *Economic Strengths* – through skills and research outcomes.

Box 8.1: Mapping to the Grand Challenges identified in the UK government's Industrial Strategy



A summary of the connection between the science and technology facilitated by the combined high space-time resolution enabled by ultrafast X-rays with the Grand Challenges identified in the UK government's Industrial Strategy is shown in **Box 8.1**.

In the **energy sector**, a UK XFEL will provide new insight into complex light harvesting materials, solar-driven carbon capture and production of biofuels, stimulating new, low-cost energy generation and storage technologies (see **Section 6.3**), which are essential for ensuring our future growth is clean and carbon neutral. Aligned to this, a UK XFEL will aid the development of **green technologies**, new

catalysts for example (**Section 6.4**), to ensure clean industrial processes and sustainable industrial chemistry using Earth-abundant elements. It will enable the development of new and **advanced materials** with direct applicability to industry, mobility, digital manufacturing (**Section 5**), nuclear energy (**Section 3.6** and this section, **8**) and the defence community (**Section 4**). It will contribute critical new understanding at the nanoscopic level to **energy efficient fast data storage** that is crucial for the expansion of the data driven economy (**Sections 5.2** and **6.3**). In the **life sciences**, it will permit the mapping of conformational pathways for biomolecules (**Section 3.4**) and aid the understanding of the chemistry of complex molecular processes (**Sections 6** and **7**) that govern life and disease – well beyond what is possible using current approaches. Advanced imaging capabilities will, when applied to structural biology (**Section 7**), aid the discovery of advanced drugs and new antibiotics essential to address the **challenges of an ageing society**.

8.1.2 Building a skilled workforce

This investment will naturally support advanced **STEM skills** development in the UK workforce, both locally where the machine is built and nationally within its user community. Many thousands of **scientists, engineers, computer scientists, technicians and apprentices** will pass through the UK XFEL over its life-cycle. This will seed the skills base with essential capabilities – addressing everything from the challenges of the civil engineering required for such a precision machine, through to the handling of the vast quantities of data such a machine will generate. Extracting maximum value from these datasets will stimulate advances in artificial intelligence, as already demonstrated at LCLS.

The facility activities will support skills development in the UK workforce, particularly in key areas of high value to the economy:

- Advanced electronics
- Control systems
- Optics (from THz to hard X-ray)
- Hardware for handling unprecedented data volumes
- AI and machine-learning to operate the facility and manage the huge data flow
- Advanced modelling of materials at the quantum scale
- Precision engineering and advanced manufacturing
- Detector technologies
- Cryo-technology
- Carbon neutral operation of large infrastructure.

It is anticipated that a UK XFEL will operate its own apprenticeship schemes and that although a large fraction will be initially retained as employees following training, many will, in the fullness of time, move out into the wider workforce, taking with them their skills. STFC's existing large facilities employ 131 apprentices across 15 diverse disciplines from Mechanical Engineering to Project Management and IT Infrastructure. As well as providing specialist technical training on a world-leading facility, apprenticeship and graduate schemes should provide core, transferable training in areas such as communication skills, team-working and leadership. Likewise, undergraduate degree, masters and PhD level trained staff will also be required in large numbers in the facility. Some of their training can be associated with activities at the facility, with existing facilities such as ISIS, Diamond and the CLF providing around 20,000 training days per year for university PhD students. The typically rapid churn associated with such staff will also efficiently seed the wider workforce, benefiting the industrial, defence, finance, medical and university sectors.

There are large opportunities for technical and research internships, some leading to permanent jobs, and this has been used at LCLS to deliberately increase diversity in the workforce by recruiting from local high schools with a strong emphasis on women, as well as ethnic and social minorities.

As a user facility, thousands of scientists will use the machine each year and the benefit of the investment will, as a result, be nationally distributed. There will be opportunities to directly influence diversity within it and the broader scientific community, especially via choice of location and stimulus of the user base. And, of course, such a machine will act as a beacon for UK science internationally, attracting the best and the brightest to the UK, and championing the UK's place in the world.

8.1.3 Intellectual property and enterprise

The user research of the facility is likely to play a prominent role in innovation and discovery, leading to the creation of intellectual property, as has been the experience of the large-scale facilities at STFC's national laboratories. IP can be either generated by (and reside with) the home university and investigator, or by the laboratory through research and development programmes into end-station capabilities, procedures and sample preparation. Hence there is also considerable scope for IP generation with the ownership residing primarily with the facility. This IP can be further exploited via Proof of Concept Funding, technology transfer into spin out companies and licensing technology and skills transfer to industry. By the end of 2017-2018 FY, STFC's national labs had generated over 200 patents and supported the creation of 19 spin-out companies. These companies have raised over £78M in third-party investment and created over 230 jobs.

Experience has shown (Daresbury, Diamond, DESY, SLAC) that a cluster of new businesses grow up around large facilities, driven by entrepreneurs moving out from the facility to develop their own ideas and by others coming from further afield to position themselves as suppliers of equipment, consumables and services or simply to benefit from the locally-created high-tech ecology. It is no accident that Sand Hill Road, Menlo Park is the centre of Silicon Valley's massive venture capital industry – down the road from the Stanford Campus and on the street where the main gate to SLAC is located. The combined UK Research and Innovation campuses of Daresbury and Harwell were established in order to co-locate academia, industry and commercial organisations with cutting-edge large-scale facilities. Together these are home to over 300 companies, employing some 6,500 people. Provision of space on or close to the site to establish a science park and potential small business incubator support services could be a very beneficial additional investment.

8.1.4 Outreach and promoting public understanding of science

As a state-of-the art facility, conducting cutting-edge scientific and technological research across many disciplines, UK XFEL will be a focus for activities centred around outreach and public understanding. Every effort should be made to involve the public (young people especially) with the science programmes of the facility, in order to both encourage people into STEM subjects and to convey the benefits of scientific research to the UK's wider economy and society generally.

It can have a large programme of outreach to schools, both regionally and nationally, and host visitor facilities to ensure visits are informative, stimulating and fun. Equivalent large facilities based at Harwell typically host around 3000 school visitors per year, with many more students reached by facility staff visiting schools in the local area and nationwide. It can thus be a very concrete and high-profile recruiter and promoter of STEM subjects in school-age children, with feedback frequently showing that outreach events with primary and secondary school students boosts future interest in pursuing STEM subjects by 28 – 44% depending on school age. The possibility of internships (see above) should also be used to ensure the growth of a diverse training programme starting with school age young people. Older members of the public should not be overlooked and an appropriate visitor centre to cater for their interests must also be a priority. Facility open days could also be used to promote the broad range of cutting-edge science technological development that a UK XFEL would undertake and emphasise the significant impact of such work on wider society. The Harwell Open Week in 2015, which included large facilities such as Diamond, ISIS and the CLF, welcomed some 16,000 visitors who got an opportunity to go behind-the-scenes and meet the many scientists, engineers and technologists who work there.

So that UK XFEL can play a full role in promoting the sciences and technology, it is important that it be as visually striking as possible, both from the ground and from the air. In that way it can be an iconic symbol for the sciences that propagate through the media, newspapers and social media and into the public consciousness.

8.1.5 Selected areas of industrial and societal Impact

Throughout this case we have endeavoured to highlight important areas of application in the science and technology opportunities discussed. In the remainder of this section we look at selected areas of special relevance to industry and society where an XFEL will have significant impact. These are: Properties of shocked materials for engineering and defence (**Section 8.2**); Nucleation, solidification and crystallization in soft-matter (**Section 8.3**); Dynamic processes in additive manufacturing, combustion, laser machining and photolithography (**Section 8.4**); Nuclear security and materials in nuclear industry (**Section 8.5**); and Industrial inspirations from deeper insights into biology: pharma to clean energy (**Section 8.6**). We conclude with an overview of anticipated economic benefits associated with construction and operation of a UK XFEL (**Section 8.7**).

We have already received support and undertaken discussions with a range of companies (e.g. Rolls Royce, ASML, Infineum) and industry-facing research organisations (e.g. the Henry Royce Institute). So far, we have found strong support for the new infrastructure from all consultations. As an example of the support we have received, we add the following statement released by AWE:

> *AWE support the case for a UK XFEL because in addition to answering fundamental scientific questions, it enables experiments which support the assurance of the UK's nuclear deterrent in a UK facility. Furthermore, the possibility of a unique, inverse Compton scattering gamma source in the UK would open up significant opportunities for national nuclear security applications.*

In the next stages of this project we anticipate a fuller engagement with industry and to more fully define the wider societal benefits.

8.2 Properties of shocked materials for engineering and defence

The properties of materials under shock loading conditions are both of fundamental scientific interest and important across a wide range of engineering domains, from aerospace through to defence.[4] XFEL technology is driving rapid progress in the underpinning science in this area, and represents an accelerated pathway for the manufacturing and qualification of the next generation of engineering materials and processes.

8.2.1 New understanding of materials response at multiple scales

With the advent of high-brilliance, femtosecond duration hard X-ray FEL sources, an understanding of the rich array of the underlying microscopic processes which govern the macroscopic response of heterogenous engineering-relevant materials to rapid loading and unloading is now within reach. The routes by which materials deform and respond to external stresses are complex, as they depend not only on the underlying structure (the particular crystal phase), but also on the evolution of the population of defects within the system that mediate plastic flow. Given that defect density itself is strain and strain-rate dependent, a comprehensive understanding of material strength, and response to impact, all the way from the microscale of the lattice dynamics to the macroscale of system response on engineering length-scales remains largely elusive. XFELs are starting to have significant impact in bridging this important gap in our knowledge, with large angle diffraction techniques (that measure structure, lattice spacings and orientations) and small angle scattering (which can measure void evolution) combining to provide hitherto inaccessible insights into the pertinent physics on the atomic scale. Furthermore, the femtosecond nature of the X-ray beam ensures that all measurements are free from motional blurring, with the diffraction signals being recorded on a timescale even shorter than that of the oscillation period of atomic vibrations.

Importantly, these measurements can also now be augmented with computer simulations on precisely the same length scales (several microns) and timescales (spanning picoseconds to nanoseconds). Multi-million (or billion) atom molecular dynamics simulations can now be performed, from which simulated diffraction patterns (linking the micro and macro properties) can be extracted and compared with experiment. The fidelity of these simulations itself relies on a good knowledge of the interatomic potentials between atoms, but here a feedback loop engendered by a comparison of experimental results and theoretical prediction will play an increasingly important role in verifying the development of the potentials themselves.

An understanding of material flow under rapid impact is important in both fundamental and applied sciences. At the fundamental level, impact phenomena have played an important part in the evolution and modification of our own and other planets, and the resultant flow of material can be seen at the extremes of the macroscale in geological features such as the Chicxulub crater in Mexico, or are readily apparent from a casual glance upwards at our moon. In the applied sciences arena, the applications in the defence industry are obvious, whilst the response of matter to high velocity impact is also important in design of protection for satellites, the space station, future space habitats and their electronics from impact with high velocity grains of dust of even few micron dimension.[5] What is perhaps less known is that laser-ablative impact treatment of materials via so-called ‘laser-peening’ can induce residual compressive stresses in the surface of materials, which can retard crack initiation and growth, thus increasing the fatigue strength of important engineering components.[6,7] However, very little in situ experimental data exists on the underpinning evolution of the defect landscape and microstructure during this process, and enhanced physical understanding could well lead to improved material-properties outcomes.

Progress to date in using XFELs to reveal lattice-level information has already been spectacular. As noted above, both structure and strain rate play important roles in the dynamic response of materials. At extremely high strain rates, it had long been predicted that the initial response of a material would

be purely elastic until its ultimate yield strength limit (hundreds of times greater than realised in practice) was reached, as even pre-existing defects and dislocations would not have time to relieve plastic flow under high-velocity impact for the first few tens of picoseconds.[8] Such 'super-elastic' response, reaching the ultimate compressive strength of a pure crystal but within an initially defective sample, has been demonstrated and observed via such femtosecond diffraction in copper samples.[9] It is also now known that some of the most complex phase transitions that a single element can undergo can be induced and observed within samples compressed for just a few nanoseconds, with the transitions in both scandium[10] and antimony[11] exhibiting the change from regular crystalline matter to a complex incommensurate 'host-guest' phase under rapid compression.

The opportunity to study the relative importance of plasticity mechanisms within a given sample has also been demonstrated. The femtosecond pulses of X-rays not only afford information on structure and lattice spacing, but also on the orientation of the lattice planes during deformation, allowing us to distinguish between the amount of impact damage internalised as twinning, as opposed to direct dislocation motion – such proof of principle experiments have been conducted in tantalum samples.[12] Importantly, the defective nature of the sample was monitored during the release of the shock pressure from the sample, and the microstructural changes induced by the shock (that is to say the density of both twins and lattice rotation due to other defects) was shown to be largely annihilated upon rarefaction:[13] the state of the sample (in terms of its microstructure) during impact is very different from that which one would observe in a sample that was recovered and analysed after the event itself. This observation highlights the imperative of performing such in situ real-time experiments that X-ray lasers make possible.

In other experiments, small-angle X-ray scattering has been used to diagnose the details of cavitation underlying spall failure and excellent agreement was obtained with molecular dynamics simulations.[14] These experiments typically employ a sample thickness on the order of a few microns and X-ray photon energy on the order of 10 keV, although an FEL with higher photon energies would allow study of thicker samples approaching engineering length scales, as well as provide for greater exploration of reciprocal space, which would be especially useful in elucidating complex structures formed under shock and ramp compression.

At the mesoscale, the relationship between material response and microstructural parameters, such as grain size distribution and orientation (texture), must be understood. With this understanding, the opportunity for new engineering materials with designed-in properties arises.[15] Molecular dynamics calculations of the role of individual and idealised collections of grains under impact has started to be studied,[16] affording opportunities for transferring the lessons learnt from the modelling to the design of specific FEL-based experiments to learn about grain-grain interactions, and the dependence of material response on grain size as well as texture.

It should be noted that the methods described above are not limited to metals and metal alloys but are applicable to a wide range of engineering materials which include polymers, ceramics and their composites. These systems too have outstanding fundamental questions surrounding their responses to impact loading. Explosives for example, are heterogeneous systems containing grains, pores and cracks,[17] and consequently exhibit complex physical phenomena over multiple length scales[18] (see **Figure 8.1**) which underpin performance and safety. Recently, XFEL experiments employing explosive samples have studied phase changes under shock compression and the role of micron-scale inhomogeneities in detonation initiation.[19]

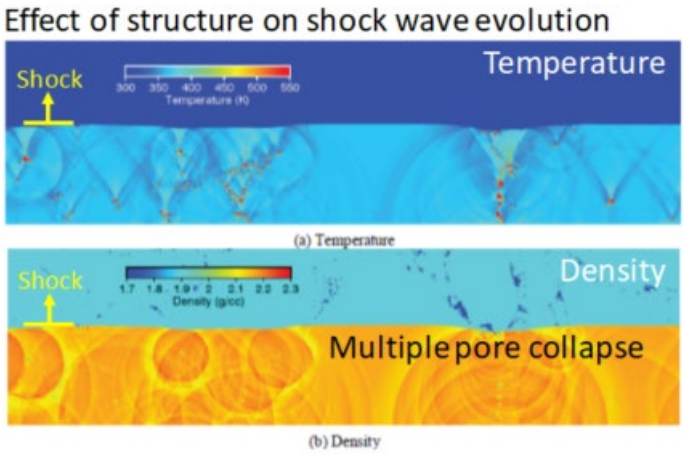


Figure 8.1: Shock propagation in an explosive (from Ref. [17])

(Ministry of Defence © Crown Owned Copyright 2020/AWE)

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At the macroscale, the sample size is representative of components used in applications, and so engineering processes can be studied and optimised. These include (as noted above) laser peening,[6,7] foreign object damage to turbine blades,[20] laser powder additive manufacturing (AM) (reference,[21] and **Section 8.3**) and explosive initiators.[22] At the typical operating scale of several millimetres, X-ray energies up to ~100 keV are required for single-shot imaging and X-ray diffraction studies.[23] Although these processes occur on relatively slow timescales (< 100 ns), the fast time resolution offered by an XFEL can help to elucidate dynamics occurring very early in time.

8.2.2 Future Opportunities

In order to access the high-pressure shock conditions of interest in samples with thickness of a few microns, an optical driver is necessary, and this would also be a requirement for a UK XFEL facility. The newly developed UK DiPOLE laser system,[24] for example, can access multi-MBar pressures at a 10 Hz repetition rate (**Section 4.1**) and we anticipate increasing both energy and repetition rate. Such a laser would also find application in laser peening and particle impact studies (in the latter case by using the laser to propel a particle off a surface towards a target), but a higher energy (multi-kJ) system would allow us to access even higher pressures, taking us into the regime of relevance for planetary science. Opportunities exist for overlap with interests in a laser-driven compression facility (see **Section 4.4**).

For studies at longer length-scales and loading durations, a bespoke precision impact system, analogous to a single- or multiple-stage gas gun, will be required. Such a system will enable sustained loading over several 10s of nanoseconds in samples ranging from 10s – 100s of micrometres, thereby bridging the gap between crystal physics and the mesoscale, permitting study of cumulative deformation and damage processes such as adiabatic shear, spallation, jetting and fragmentation, and potentially the study of samples of shape and geometry that are analogous to those in real engineering applications. We note that the coupling of such a mechanical driver to a short-pulse X-ray source has already been proven at the Advanced Photon Source synchrotron,[25] albeit with X-ray pulses of much longer duration (100 ps) than can be produced at a FEL. As we move up in length scale and Z, the photon energies required will increase, and further studies of the flux of the higher harmonics of any FEL design will need to be taken into consideration. Finally, we note that as well as shock drivers specifically tailored for the FEL, this branch of science will also require state-of-the-art secondary shock diagnostics to understand the states generated, including, velocimetry, pyrometry, and imaging. For other applications, specialised equipment is required – such as a process replicator for Additive Manufacturing studies.[21]

8.3 Nucleation, solidification and crystallisation in soft-matter

Consumer product, chemical and pharmaceutical manufacturing are part of the chemistry-using industries and make a gross value-added (GVA) annual contribution of more than £65 billion to the UK economy.[3] The properties of organic crystalline solids in particular present enormous industrial R&D challenges, because key transformations are poorly understood at the molecular level. These include, for example, nucleation, crystal growth, dissolution and agglomeration. For decades, the science of these phenomena has been slow due to the experimental challenges of localised spatiotemporally rare events. The time and imaging capabilities afforded by XFEL scattering and spectroscopies now open up a realistic perspective to progress in this area.

Control of phase separations, such as nucleation, solidification and crystallisation, is essential for the manufacture of formulated products across virtually all industry sectors involving chemicals, for example medicines, foods, detergents, lubricants and agrochemicals. Practical bottlenecks in chemical product design and manufacture arise from the challenging properties of crystalline solids. Especially for organic materials, crystal structure, size, morphology, mechanical properties, solubility and surface properties of particles combine to set up complex manufacturing demands. Predictive design of products would need a deep understanding of key transformations (e.g. nucleation, crystal growth, dissolution, agglomeration) and of the impact of typical process conditions (temperature, pressure, composition, mixing). The associated complex multiscale transformations start through localised rare events at the molecular level that are insufficiently understood to permit the establishment of predictive relationships between structure and performance.

For decades, scientific progress has been slow due to the experimental challenges of localised spatiotemporally rare events. For example, the molecular nature of self-assembled nuclei of new phases, their dynamics and rates of formation remain uncertain.[26-28] Nucleation events create structure from the molecular and nanoscale all the way up to the colloidal domain that are characterised by complex interfacial energetics involving electrostatics, covalent and non-covalent interactions. It has recently been recognised, through time-resolved synchrotron X-ray phase contrast imaging, that a seemingly simple process such as nucleation in antisolvent crystallisation can follow self-assembly paths that are fundamentally different from the hypothetical nucleation processes used in conventional modelling (**Figure 8.2**).[29]

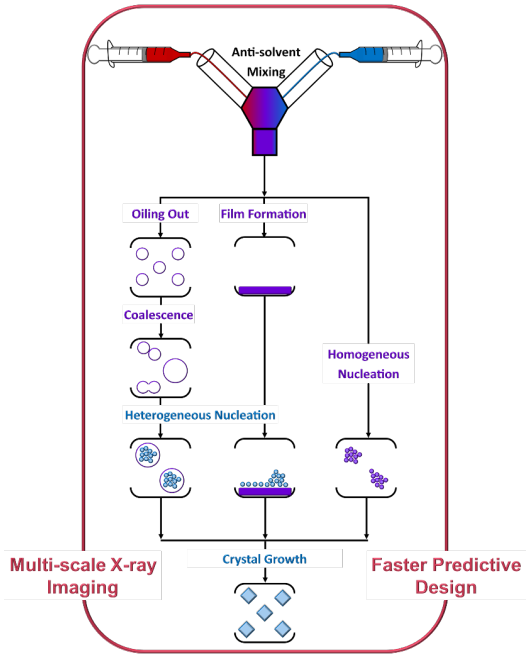

Figure 8.2: Alternative nucleation and crystal growth pathways in anti-solvent crystallisation process.[29]

Crystallisation from homogeneous solution is believed to start with a nucleus (or nuclei) of interacting solute molecules, which initiate phase-separation.[27,28,30] Classical Nucleation Theory (CNT), widely used in describing these phenomena,[26,31] poses that in supersaturated solutions nuclei of a critical size are formed, whose structure matches that of the final product.[32,33] Dynamic equilibria (fluctuations) in supersaturated phases create unstable small clusters ('sub-critical nuclei') and other transient aggregates.[31,33] The experimental challenge is to detect the relevant nucleation event(s) at the nanoscale events, which are stochastic in time and in space. It is now also believed that alternative

molecular pathways to CNT exist (**Figure 8.3**). Localisation of homogeneous events by, e.g. use of liquid liquid interfaces[34] and small volume electron microscopy imaging,[35] are a viable way forward, but they also interfere with the nucleation dynamics through interface formation or radiolysis.

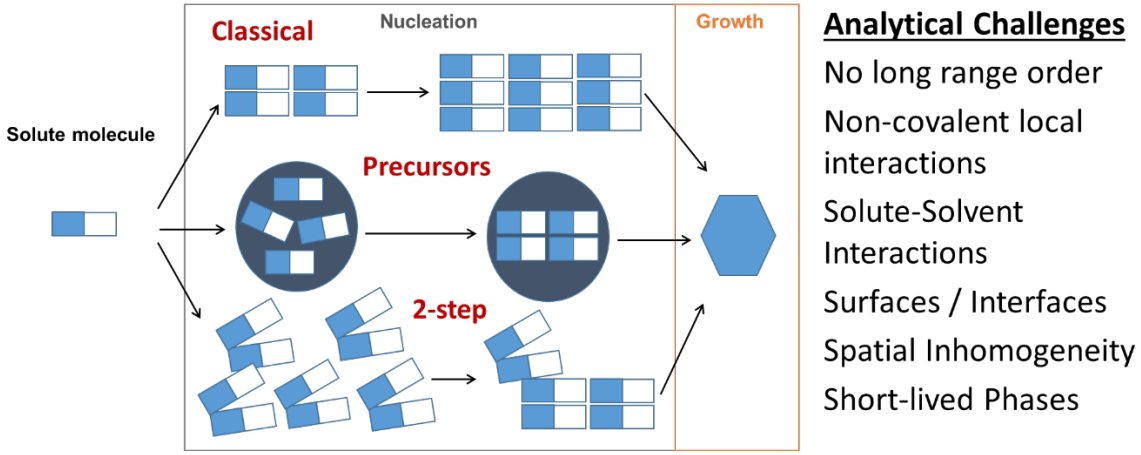

Figure 8.3: Alternatives to classical nucleation theory pathways in crystallisation, and the associated experimental science challenges to nucleation science.[27,36]

XFEL scattering and spectroscopy methodologies will for the first time provide the required multiscale combination of time and spatial resolution to overcome these challenges, through high experiment repetition rate, multi-detector probing and molecular level imaging taking snapshots of small sample volumes under nucleation conditions. Advanced synchrotron and neutron characterisation, with core level spectroscopies, PDF (see also **Section 5.5**), scattering and diffraction methods, has indicated that, in combination with modelling, these techniques can provide the required deep structural understanding. For taking this field of hybrid fundamental and applied research in small molecule crystallography forward, we can take cues from the already fledgling field of time-resolved serial femtosecond crystallography (SFX) of proteins. Indeed, SFX studies of enzyme reactions are one of the major use cases for XFELs in life science (see **Section 7**).[37-41] Just as in applied particle research, R&D efforts are significantly impacted by crystal size and size-distribution within the slurry (homogeneity).[41-44] The principal reason is because the fraction of macromolecules on the surface of a crystal increases with smaller crystals. Consider, for example, a cubic crystal with 150 Å unit cell dimensions (**Figure 8.4**), which is a typical size for enzymes. A slurry comprised of 1 µm crystals will have just under 10% of the unit cells on the exterior layer of each crystal, but the exterior surface layer of 0.3 µm crystals includes 30% of the unit cells. Substrates must diffuse throughout the mother liquor and the microcrystals to initiate enzyme reactions. Macromolecular crystals are about 50% solvent/ mother liquor and 50% protein.[45-48] Enzymes on the surface of the crystal will bind substrates faster than those buried inside. Typical substrate molecules diffuse at roughly 1 μm^2 μs^{-1} and the rate depends upon viscosity as well as the size, shape and electrostatics of the intermolecular solve channels within the crystal lattice.[49-54] Diffusion through micron-size crystals is significantly faster than the average 70 ms reaction time for enzyme catalysis. A variety of mix and inject sample delivery methods are available and there is significant R&D activity in this area.[52-58] Therefore, time-resolved SFX is generalisable; however, cleaner results will be derived from more homogenous microcrystal slurries.

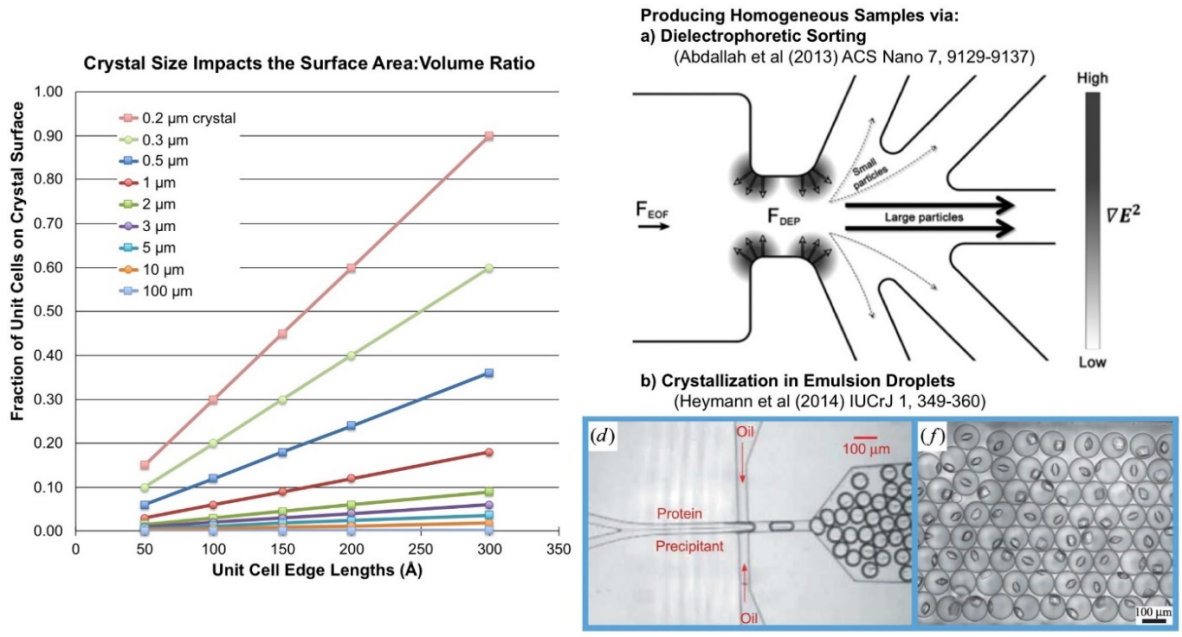

Figure 8.4: (Left) The fraction of unit cells on the surface of a crystal increases with smaller crystal size. (Right) Some methods to produce uniform slurries of microcrystal that are suitable for time-resolved SFX studies.

*Top Right (a) reprinted with permission from B.G. Abdallah et al. ACS Nano **7**, 9129-9137. Copyright (2013) American Chemical Society. DOI: 10.1021/nn403760q; Bottom Right (b) reproduced from M. Heymann et al. IUCrJ **1**, 349-360 (2014) under the terms of the Creative Commons Attribution International License. DOI: 10.1107/S2052252514016960*

The influences of the homogeneity of the slurry, crystal size, morphology, lattice packing and solvent content upon the reaction rates have not been quantified. These should be measured for each system of interest and include more than one space group and/or crystal morphology whenever possible. For example, the ratio of surface area to volume changes as a function of crystal size and becomes pronounced in samples of submicron crystals composed of macromolecules in large unit cells (cf. **Section 7**). This may impact the overall k_{cat} measured from a slurry, especially if the molecules on the outside catalyse reactions with a different rate than those buried within the interior. If so, this suggests that lattice constraints may impact the reaction of interest, which may be alleviated in an alternative space group with different crystal packing. To date, microcrystal slurries are often grown in batch mode with relatively few constraints that do not always produce homogenous results. Therefore, heterogeneous microcrystal slurries can be filtered through pores of known size and/or sorted with microfluidic methods and dielectrophoresis (DEP) focusing.[59-61] In contrast, producing homogenous slurries of microcrystals often benefits from the use of microfluidic methods to grow individual crystals of predefined dimensions based upon nucleation in nL volume drops encapsulated in oil.[62] Using the SFX approach we can therefore realistically hope to also unravel sequences of events in the nucleation and crystal growth processes in small molecule systems. Moreover, we can build on a rich existing knowledge transfer network in the field of small molecule particle science, including an engrained culture of industrial collaborations, exemplified by the EPSRC CMAC Hub, which brings seven UK universities together with dozens of companies, including Tier-1 partners AstraZeneca, Bayer, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, Roche and Takeda. These existing dissemination and collaboration relationships can be built on seamlessly for creating economic impact.

Finally, going beyond studies of supramolecular interactions in small molecule crystallisation, femtosecond X-ray scattering also offers opportunities to study the dynamics in more complex systems, including self-assembly of larger molecules, for example in peptide and protein folding.[63-65] Peptide and protein *mis-folding* into amyloid structures, such as fibrils, is well established as the origin of Alzheimer's disease,[66] but amyloidosis is now believed to be associated with other pathological conditions, for example Parkinson's disease.[67] A fundamental challenge to progress is polymorphism,

which can be overcome using an ultrafast X-ray diffraction imaging approach that provides information on individual fibrils. In a recent study, graphene was used as a support, realising low background scattering from the support.[65] Using nanofocused femtosecond X-ray pulses, diffraction from amyloid protofibrils was obtained with resolution down to 2.4 Å in single diffraction patterns. The ability to focus on fibril dynamics with high spatiotemporal resolution could open new technological developments towards rapid point-of-care diagnosis as well as therapeutics.

8.4 Dynamic processes in additive manufacturing, combustion, laser machining and photolithography

Various advanced technologies vital to the manufacturing base, including friction welding, additive manufacturing and laser machining, require an understanding of microstructural phenomena frequently occurring at fast timescales. XFELs offer probing capabilities that surpass the current state-of-the-art and allow these processes to be followed from milliseconds to sub-picosecond timescales. Soft X-ray/extreme UV pulses of high brightness from a high repetition rate XFEL may lead to new prospects in matching Moore's law with nanometre scale resolution photolithography.

8.4.1 Rapid events in materials science and advanced manufacturing

During various novel manufacturing processes (e.g. friction welding, laser micro-machining, additive manufacturing, forging, etc.), metallic materials experience rapid microstructural events due to the high temperatures and stresses during these processes, especially when accompanied by both high strain rate deformation ($\sim 10^3$/s) and high heating rates ($10^6 - 10^9$ K/s). These microstructural phenomena need to be understood and controlled in order to achieve the required quality and performance. This has raised the need for experimental tools that enable real-time observation of the microstructural development and phase transformations (PTs) during these manufacturing processes. Synchrotron X-ray diffraction (XRD) and in situ high temperature microscopy (Attallah *et al*.) have been successfully used in several studies to in situ investigate the phase evolution during melting and solidification, as well as the solid-to-solid phase transformations. However, more research is needed within an X-ray (synchrotron and XFEL) context, and higher temporal resolution demanded to capture all of the timescales of these processes.

Friction welding: high strain rate thermo-mechanical deformation and rapid heating

During friction welding or forging operations, the material experiences rapid thermomechanical deformation (typically in a shear deformation mode). Friction welding is a high integrity welding process that is employed in welding aero-engine components; notably the bladed disk (BLISK) structures. Previous work used high speed imaging to visualise the complex thermomechanical deformation **(Figure 8.5**). Future investigations can develop new material models to describe the rapid thermal and thermomechanical conditions associated with friction welding, taking into consideration microstructural development in addition to the flow stress/strain behaviour at these rapid rates. This will address the limitation in the current models, which rely on thermomechanical and thermodynamic/phase transformation data that do not consider the rapid and transient nature of the thermal and thermomechanical fields during friction welding. Such a limitation hinders the development of models to predict the microstructure-property development in friction welds. Some of the proposed work can include in-situ X-ray diffraction measurements during high strain rate testing (Hopkinson bar) at high temperature, to deliver both flow-stress/strain behaviour as well as microstructural (phase transformation) information to understand the microstructural phenomena (e.g. dynamic recrystallisation, precipitation, etc.) and micromechanical development (e.g. crystallographic texture). Furthermore, the influence of rapid heating on the phase transformations kinetics and other microstructural phenomena (e.g. liquation) can be explored to model the microstructural development within the heat-affected zone (HAZ).

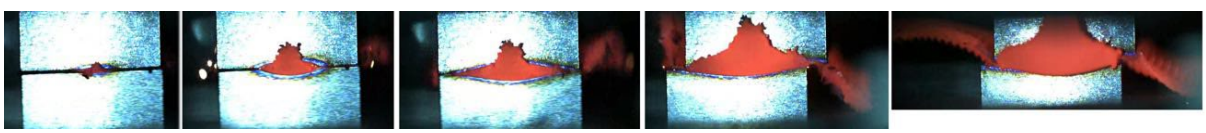

Figure 8.5: High speed imaging still shots during linear friction welding, showing the extrusion of the hot material during the process (typical weld cycle is <5 s)[68]

*Figure reproduced from F. Schröder et al. "Linear friction welding of Ti6Al4V: experiments and modelling", Materials Science and Technology, **31**:3, 372-384 (2015), DOI: 10.1179/1743284714Y.0000000575, reprinted by permission of the publisher (Taylor & Francis Ltd, http://www.tandfonline.com)*

Additive manufacturing: Laser-material Interaction

Recently, there has been a growing interest in the development and utilisation of in situ X-ray techniques[69] and high-speed imaging[21,70] to study the physical phenomena of additive manufacturing (**Figure 8.6**), especially the laser-material interaction, to understand the defect formation mechanisms.

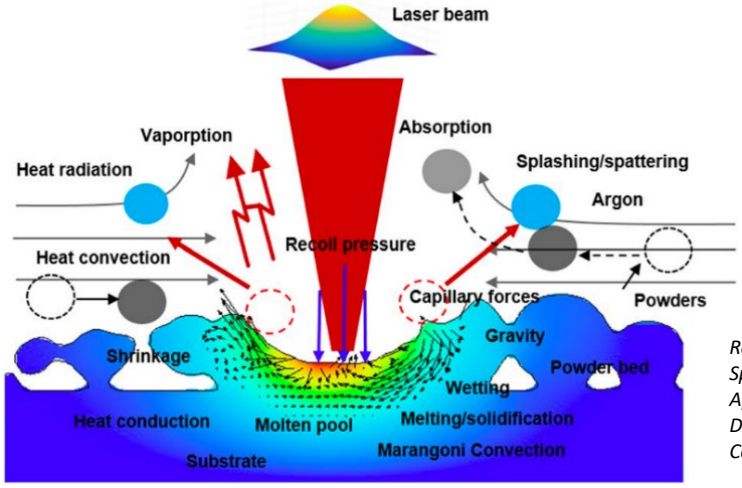

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Figure 8.6: An overview of the physical phenomena associated with laser-material interaction during metallic materials additive manufacturing[71]

Further studies are needed to improve our understanding of the rapid phenomena during additive manufacturing, specifically by exploring the following areas:

- Residual stress development: it is important to understand the influence of the repeated thermal cycling during additive manufacturing on the development of residual stresses, due to their detrimental impact on the mechanical properties, part tolerances and process.

- Phase transformations: additive manufacturing is estimated to have a cooling rate of 10^6 K/s, and a very high heating rate. Understanding the impact of the rapid phenomena on the solid-to-solid and liquid-to-solid phase transformation will achieve the holy grail of additive manufacturing, which is enabling localised microstructural control and customisation of the local properties to improve the product performance.

To implement this research, ultrafast hard X-ray pulses are needed along with 2D detectors required to record crystallographic information, and EDX detectors to record residual stress development. Sample environments that allow us to mimic the real-world processes (see **Figure 8.7**) need to be further developed. Acquisition rates should be faster than > 1 kHz.

Figure 8.7: Example additive manufacturing platform that can fit within the experimental facilities, the 'shoe box' laser additive manufacturing system which was used by Bidare et al. in monitoring the process using high-speed imaging.

*Figure reproduced from P.Bidare et al. Additive Manufacturing **16** (2017) 177-185 under the terms of the Creative Commons Attribution International License 4.0 DOI: 10.1016/j.addma.2017.06.007*

8.4.2 Laser Machining

Laser machining is a widely used technology in UK industrial production and there are domestic companies providing automated tooling for this process. In engineering literature, there is ongoing discussion on the choice between short-pulse (fs), long-pulse (ns) or continuous-wave (CW) lasers. Often different solutions are used for different applications, but there are fundamental questions why these choices produces such different results.

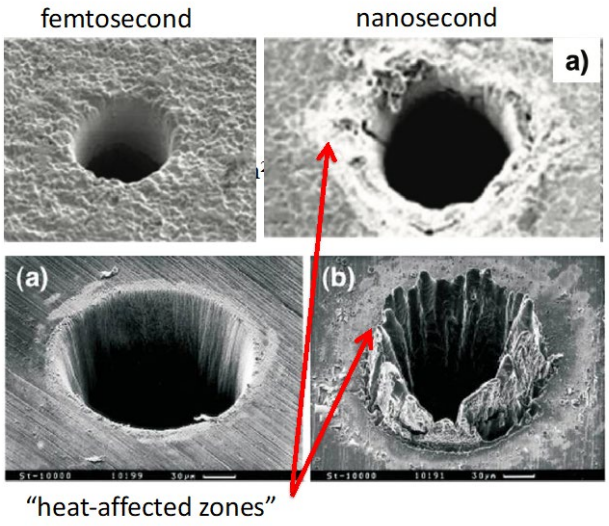

Figure 8.8: Comparisons of the results of fs and ns laser machining, in thin sheets of aluminium[71] and steel[72]

Top left & right figures reproduced from T. Aizawa and T. Inohara, "Pico- and Femtosecond Laser Micromachining for Surface Texturing", Micromachining (2019). Published by IntechOpen DOI: 10.5772/intechopen.83741
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The high-power laser research world is similarly divided between the "petawatt (PW)" communities exploring very fast electron processes in molecules or materials, and the "kilojoule" communities interested in compression, ramping, pressure generation and heating processes in materials. These represent the same differences between the fs and ns laser worlds. Comparisons of the results of fs and ns laser hole drilling, carried out side-by-side on samples of thin sheets of aluminium[72] and steel,[73] are shown in **Figure 8.8**. The authors both note striking improvements in the sharpness of the laser cut obtained with the fs pulses, and also the presence of a "heat affected zone" in the case of the ns cutting. This is only qualitatively understood at the present time.

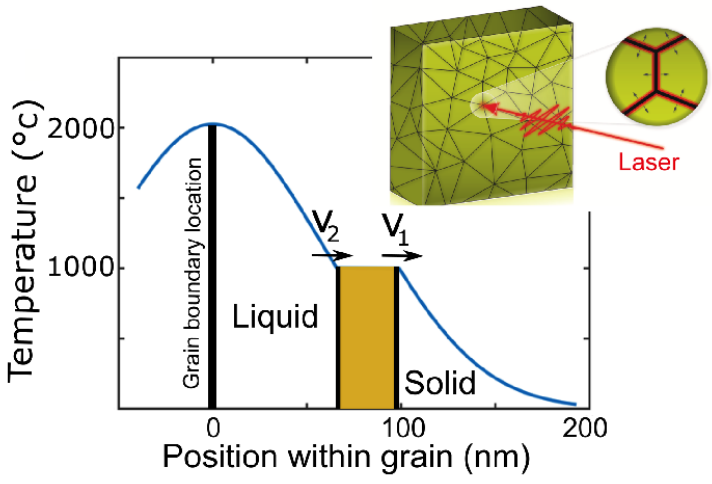

Figure 8.9: Model of the behaviour seen in laser pump, XFEL X-ray probe measurements of the spatial of melting of a 300 nm gold thin film near a grain boundary[73]

*Figure reproduced from T.A. Assefa et al. Science Advances **6**, 3, eaax2445 (2020) under the terms of the Creative Commons 4.0 Attribution International License. DOI: 10.1126/sciadv.aax2445*

An example of a recent result[74] representing a possible future direction of study that could be undertaken at a UK XFEL is illustrated in **Figure 8.9**. A 300 nm thin film of gold was melted with a single laser pulse tuned to just provide enough heat to melt the film over a 100 µm focused area. A single X-ray pulse from the PAL XFEL facility in South Korea was brought in to measure the X-ray diffraction pattern of a 50 µm region in the centre of the focus, as a function of time delay. From the shape of the diffraction showing a split peak, it was clear that the melting of the polycrystalline film takes place inhomogeneously. The model in the figure assumes that all the energy is deposited at the grain boundaries, where the heated

electrons couple to the crystal lattice. This heat conducts on a ps time scale into the surrounding grains, which are micron-sized. The result is a pair of melt fronts, separating in time, which bracket a block of gold undergoing melting by absorption of the latent heat of melting. This block gives the distinct second peak in the transient diffraction pattern seen.

8.4.3 Extreme ultraviolet lithography

Standard lithography of semiconductor chips with ArF laser-produced 193 nm radiation is gradually being augmented/replaced by the finer patterning enabled by 13.5 nm illumination, referred to in the industry as EUV. This is the main contemporary technique allowing the industry to keep up with Moore's Law. Currently, EUV is produced through the excitation of a tin or xenon plasma with an excimer laser. Commercial scanners can now produce EUV at the few 100 W level. An alternative method would be the deployment at chip fabrication plants of an EUV FEL capable of operating at multi-kW average power. Such a possibility has been investigated in detail by a leading company in lithography apparatus, but as yet the low level of technical maturity of FELs has prohibited commercial commitment.

Driving the UK XFEL soft X-ray FEL with a ~1 GeV Energy Recovery Linac (ERL) would enable multi-kW production of EUV. This would benefit the global semiconductor industry by allowing study of FEL capabilities at an industrial output level, and developing and proving kW-capable EUV optical elements/beamlines for photon transport to chip scanners. Such a flexible, industrial research-led tool would also facilitate investigations beyond the current industry state-of-the-art. The superior flexibility and controllability of FEL photons as compared to "brute-force" laser-plasma produced photons would have far-reaching implications for many diverse aspects of lithography. Examples of this could include shorter wavelengths, or indeed variation of wavelength (two-colour exposures), variation of polarisation or transverse coherence in differentiating patterning layers, or generation of orbital angular momentum photons to manipulate helicity within a wafer. There is clear potential for novel semiconductor devices to be developed utilising such source capability.

8.5 Gamma source application in nuclear security and materials in nuclear industry

With the globally unique quality and quantity of gamma production from the ICS source [Section 3.6], a number of techniques of great value to nuclear security and industry sectors will become possible. Impact would be in the fields of nuclear waste management, nuclear forensics such as active nuclear materials and contraband detection, and medical isotope production. Further applications may include treaty verification and stockpile stewardship. For further reading, please see references [75-87].

Presently, the most intense dedicated ICS source at MeV energies is the High Intensity Gamma Source (HIGS) at Duke University, USA. Important measurements have been made, such as photonuclear resonances in ^{235}U, where 13 new resonances were identified. This data was important in the development of nuclear resonance fluorescence as an assay methodology. HIGS is, however, limited in flux and bandwidth, as it is a storage ring-based source. The key technology improvement proposed for the UK XFEL ICS source is the replacement of the electron storage ring with an Energy Recovery Linac (ERL), which allows for orders of magnitude increase in flux (and narrowing of bandwidth). Higher flux means shorter integration times in the applications described below; narrower bandwidth means better energy resolution and the ability to tune into narrow nuclear resonances with less background signal and less absorbed dose into the object under inspection.

8.5.1 Non-destructive assay via radiography, nuclear resonance fluorescence and photofission

Radiographic imaging (< 10 MeV) of assemblies (e.g. shipping container contents) can be conducted with broadband (bremsstrahlung) systems, but a near-monoenergetic ICS source would significantly simplify the deconvolution of detector and filter responses during the post-processing of radiographic data whilst reducing dose to the object. Tunability of the source (including below 1 MeV) may permit some degree of discrimination between materials.

1 – 5 MeV photons with around few percent bandwidth are expected to enable development of verification techniques for non-proliferation security through nuclear resonance fluorescence (NRF) computed tomography. AWE desire to be partners as this would be a source of high quality underpinning data for future, smaller systems deployable in the field (e.g. at ports of entry into the UK, or at other locations where there is a requirement to rapidly detect and diagnose materials of concern, including possible contraband). Specifically, nuclear cross-sections and the resonance characteristics of materials could be acquired across the photon energy range of operational interest. The narrow bandwidth and tunability of the source are also key, in that specific resonances can be targeted with the aim of demonstrating materials identification from the resulting fluorescence signature. Furthermore, the narrowband nature of the ICS source ensures that the input dose to the target can be significantly reduced compared to existing broadband sources. NNL desire to be partners in the context of the non-destructive assay of components through the whole nuclear fuel cycle, for example spent fuels and unknown legacy wastes. The gamma rays from the ICS system would allow fast, high-resolution, isotopically sensitive probing of waste packages, allowing nuclear assay even through shielded flask walls.

From a national security perspective, the ICS source could be used to demonstrate the feasibility of using induced photofission signatures (5 MeV < E < 10 MeV) for low-dose identification of specific isotopes. As for NRF, underpinning materials data (in this case, nuclear photofission cross-sections) acquired using the ICS source would be central for developing this new detection methodology

8.5.2 Nuclear waste management via photonuclear transmutation

Combining NRF with irradiation at higher photon energy (5 – 40 MeV) and narrower bandwidth (0.1 – 0.01 %) is expected to enable development of techniques to possibly selectively transmute specific isotopes. This would allow investigation of improved nuclear waste management techniques via induced photofission of actinides and long-lived fission products. Crucially, a high value source or product oxide could be purified without the need for wet chemical partitioning, thus allowing purification of a mixture of isotopes or, alternatively, selective destruction of a contaminant that has grown into a material. For example, ingrowth of ^{241}Am in a can of PuO_2 greatly increases operator dose when this is recycled as MOX fuel. This could be mitigated if the ^{241}Am could be eliminated in situ.

For future reprocessing plant, new reprocessing strategies are being investigated to segregate actinides in differing combinations, to improve long term waste handling options. It may be practical to selectively destroy a specific high hazard actinide or alternatively a fission product waste such as ^{129}I or ^{99}Tc. To be economically viable, the waste volume would need to be small and specific long-term waste storage and waste stabilisation costs be high. Major economic benefit may therefore arise in, for example, reconfiguring the long-term management of the UK's current and future stockpiles of problematic legacy wastes on the Sellafield site

8.5.3 Medical radionuclide production

The high spectral flux available may make the production of novel medical radioisotopes economically viable, including by harvesting them from legacy material currently considered as waste. The pencil nature of the gamma beam implies potential for very high specific activity in the material produced. Applications would include new medical diagnostic techniques, such as gamma-PET (photonuclear generation of ^{44}Ti, ^{195m}Pt, ^{117m}Sn, ^{44}Sc).

8.5.4 Detector calibration

For example, calibrated gas Cherenkov detectors (GCD) are routinely used to monitor burn characteristics in Inertial Confinement Fusion (ICF) schemes.[88] The monochromatic but tuneable characteristics of the ICS source are ideal for determining detector response as a function of gamma photon energy.

8.5.5 Conclusion

The availability of a gamma source as described would be a unique capability globally. It would therefore comprise an advantage for both UK defence and civil nuclear industry, with significant potential for high-value spin off activity. Locating it as part of a larger XFEL facility would be advantageous in two respects: firstly the electron beam infrastructure required is common to both FEL and ICS sources; secondly the analytic capability of FELs is complementary. The wider infrastructural considerations of enabling handling of nuclear materials within an XFEL facility presents challenges, but also significant opportunities, and will be evaluated in a conceptual design phase.

8.6 Industrial inspirations from deeper insights into biology: Pharma to clean energy

Industrial XFEL users in life science want faster, better structures from smaller samples. They demand reliability and automation, especially for proprietary R&D efforts. Industry is already using Diamond and eBIC extensively, and starting to explore options at XFELs. They are watching for developments in cryo-EM, serial crystallography and time-resolved studies that couple structure and function from the same sample. New opportunities for drug discovery impacting human health are profound and progress has recently been demonstrated with serial femtosecond crystallography (SFX) results on several membrane proteins involved cell signalling. Time-resolved SFX results targeting photosystem II, hydrogenases, and nitrogenases promise molecular level insights that will inspire the next generation of solar and full cells, and green catalysts to convert N_2 into fertilizer.

An outstanding grand challenge in the life sciences is to understand the molecular basis of symbiosis *versus* pathogenicity. *Why are some interactions beneficial, and how can these be protected or enhanced while simultaneously degrading those that cause disease?* The need to distinguish between "friend or foe" impacts the entire biosphere and is one of the critical factors that drives evolution on Earth; often a life or death process. This ongoing struggle is a fundamental underlying basis of the $1.2 trillion pharmaceutical industry focused upon human health, and similar global efforts targeting agriculture. Despite the extinction of more than 99% of all organisms that have ever lived on Earth (see **Section 7**), the current diversity of life is immense and always evolving.[89]

As we write this, the COVID-19 pandemic is roiling around the world, with more than 4.2 million confirmed cases and 289,349 deaths reported as of 18:30 on 12 May 2020 (**Figure 8.10**).[90-93] This is the third coronavirus outbreak to emerge in the 21st century that causes severe respiratory syndrome and death on a large scale (SARS in 2002, MERS in 2012, and COVID-19 in December 2019). COVID-19 is likely to have evolved recently from a SARS precursor. Consequently, humans have no immunity to this novel, positive-strand RNA virus and treatments, ranging from symptom mitigation to vaccines, will take time to develop. In the meantime, social distancing is the dominant health strategy.

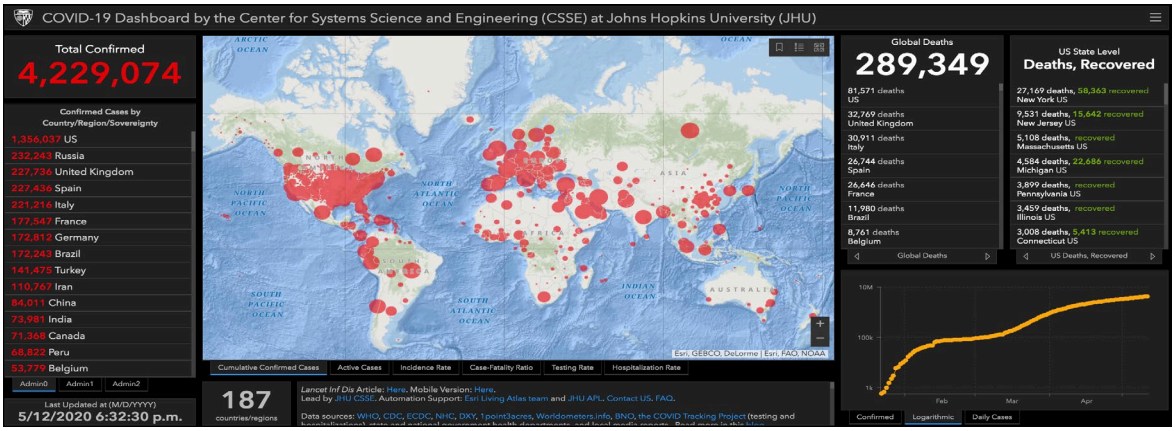

Figure 8.10: A snapshot on 12 May 2020 of the COVID-19 outbreak as tracked by the Johns Hopkins University Coronavirus COVID-19 Global Cases server.
E. Dong et al (2020) Lancet Infect Dis

Structural biologists in academic and industrial labs around the world are vigorously working on the problem, including analyses of key proteins from the COVID-19 virus genome using cryo-EM, X-ray crystallography and homology modelling approaches (**Figure 8.11**).[94-100] Among the first results are cryo-EM single particle analysis of the whole virus and the complex that likely mediates entry into human cells. These results suggest that the COVID-19 virus hijacks the normal physiological roles of angiotensin-converting enzyme 2 (ACE2) and transporters for the uptake of large neutral amino acids like B^0AT1 and/or its homologues. In parallel, chemical fragment library screening with X-ray

crystallography at Diamond target inhibition of the COVID-19 protease that is critical to the virus life cycle. The XChem crystallographic results link directly to industrial partners including Exscientia (Oxford, UK) to assay hits and follow-up lead compounds, and Enamine (Rīga, Latvia) for selected compounds to be used for bioassays. The rapid progress across all R&D fronts is impressive.

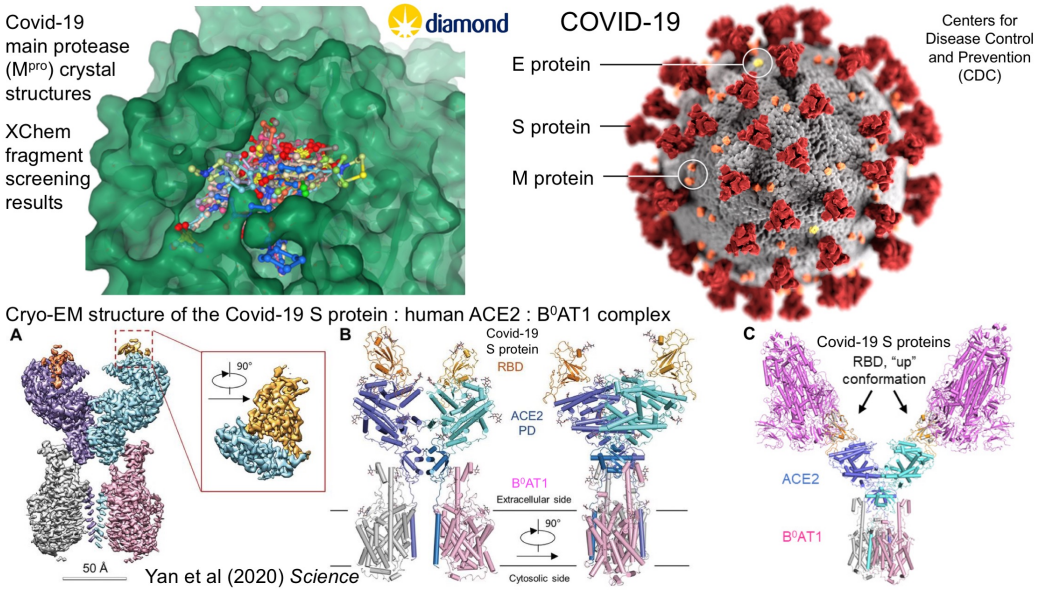

Figure 8.11: Morphology of the COVID-19 virus (top right) and structure-based drug discovery. (top left) Fragment screening by crystallography of the M^{pro} protease at Diamond identified > 50 ligand hits in and around the active site. (bottom) 2.9 Å resolution cryo-EM map (A) and overall structure (B) of the RBD-ACE2-B^{0}AT1 ternary complex. (C) The ternary complex superimposed with the S protein of COVID-19 (PDB code: 6VSB)

*Bottom figure reproduced from R. Yan et al. Science **367**, 6485, 1444-1448 (2020) under the terms of the Creative Commons 4.0 Attribution International License. DOI: 10.1126/science.abb2762*

However, this is also a tragic example of a missed opportunity. The original SARS outbreak in 2002 actually did yield high resolution crystal structures of the main protease, which is very homologous to the COVID-19 main protease.[94,101,102] As Dr Stephen Burley (director of the Research Collaboratory for Structural Bioinformatics Protein Data Bank, Institute for Quantitative Biomedicine, Rutgers, The State University of New Jersey) said on 04 March 2020, "*Had an effective blocker of the SARS main protease been discovered and developed [to fruition] in 2003, it would have stopped the current infection dead in its tracks.*"[103] Since they are so closely related by evolution, an inhibitor developed for the SARS coronavirus main proteas will also very likely be effective against COVID-19.

Although very successful, these approaches largely ignore dynamic components because they derive from samples held at cryogenic temperature. In contrast, many of the XFEL-based approaches described in **Section 7** are performed at physiological temperature and thereby enable scientists to simultaneously probe dynamics and structure. This capability is germane to COVID-19 R&D efforts. The receptor binding domain (RBD) of the COVID-19 spike protein has at least two configurations, up and down. The molecular basis and dynamics for the transition between these two states is unknown; however, only the up state binds to ACE2. The interactions between the COVID-19 S protein and ACE2 indicate that the new virus binds with four-times higher affinity than its SARS precursor (1.2 nM compared to 5.0 nM) and that most of this difference is apparent in the slower off-rate kinetics for COVID-19 (1.6×10^{-4} s^{-1} versus 7.1×10^{-4} s^{-1}).[100] The fragment screening results do not address any of the dynamic steps within the protease reaction kinetics or catalytic mechanism.

Structure-based drug discovery and/or design is a hallmark strategy used across the pharmaceutical industry. Its success is illustrated by the fact that more than 90% of new molecular entities (NEM) to receive US FDA approval since 2010 leveraged structural biology.[104-106] Almost all of the atomic models for the new drug targets were released into the public domain, and many about 10 years before a

drug compound came to market. Thus, the linkages between the public and private sectors are historic and extensive.[107] At Diamond, up to 10% of the available experiment time is set aside for proprietary access used by many industrial partners. More than 160,000 atomic models are curated by the PDB with an estimated economic value of more than $16B. Screening macromolecular targets against the vast chemical space using fragment libraries is highly automated, especially at the XChem facility at Diamond Light Source.[108-114] To date, this has almost always exploited cryogenic conditions. Indeed, as of 08 May 2020, Diamond Light Source is responsible for 94 of the 163 atomic models of COVID-19 proteins released by the PDB (overall 150 are by X-ray crystallography with data collected at 100 K). Most of the results are from the SARS-CoV-2 main protease (M^{pro}) ± inhibitor(s) or chemical fragment(s). However, room temperature serial MX approaches are also progressing in parallel at Diamond. Moreover, all XFELs around the world are calling for proposals for COVID-19 research. To this end, members of the UK community and Diamond are proposing time-resolved SFX studies of ligand binding and/or catalytic turnover of substrate(s) by the M^{pro} enzyme. Thus, XFELs offer new opportunities to couple functional dynamics with ligand discovery of new drugs and therapies at physiological temperature.

XFEL-based structural biology methods efficiently use slurries of micron-size crystals to generate high resolution atomic models. An example of the impact is illustrated with G protein-coupled receptors (GPCRs, **Figure 8.12**).[115-120] These integral membrane proteins tend to exhibit a seven transmembrane protein fold that is often difficult to crystallise and study by traditional methods. Nevertheless, many have produced microcrystals with lipidic cubic phase conditions, that have generated important results from XFELs using SFX approaches.[121-132] There are more than 800 human GPCRs that respond to thousands of chemicals or photons, and elicit responses that touch nearly every physiological aspect of cells. Ligand binding or photoisomerization elicit dynamic conformational changes that propagate across the membrane and initiate intracellular signalling cascades. More than 40% of all prescribed drugs target GPCRs with impact to the central nervous, cardiovascular, immune, metabolic, and reproductive systems, as well as to many human cancers. The importance of GPCRs was the recognised by the 2012 Nobel Prize in Chemistry to Lefkowitz and Kobilka "for studies of G-protein-coupled receptors." Membrane proteins, and especially GPCRs, will be a strong use case for Industrial users for XFELs in the coming decades.

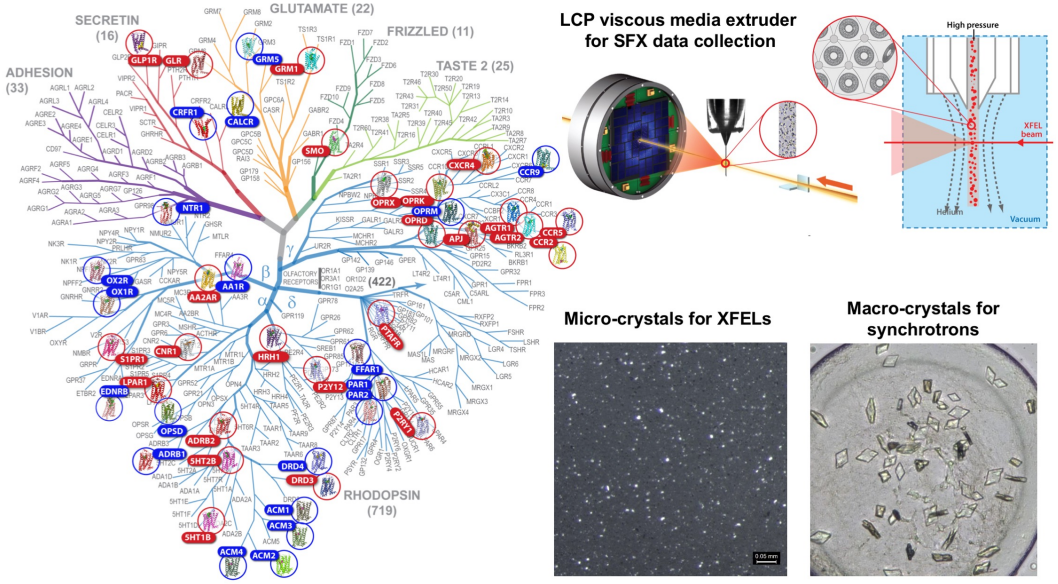

Figure 8.12: (Left) High-resolution crystal structures of GPCRs in 2019 superimposed upon the phylogenomic family tree. (Top right) SFX data collection strategy using an LCP injector at XFELs and microcrystal. (Bottom right) Comparison of micro- and macro-crystals.

Left figure courtesy of Vadim Cherezov and adapted from V. Katritch et al. Trends Pharmacol Sci 33, 17-27 (2012). DOI: 10.1016/j.tips.2011.09.003
Top right figure adapted with permission from W. Liu et al. Science 342 1521-1524. DOI: 10.1126/science.1244142. Copyright The American Association for the Advancement of Science (2013)
Bottom right figure courtesy of Vadim Cherezov

Metalloenzymes catalyse the most difficult reactions in biology.[133-137] They evolve to produce high energy intermediates when and where they are needed to transform a wide range of compounds. For instance, **Section 7.2** highlights photosystem II and how XFELs provide experimental approaches to watch visible light photons elicit charge separation, that sequentially oxidises the Mn atoms within the oxygen evolving complex, that ultimately converts two H_2O molecules into O_2.[138-148] These mechanistic insights serve as inspiration for advanced generation photovoltaic cells for industrial applications. Fuel cells will also take inspiration from hydrogenases, metalloenzyme that use complex iron-sulfur and nickel clusters to catalyse the reversible reaction of two H^+ plus two electrons to produce H_2.[149-159] Methane monooxygenase uses dinuclear iron centre to catalyse the conversion of methane into methanol by creating a bis-Fe(IV)=O reactive intermediate.[160-172] Indeed, Fe(IV)=O intermediates are critically important across all aerobic life and are extraordinarily difficult to study by traditional synchrotron methods, because they are easily perturbed by photoelectrons generated during the X-ray exposure.[134,137,173,174] Metalloproteins will be a strong use case at XFELs and will inspire small molecule catalysis for many industrial applications.

For most of the Earth's history, natural sources have provided enough bio-available nitrogen to support all life in the biosphere. The most important reason is nitrogenase, a class of complex metalloenzymes that evolved in microbes to fix N_2 at atmospheric pressure and ambient temperature, converting it to NH_3.[175,176] The enzyme needs eight electrons and uses the energy released by ATP hydrolysis to drive protein conformational changes (**Figure 8.13**). Microbial species that carry genes for nitrogenase are widely distributed across terrestrial and oceanic environments. Some symbiotic bacteria inhabit the root nodules of legumes and express nitrogenases, which supply all of the reduced nitrogen needed by the plant. In exchange, the plants supply reduced carbon from photosynthesis to the microbes, which is used for carbon and energy needed to fix N_2. The photosynthetic cyanobacteria *Crocosphaera watsonii* in the ocean expresses photosystem II during the day to generate electrons and fix CO_2, then during the night, it express nitrogenase to fix N_2.[177-179] An outstanding frontier challenge is to understand the molecular basis of nitrogenase catalysis, especially how protein and metal cluster dynamics impact reactivity. Indeed, structural and spectroscopic results demonstrate that the ground-state crystal structures of nitrogenase determined at cryogenic temperatures are inactive.[180-192] This supports the hypothesis that dynamic motion of the active site cluster is essential to catalysis.

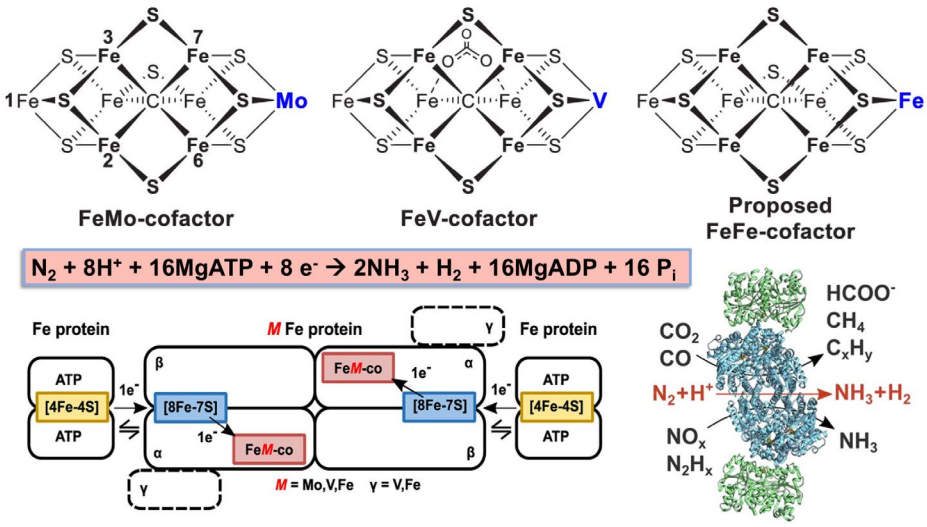

Figure 8.13: (Bottom, left) Schematic of nitrogenase structures showing the electron delivery Fe protein component and the catalytic MFe protein component (M = Mo, V, Fe). (Bottom, right) Overall structure of Fe protein - MoFe protein complex and reactions catalysed. (Centre) The nitrogenase reaction is catalysed by the metal FeM-co centres (top) that incorporate similar but distinct clusters from various microbes.

Adapted with permission from L.C. Seefeldt et al. Chemical Reviews. Copyright (2020) American Chemical Society.
DOI: 10.1021/acs.chemrev.9b00556

The Haber-Bosch process is the industrial equivalent of nitrogenase and N_2 fixation.[175,176] It was invented just over 100 years ago and now produces as much NH_3 globally as all natural sources. It has not changed significantly over the past century. Unfortunately, the Haber-Bosch process requires high pressure and temperature, as well as annually consuming about 5% of the global natural gas; thus, it is not sustainable. Moreover, feeding the current world population of ~7.7 billion critically depends upon industrial fertilisers; but natural N_2 fixation processes alone can support only about 50% of the current population.[176,193,194] Consequently, there is an urgent need to develop alternatives to the Haber-Bosch process. Clearly a better understanding of the structure, dynamics and function of nitrogenase is an inspirational guidepost and XFELs will play a major role in the R&D effort in the years to come. The industrial scale application of green chemistry strategies to produce new N_2 fixing catalysts inspired by structural biology is essential to human survival.

8.7 Overall economic context

A UK XFEL would be a cutting-edge, large-scale scientific facility that would operate a world-leading programme of frontier research. Researchers from the UK and worldwide would tackle fundamental scientific challenges across the Life and Physical Sciences, creating substantial benefits to skills and innovation in science and technology. This fundamental research will lead to multiple innovative applications, supporting technological innovation and commercialisation over many decades.

A UK XFEL would be a strategic asset to the UK for the manufacturing, defence, medical and technology sectors. As well as the fundamental benefit to the UK economy from construction, procurement and operation, a world leading XFEL facility with unique X-ray capabilities would enhance the UK's position as a centre for advanced science and innovation. UK Industry that can collaborate with cutting-edge facilities are able to increase the rate of technological progress, improve processes and hence deliver enhanced economic benefits and job growth over the long term. With investment in a UK XFEL, UK industry would easily be able to access this unique X-ray source in a way tailored to their needs and circumventing the access challenges and higher costs of collaborating with existing facilities internationally. These sources are likely to become increasingly an essential national technology resource in the coming decades. A UK XFEL would safeguard future research and innovation capability for industrial and defence sectors for years to come, providing them with access to a world-class facility and relevant scientific and technological experts.

Locating an XFEL in the UK will create greater benefit for local firms and workers, and lead to greater capitalisation from the training of skilled scientists and engineers who would be required to design, build and operate such a facility. In addition, a UK XFEL would act as a catalyst for regional development, creating new industrial clusters and attracting investment and highly skilled workers.

Large-scale research facilities in the UK typically provide thousands of days of user access to PhD students. During this time they are receiving training and gaining valuable 'on-the-job' skills and knowledge that can be applied in the UK academic and wider economy over their future working lives. Overseas students would naturally be attracted to such a flagship facility, and many of these would settle (or return) to the UK to pursue their future careers. Staff and users of the UK XFEL would be expected to learn specialist skills that are highly valuable to industry. Aside from pursuing careers in industry following time at the facility, industry would be able to access these skills via collaborative research or knowledge exchange programmes.

8.7.1 Areas of economic impact

Many potential economic benefits would be realised from the building of a UK XFEL. These include:

- Economic benefit to external suppliers through direct employment and purchasing – construction, upgrades and maintenance of a UK XFEL. A significant fraction of the expenditure for a UK XFEL would go to companies and suppliers based in the UK, many of which would be local.
- Creation of new businesses / spin-outs to capitalise on the outputs of user research or facility developments and subsequent benefits to the supply chain of these companies. Based on the experience of other large-scale research facilities in the UK, it is expected that a number of 'spin-out' companies will be formed during the lifetime of a UK XFEL. Societal benefits from fundamental research can often take years to realise. Government-funded large facilities, however, have proven experience in accelerating this process by exploiting innovative research through IP protection, proof-of-concept funding and support for spin-out companies.
- Employment of facility staff – a UK XFEL would require hundreds of staff, many highly skilled, to operate the facility.

- PhD and post-doctoral wage premiums for students who receive training on the facility – as a result of receiving skills-related training on site during their visits, many thousands of PhD and post-doctoral visitors will benefit from an earnings premium over their subsequent careers.
- Apprenticeships and training of non-scientific staff in engineering, analytical technology, chemical- and bio-technology, IT and big data (including machine learning), optics and advanced electronics.
- Economic benefit to firms from commercial and industrial access to the XFEL, e.g. through improvements to existing materials and processes.
- Agglomeration benefits from the formation of science and technology clusters co-located with the facility. The co-location of firms working in similar sectors has been shown to positively impact rates of innovation and productivity.
- Economic benefit of visitors to the facility – it is anticipated that there would many thousands of individual scientific visits (as a user or for collaborative work) to a UK XFEL facility per year, as well as members of industry, commercial or other public bodies. These visitors would have a positive impact on the local economy in terms of spend on accommodation, subsistence and travel.

8.7.2 Return on investment

One of the primary methods to determine the value for money (VfM) of building a large-scale facility such as UK XFEL is to look at the estimated impact of R&D that results from the facility on the overall economy (see section above). While an estimate of the possible benefits that can be directly attributed to the creation of a new facility can be performed (a 'bottom-up' approach), it is important to recognise the broader benefits to the UK economy that would result from investment in an UK XFEL. For example, fundamental research performed in the short term is likely to drive technological innovation in the longer term, using knowledge developed indirectly from user experiments and facility developments. Directly estimating the benefit of attracting highly skilled scientists and organisations to a cutting-edge XFEL facility can also be hard to quantify.

An alternative 'top-down' approach can use published literature on rates of return on investment in science and technology. This approach covers the direct rate of return on the investment to the funder (the UK government), as well as wider benefits to the UK economy. Published literature (a summary of which is contained in "Rates of return to investment in science and innovation" – Frontier Economics 2014) estimates a mean rate of return of 30% on the investment to the funding source, with a mean social rate (which covers broader societal benefits through spill-over effects) of two- to three-times that. A recent comprehensive analysis was undertaken for STFC's Extreme Photonics Applications Centre (EPAC), a facility which will use high power lasers to produce unique secondary radiation sources for fundamental science and industrial applications. While EPAC is different in terms of the driving technology and capability, there are striking similarities in terms of the opportunities that both facilities would offer across many science and technology sectors. The total benefit of the related R&D of the EPAC facility was found to have a mean R&D multiplier value of 1.85.

This factor would be applied to anticipated expenditure on a UK XFEL in order to estimate the broader economic benefits of such investment, although the uniqueness of a UK XFEL would likely generate greater returns than this figure owing to the many areas of applied research across technology, engineering and healthcare that rely on high levels of contribution from core academic research.

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9. Facility Requirements and Options Analysis

The new science opportunities identified require a strategy that will ensure their delivery. Developing that strategy requires defining the specification of the X-ray and other capabilities required of any new infrastructure. We also need to map the synergy with existing UK infrastructure that can contribute to the science opportunities. In defining the way ahead we have considered, and weighed the pros and cons of, options ranging from the scientifically favoured recommendation of the development of a unique new UK XFEL to less ambitious alternatives. With a strong recommendation to create a world-leading XFEL infrastructure, we have also formed an outline path of next steps to achieve this.

The science opportunities discussed in the preceding sections will require an ambitious machine incorporating new capabilities beyond those currently available anywhere. Here we examine and summarise what capabilities are needed, both in terms of the X-ray characteristics and the other supporting features available at end-stations, to allow the full realisation of the science. The X-ray requirements include the need for a high repetition rate machine across a significant photon energy range, as well as high brightness, narrow bandwidth and ultrashort pulses. Even with a superb X-ray capability, the facility will only deliver the most exciting science with properly equipped end-stations that bring an ambitious range of laser, THz and electron beams to the interaction point. In **Section 9.1** we capture the main X-ray capability requirements to deliver the science featured in this Science Case. Following this, in **Section 9.2** we discuss other features, such as ultrafast pump and high power driver lasers, THz sources, auxiliary electron beams, sample environments, detectors and data management that are essential to ensure the maximisation of scientific opportunities.

An XFEL science capability will be an important part of future light source provision in the UK, and this must be integrated into the wider science infrastructure landscape. In **Section 9.3** we explore the synergies with existing infrastructure (and planned upgrades), such as Diamond Light Source, Cryo-EM, potential developments in UED, and the laser capabilities of CLF and EPAC. Maximum scientific benefit can be achieved if multiple techniques are effectively integrated in answering challenging scientific questions.

In **Section 9.4** we examine the options that could take the UK all of the way, or some of the way, along the path of realising the science opportunities. The pros and cons of options, ranging from developing a state-of-the-art UK XFEL infrastructure to essentially just building modestly on the status quo, are assessed. Based upon the science benefit, we conclude that the development of a world leading XFEL infrastructure is our strong recommendation, but we recognise that other factors must be accounted for in the decision (e.g. cost, timescale). In **Section 9.5** we briefly discuss the next steps that will be required to develop a state-of-the-art UK XFEL infrastructure.

9.1 Facility X-ray requirements

A diverse and ambitious range of scientific and technology opportunities has been described in Sections 3 to 8. This section summarises the key X-ray requirements distilled from all of these science areas. An analysis has also been carried out to identify key requirements of common interest across the science areas, which would lead to unique facility capability. A landscape of the various requirements has been identified that informs facility design choices in future.

9.1.1 Key requirements mapped by science area

Each of the science areas described in **Sections 3 to 8** contains a wide variety of experimental interests and methods. A summary of such a rich and complex landscape cannot capture every intricate detail; rather, some of the key requirements central to the mission of each science area have been identified. These are presented in **Figure 9.1**, and are described in turn below.

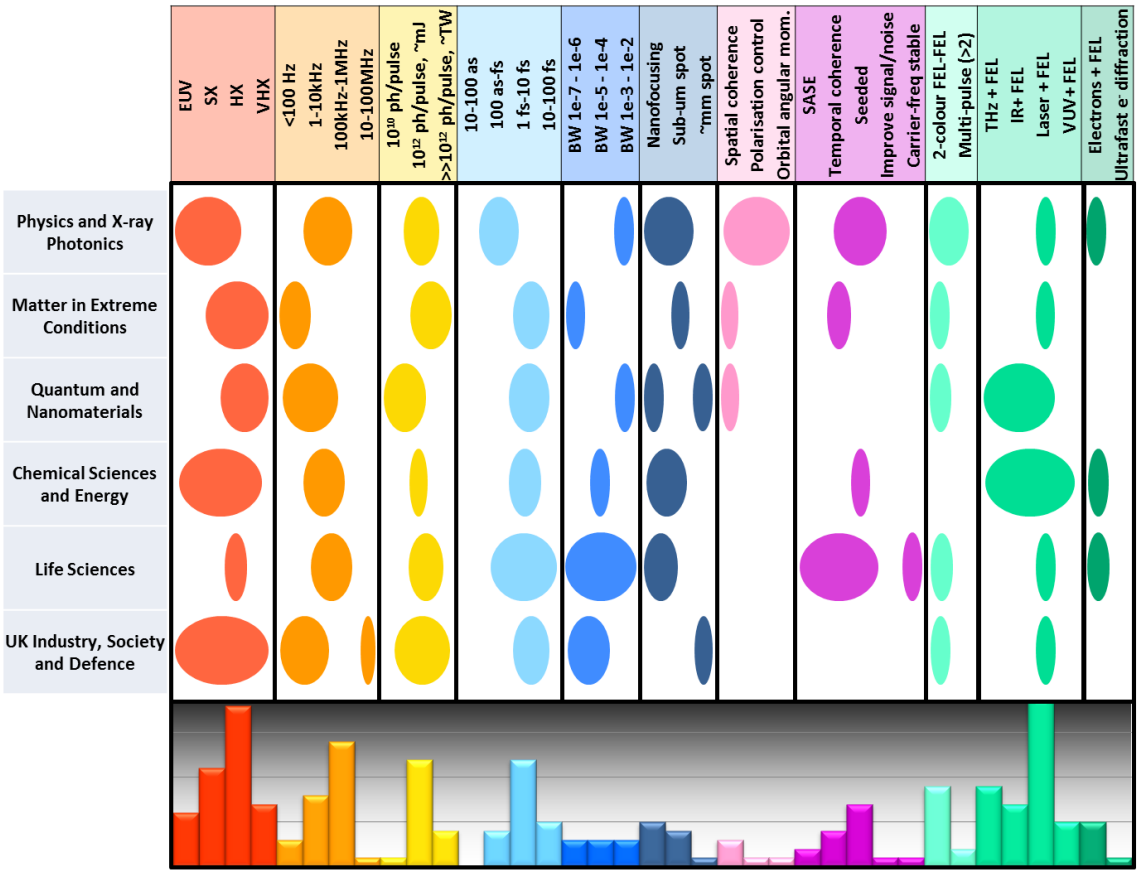


Figure 9.1: Summary of the key requirements of the different science areas

Key: *The different colours correspond to properties of the X-ray light (photon energy, repetition rate, etc.), including additional sources to be used in combination (THz, IR, etc.). Each coloured category features an internal scale or range of options (sub-category).*

*The science requirements of **Sections 3 to 8** were analysed for key features. The coloured ellipses represent the requirements in each category, for each science area. The bar chart indicates the number of sub-sections in the text (or direct input) that highlight that sub-category – allowing requirements of the highest common interest (e.g. hard X-rays, combination with optical lasers) to be identified. Associations between certain properties can also be identified.*

9.1.1.1 Physics and X-ray photonics

The key requirements are attosecond pulses (~ 100 as) across a broad range of photon energies, from 200 eV to hard X-ray, with sub-femtosecond synchronisation to optical lasers (combination with electrons and other FEL pulses is also of interest). Control of pulse properties, such as polarisation and orbital angular momentum, and through seeding are also highlighted. High repetition rates (> 10 kHz) are strongly preferred, as in many examples the anticipated signals are weak and much data must be taken for high fidelity measurements.

9.1.1.2 Matter in extreme conditions

The main requirements are X-ray pulses with high pulse energy (mJ to orders of magnitude higher) and high photon energy (up to 30 – 50 keV), in combination with very high-energy optical lasers. Repetition rate is generally less demanding, as it is limited by the relatively low repetition rate of the high energy laser that compresses the material. In other cases, where the X-ray beam is used to isochroically heat samples, a high repetition rate can be beneficial. Narrow bandwidth (10 meV), two-colour FEL capability and sub-micron spot sizes are called for.

9.1.1.3 Quantum and nanomaterials

The key requirements of this science area are soft to very hard X-rays (up to ~ 50 keV would open up new opportunities), in combination with pump sources across a broad range of wavelengths (THz to visible), as well as two-colour FEL capability. Sub-femtosecond synchronisation is important in all cases. Repetition rate can be as low as 10 Hz in some experiments, due to sample recovery times, but high average flux is needed in others.

9.1.1.4 Chemical sciences and energy

The key feature of the requirements for this science area is to combine XFEL pulses with a multitude of different sources: accelerator based THz, electron beam pump sources, along with numerous synchronised laser-based sources. The X-rays should be soft to very hard (> 25 keV for some experiments) and high repetition rate (1 kHz to 1 MHz). For some experiments, a bandwidth below 1×10^{-4} is needed. Two-colour FEL operation is also important, with the possibility of combining two XFEL pulses in various combinations of soft (from 200 eV to 3000 eV) and hard X-rays (from 5 – 25 keV).

9.1.1.5 Life sciences

This science area calls for hard X-rays (5 – 25 keV) at high repetition rates (1 kHz to potentially as high as 1 MHz, depending on detector capabilities). A key need for some applications is precise control of the X-ray pulse properties – stability of carrier frequency, pulse energy, instantaneous bandwidth and spectrum. Broadband energy-chirped hard X-ray pulses with up to 4% bandwidth, as demonstrated at SwissFEL, are also of great interest. Two-colour FEL operation with the ability for large variation in temporal (fs – μs) and energy separation is important, as well as combination with electrons.

9.1.2 Key X-ray requirements and unique facility capability

Each of the science areas in this Science Case presents a vision for the capabilities required in a UK XFEL facility to deliver world leading science, as summarised above. A simple analysis of the most frequently specified features across the science areas identifies requirements for soft to hard X-rays, high repetition rate, high pulse energy, ultrashort pulses and capability to combine multiple sources, as indicated in **Figure 9.1.** However, not all of these features are required simultaneously in any one experiment. It is, therefore, also instructive to identify clusters of associated parameters in common between science areas. Two of the most significant associated parameters that influence design choices for X-ray provision are photon energy and repetition rate (as described in **Appendix 1**). Considering the requirements of specific categories of the science case areas reveals a general trend for high repetition rates at lower photon energies, and somewhat lower repetition rates at high photon energies, as shown in **Figure 9.2**. Regions of this parameter space and other key associated parameters are described below and form the basis of the required features and unique capabilities of a UK XFEL.

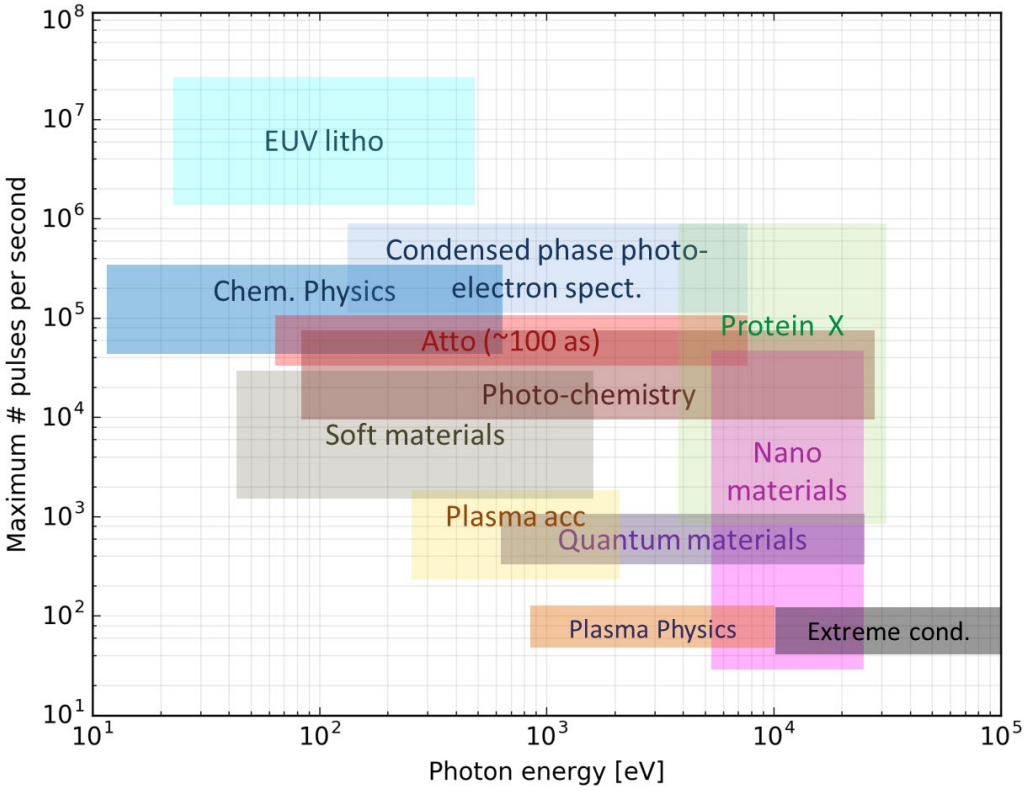


Figure 9.2: Requirements of different areas of the science case in terms of photon energy and repetition rate. Specific categories of the science case are used to clearly demonstrate the trade-off between the parameters

9.1.2.1 Soft and hard X-rays at up to MHz repetition rate

The photon energy requirements of this Science Case are predominantly focused on hard and soft X-rays – from approximately 200 eV to 25 keV – as shown in **Figure 9.1** and **Figure 9.2**. There is a clear call from the soft X-ray science in particular for high repetition rates (10 kHz – 1 MHz), requiring superconducting accelerator technology to be deployed up to an electron beam energy of at least 2 GeV, as described in **Appendix 1** (*Concept outlines 1 and 2*). To provide hard X-rays up to 25 keV requires electron beam energy up to around 7 GeV, assuming reasonably ambitious short period undulators (e.g. superconducting) to allow access to higher photon energies for a given electron beam energy. The repetition rate requirements for hard X-rays cover a wider range from around 100 Hz to 1 MHz. Therefore a fully superconducting accelerator is required to meet all the requirements (*Concept outline 1*), but a normal conducting accelerator providing up to 1 – 5 kHz repetition rate could meet a large subset of the science (*Concept outline 2*). Further R&D is required to deliver normal conducting technology with this performance, but it can be anticipated to form part of the baseline design. Superconducting accelerator technology for MHz operation is suitably mature, with two such XFEL facilities already under construction (as described in **Section 2.3**).

9.1.2.2 Very hard X-rays with high pulse energy (at lower repetition rate)

There is significant interest in photon energies above the current state of the art (25 keV), up to approximately 50 keV, with an associated desire in some cases for very high pulse energy (mJ to orders of magnitude higher). While delivering the requisite photon energies is technically challenging, it is entirely feasible for day one of UK XFEL – the focus would be to determine the most cost-effective route. The key factors for increasing FEL photon energy are increasing the energy of the electron beam, utilising novel undulator technologies (e.g. superconducting) with reduced undulator period, and improving electron beam quality through ultra-low emittance photo-injectors. A combination of these factors could deliver suitable performance with electron beam energy around 10 GeV, as described in **Appendix 1**, i.e. higher than a machine to deliver sub-25 keV photon energy and moderate pulse energy, but substantially lower than European XFEL (17.5 GeV), while being competitive. Advanced

techniques to increase pulse energy via improved efficiency should also be pursued as described in **Section 2.4.3**. In general, the specification for very hard X-rays is in science areas requiring lower repetition rate (10 – 100 Hz), as shown in **Figure 9.2**, due to sample recovery time, and auxiliary source limitations. The hybrid accelerator option, *Concept outline 2*, could potentially trade off repetition rate to increase electron beam energy, and so excel for these science areas. Very advanced concepts, such as plasma acceleration, are not yet considered mature enough to be on the critical path, but could potentially be part of an upgrade route.

9.1.2.3 Reproducibility, high spectral purity and control of other pulse properties

A clear requirement from multiple areas of this Science Case is for greater control of the X-ray pulse properties over the full range of photon energies and repetition rates. This would add a multitude of advantages for the science – from the conceptually simple but critical advantage of shot-to-shot reproducibility (as described in **Section 9.2.7**), to a host of advanced features in the pulse properties. As described in **Section 2.1**, seeding can greatly improve the coherence properties and stability of the output. The present state-of-the-art facility for seeding is the FERMI facility in Italy, which has demonstrated the technique up to approximately 400 eV at 50 Hz. A UK XFEL could be confidently expected to provide seeded output with repetition rate orders of magnitude higher at the outset, as described in **Section 2.4.1**. Furthermore, seeding may be extended to higher photon energies (> 1 keV), for example using the latest non-linear optical laser technology (see **Section 9.2.1**), thereby spanning an important range of critical absorption edges in carbon, nitrogen, oxygen and metals. Laser seeding to substantially higher than 1 keV is anticipated to require long-term development. In the shorter term, however, greater control of the pulse properties at hard X-ray is likely to come from methods described in **Section 2.4.2**, such as High-Brightness SASE for higher spectral purity; ongoing R&D into X-ray FEL Oscillators and X-ray seed sources will determine timescales for potential deployment in a UK XFEL. Several areas would also benefit from advanced control of other properties including polarisation, orbital angular momentum, energy chirp, and carrier-envelope phase.

9.1.2.4 Attosecond pulses at all photon energies, synchronised to external sources

The ability to probe structural dynamics at timescales down to attoseconds is one of the defining features of this Science Case. Pulse durations down to approximately 100 as are required across a broad range of photon energies from 200 eV to hard X-ray, with sub-femtosecond synchronisation to optical lasers and other sources. The required pulse durations have recently been demonstrated at existing facilities (as described in **Section 3.3.1**), but there is opportunity to significantly enhance capabilities in terms of synchronisation and applicability across all photon energies. The use of external lasers to control the lasing portion of the electron beam would greatly improve synchronisation to external sources, as described in **Section 2.4.4**. Given UK strengths in the required technologies, it is feasible for a UK XFEL to implement world-leading capabilities from day one and to further enhance these capabilities throughout the lifetime of the facility.

9.1.2.5 Multi-colour modes and combination between sources

As shown in **Figure 9.1**, some of the most pressing requirements from this Science Case are for multi-colour FEL operation and the combination of X-rays with external sources. The most frequently highlighted requirement of all is to combine X-rays with optical lasers, while combination with THz-IR and electrons are also commonly highlighted. These requirements are discussed in **Section 9.2**. Two-colour or multi-colour FEL capabilities are required by many science areas. Several innovative methods have been developed to retrofit multi-colour FEL capability to existing XFELs – a new facility offers the opportunity to include these in an optimised way, with potentially unique capabilities, including extending the range of energy/temporal separation.

9.1.2.6 High power EUV/gamma source (multi-MHz repetition rate)

Opportunities to develop symbiotically a high power EUV source for lithography and a high brightness gamma source for use in nuclear applications were identified. These would benefit from higher repetition rates (up to approximately 100 MHz) but require relatively low electron beam energy (1 GeV). There is potential to incorporate these capabilities as described in **Section 2.4.5**.

9.2 Facility general requirements

Although the X-ray properties are at the core of the new science made possible by XFELs, a successful XFEL facility with unique scientific reach must have provision for many other features. These features, if properly configured, can add greatly to the capability of a world-leading UK XFEL.

A great deal of the added value of the UK XFEL plans can come from these auxiliary features that will enable a broad swathe of new science not possible elsewhere. These general requirements are discussed here. They are informed by the Science Case **Sections 3 – 8**, and by the many years of collective experience of XFEL users and operators of existing facilities.

Since the time-resolved capabilities of XFELs arise largely from pump-probe experiments, it is inevitable that ultrafast lasers are a key requirement. By looking to the latest optical technologies, we can ensure the availability of ultrafast pulses spanning the wavelength range from 10 µm to less than 10 nm (photon energies 0.12 – 120 eV). The synchronisation and time tool strategies explained in **Section 9.1** can then be used to deliver pump-probe timing determination approaching 1 fs (and eventually better than this). For still longer wavelengths of importance to, for example, chemistry and condensed phase systems, accelerator-based THz options (based on bends or short undulators) can be developed (see below). For some of the most adventurous physical science in this case (**Sections 3.5** and **3.6**, and **Section 4**) high power lasers capable of reaching focused intensities > 10^{22} W cm^{-2} are required to operate at a repetition rate matching to the HXR beamlines. For shock compression and high energy density systems, a rep-rated (> 10 Hz) high energy laser (of a kJ class) would permit world leading science. Electron beams and high magnetic fields are other capabilities that when offered at the interaction points with the X-rays will greatly extend the science range. Beyond this, sample delivery and sample preparation of the most advanced kind are required to enable a truly world-beating range of experiments. The most advanced detectors for X-rays and emitted charged particles, of exceptional sensitivity, dynamic range and ability to accept the full repetition rate of the X-rays pulses, are also essential. All the detectors and diagnostics systems will generate vast quantities of data at the increased repetition rates planned, and the hardware, software and administrative strategies to handle these must be designed into the facility at the outset.

9.2.1 Femtosecond optical pump sources 10 µm to less than 100 nm

The dynamics of matter can be studied by selectively probing excitations, e.g. electronic, vibrational and rotational. These naturally lie in a range of photon energies (wavelengths) ranging from the deep UV through the optical to the far IR part of the electromagnetic spectrum, as reflected by the commensurate timescales illustrated in **Figure 9.1**. Electronic excitations of the valence states of neutrals and ions lie in energy ranges typically from 20 eV to 0.4 eV (50 nm to 2 µm). Vibrational excitations/ phonons lie in the range from 0.4 eV – 0.02 eV (2 – 20 µm), whilst rotations are at still lower energies/ longer wavelengths. Raman excitation, as opposed to direct single photon excitation, offers ways to access these excitations using shorter wavelength sources, but sometimes direct excitation is required. This sets a wide variety of target photon energies/wavelengths that must be provided from a femtosecond laser. This is generally done using a range of non-linear optical techniques: optical parametric amplification (OPA), difference frequency generation (DFG), harmonic generation (second to fifth), and high harmonic generation. OPAs are especially attractive, as they offer continuous tunability over significantly wide wavelength ranges and can produce a wide range of other wavelengths through coupling to the other non-linear techniques.

Most early experiments at XFELs used Ti:S chirped pulse amplified (CPA) architecture femtosecond lasers, but, as the repetition rates of XFELs have increased, this technology is sometimes limiting, although it will doubtless still continue as a workhorse for decades to come. New technologies include: disc laser pumped OPCPA lasers offering 100 – 200 kHz repetition rate and intrinsically short pulses; and fibre lasers using coherent combination of multiple fibre outputs that can approach the 1 MHz repetition rate, be pulse compressed to short duration, and be used in conjunction with OPAs and

other non-linear methods to cover the required spectral ranges. It is likely that a UK XFEL will embrace all of these technologies, plus others currently under development, to provide the full range of required wavelengths at the required repetition rate.

Although in most current XFEL facilities, pump laser pulse durations of 30 fs have been deemed adequate, as the X-ray pulses become shorter the laser pump pulses must be matched with comparably short pulses. Some XFEL end-stations are starting to use hollow core fibre pulse compression, and new fibre and structured fibre technologies are likely to see widespread use across diverse wavelength ranges. Recent work has shown the utility of structured (Kagome) fibres for deep UV pulses of ~ 3 fs duration,[1] and exceptional performance of stretched hollow core fibres in non-linear pulse generation across a broad spectral range.[2]

The need to go to longer wavelengths will require a combination of laser-based THz generation methods to reach 10 THz, and potentially electron beam-based THz methods to cover the 10 – 30 THz range (see below). These pulses are necessarily far longer in duration than the optical domain pulses (picoseconds rather than femtoseconds), but their key role in exciting the modes of importance to thermally-excited samples (**Section 6**), and of driving condensed phase systems beyond normal equilibrium (**Section 5**), mandate that they be available.

For wavelengths shorter than 220 nm a number of options exist. There are some promising structured and hollow fibre-based approaches that offer relatively high power to around 120 nm.[3,4] To reach into the VUV – XUV range (10 – 100 eV), the conventional choice is high order harmonic generation that has been shown to be driven by high repetition rate lasers.[5] In the energy range to 25 eV, relatively high conversion efficiencies (10^{-5} – 10^{-6}) have been demonstrated, so pulses of 1 – 10 nJ are possible, even for high repetition rates, which are of sufficient energy to pump the small sample volumes probed in typical XFEL experiments.

9.2.2 High energy and high power lasers

The requirement for LWFA and other MEC-related high energy density pumping (**Section 4**) necessitates the availability of a high power multi-petawatt class laser with < 30 fs pulse duration, that can be focused to intensities from 10^{18} W cm^{-2} to those exceeding 10^{22} W cm^{-2}. Multiple focusing geometries (and hence focused laser intensities), coupled with high repetition-rate targetry, would permit access to a broad range of extreme conditions and laser-driven secondary sources. In order to access extreme fields, and many of the regimes needed for the fundamental physics experiments described in **Section 3.5**, laser powers on the order of 100 PW (and focused intensities exceeding 10^{24} W cm^{-2}) could be required. While this would require long-term technological development, it would be viable for a UK XFEL facility.

To provide a really unique capability, we should aspire to a 100 Hz repetition rate laser system. These higher repetition rates will greatly benefit the observation of rare events, including the study of non-linear QED systems driven by ultra-intense electromagnetic fields, where statistical analysis of multiple events will be required. Many applications of secondary sources generated by high intensity lasers will also require higher repetition rates. A new high repetition-rate, high intensity laser would provide an attractive platform to optimise existing applications, and draw users from a broad range of research fields when coupled with a powerful X-ray probe. Conversely a high-power laser could also be used to probe XFEL-driven non-linear dynamics; hence a high-repetition rate source should be a priority, to exploit the capability of an ultra-intense hard X-ray source.

The rapid advancement of diode-pumped laser technology has made possible the construction of lasers such as D-100X (developed by the Central Laser Facility in the UK and recently installed at the European XFEL). D-100X uses innovative diode-pumped, cryogenically gas cooled amplification medium to produce high energy (> 100 J) laser pulses at high repetition rates (10 Hz). The same diode pumped laser system will also power the 10 Hz petawatt laser source for the new Extreme Photonics Applications Centre (EPAC), for which construction is currently underway. This innovative technology

could be scaled to produce higher energies and/or repetition rates, depending on the evolution of the science drivers.

To ensure unique new science is possible in the dynamic compression area and studies of warm dense matter (WDM), a high-energy frequency-tripled kJ class nanosecond laser is required in order to reach the highest energy densities and pressures. A 10 Hz repetition rate is highly desirable – going to higher rep rates as the technology evolves. Multiple high-energy beams could be combined in order to provide novel geometries for compressed matter experiments, as well as to provide a more scalable path to the highest laser energies (and hence experimental pressures). The laser temporal profile should be highly tuneable (as per D-100X), in order to provide access to the largest possible range of energy states. The scalable and flexible nature of the DiPOLE laser technology would underpin the operation of both a high power and high energy laser system, thus delivering a wide range of experimental capability at a considerably lower cost compared to that required to build two independent laser systems. A high-repetition rate, multi-petawatt class laser would require hundreds of joules of pump energy (possibly over a kJ for the highest powers); hence when not in use (or running at lower power), the high energy DiPOLE system could be fully customised and optimised for dynamic compression experiments. Should both ultra-high power (multi-petawatt) and high energy lasers be required simultaneously in the future, then the total pumping capacity could easily be expanded to meet the requirements of the user community.

9.2.3 THz, high magnetic fields and relativistic e-beams at interaction points

It is possible to obtain intense pulses of THz light, synchronised to the FEL pulse, from electron beams using a number of different mechanisms. The FEL electron beam is used at the TeraFERMI beamline[6] after it has passed through the FEL and just before it is dumped. In this example, the electrons pass through a thin metal foil and emit coherent transition radiation. An alternative is to pass the spent beam through a long period undulator to generate the THz, as is the case at FLASH.[7] Recent technological breakthroughs in this method[8] make it feasible to use the GeV-scale electron bunches at hard X-ray FELs to generate synchronised, narrowband THz with the required 100 MV cm^{-1} peak electric fields and > 10 T peak magnetic fields specified in this Science Case (**Section 6.2**). Another option to consider would be the generation of a low energy, short bunch, electron beam (of order 10 MeV) close to the FEL beamline for efficient undulator light production. This electron beam would be well synchronised to the FEL pulse using established techniques, and could also be used as a source for electron radiolysis and diffraction at the end-stations.

The interaction of materials with magnetic fields is a rich source of information on their magnetic and spin quantum properties. Work at LCLS investigating X-ray scattering from materials using their 30 T pulsed magnetic field apparatus has revealed new insights into quantum materials.[9] It would seem an excellent aspiration to equip at least one hard X-ray end-station with a pulsed high B field facility to progress research in this direction. The possibility for a high field DC magnet might also be considered, given that the pulse repetition rate in both hard- and soft-X-ray would deliver unprecedented measurement sensitivity that could transform our understanding. The options for doing this would need to be further reviewed under the activities associated with preparing a Conceptual Design Report.

The demands for pulsed radiolysis (**Section 6**) and the prospects for UED (**Appendix 2.3**), potentially combined with correlated X-ray spectroscopy and X-ray scattering on the same sample, demand that a synchronised relativistic (1 – 5 MeV) electron gun be located at least at one of the end-stations. This will open up new science not available at any existing XFEL facility, as well as enabling an independent programme of research driven by UED alone. The technology of these guns is now mature enough that we can be confident that this is achievable.[10,11] The Conceptual Design process will need to analyse the strategies for synchronisation with the X-rays, the extent to which a common suite of scattering detectors can be used, as well as addressing any radiological protection issues. Other laser accelerated electron and ion beam capability will be developed to extend possibilities to higher energy electrons to the GeV range (see **Section 4.3**), accelerated protons and various ions. This will lead to a world-leading capability.

9.2.4 Sample delivery, sample environments and fabrication

The particular characteristics of X-ray scattering experiments at XFELs, i.e. the powerful concept of "diffract-before-destroy" that has driven progress in serial femtosecond nano-crystallography and coherent diffraction imaging, have demanded the development of new concepts in sample delivery. Great progress has produced an array of sample delivery methods, starting with liquid injector and gas dynamic virtual nozzle (GVDN) injectors,[12] and expanding into several alternatives as described in **Section 7**.

Table 9.1: Minimum time required for one SFX dataset with 25,000 indexed images

Facility	Detector	Image Rate	Time to Collect Dataset with			
			5% hit ratio		80% hit ratio	
		Hz	seconds	minutes	seconds	minutes
LCLS	CSPAD	120	4167	69.4	260	4.3
LCLS	Rayonix [a]	10	50000	833.3	3125	52.1
LCLS	Rayonix [a]	30	16667	277.8	1042	17.4
SACLA / PAL-XFEL	MPCCD	60	8333	138.9	521	8.7
SwissFEL	Jungfrau [b]	100	5000	83.3	313	5.2
European XFEL	Jungfrau [b]	160	3125	52.1	195	3.3
Diamond VMXi	Eiger2 [c]	500	1000	16.7	63	1.1
European XFEL	AGPID [d]	3,520	142	2.4	9	0.15
LCLS-II-HE	ePIX [e]	10,000	50	0.83	3	0.05
SHINE	tbd [f]	17,000	29	0.48	2	0.03

[a] Rayonix MX340-XFEL detector with different on-chip pixel binning modes impact pixel size and image readout rate; e.g. 2x2 = 10 Hz, 4x4 = 30 Hz

[b] A JUNGFRAU detector with 16 "on-board" memory cells that can collect 16 images across a 300 µs pulse train arriving at 10 Hz (equivalent to 53.3 kHz intra-train frequency) at the Eu.XFEL or at 100 Hz at the SwissFEL.

[c] The Dectris Eiger2 is a counting detector and is shown for comparison at the VMXi beamline at Diamond Light Source. The detector does permit electronic gating to collect factions of the 2 ms image rate.

[d] The European XFEL can deliver up to 27,000 pulses in 600 µs duration trains at 10 Hz, to achieve an intra-train frequency of 4.5 MHz. The Adaptive Gain Integrating Pixel Detector has "on-board" memory sufficient to save 352 images per train at 10 Hz.

[e] Under development and likely to collect at 10 kHz evenly spaced across the 1 MHz pulses

[f] Under development and likely to collect at ~17 kHz evenly spaced across the 1 MHz pulses

Table 9.1 shows a comparison of the typical data collection rates between XFEL facilities in operation now and under construction. These rates are driven by a combination of the X-ray pulse frequency and the detector capabilities. For example, the LCLS-II-HE facility anticipates fielding a 10 kHz ePIX 4M detector for SFX, which will collect scattered photons from only a fraction of their 1 MHz pulses. The impact is profound as illustrated by the expectation that a 25,000 image dataset will require only 50 seconds even with a very modest 5% hit ratio. For comparison, at LCLS this same dataset takes more than an hour when collected at 120 Hz. Moreover, if an 80% hit ratio is realised, then slower XFELs still yield datasets relatively fast – e.g. 10 Hz with a 80% ratio (52.1 minutes) is quicker than 120 Hz at 5% ratio (69.4 minutes).[13,14] If a high sample hit ratio is ultimately coupled with high X-ray pulse repetition rate, then each dataset may only require a few seconds. Some of the current on-demand sample delivery methods can operate at up to 50 kHz, but further developments are needed to achieve 0.5 MHz or faster on-demand sample delivery strategies. It is also clear that future SFX experiments will tax computational resources by generating very large datasets, which may require varying degrees of image triage, and will need merging as fast as possible so that scientists make the most effective use of XFEL beamtime. Thus, very quickly one will ask these fundamental questions that get to the heart of the data processing and sample delivery aspects of SFX research at XFEL facilities:

- *When will I know what is overall quality of the SFX data we just collected?*
- *How long will it take to collect the second, third, fourth, … datasets, especially in a time-resolved series?*

The remaining challenges include increasing the throughput and developing sample on demand technology that will ensure every X-ray pulse yields useful data (rather than the high fraction of "misses" that is the current norm for some sample delivery methods). Technology is moving quickly, with sample array technologies as well as sample on demand injectors being developed. The aspiration should be to ensure the most efficient data collection and highest throughput. A further aspiration is that users eventually may not even need to accompany their samples to the XFEL, which will greatly expand the number of scientists and Pharma companies who use XFELs as a routine part of their research efforts. Finally, the XFEL Single Particle Imaging initiative strives to collect scattering data from macromolecules under near physiological conditions to support sub-nanometre resolution atomic models and time-resolved studies. Recent theoretical analysis suggests that 3 Å resolution models might be reconstructed from about 66,000 good quality images.[15-18] With appropriate noise mitigation strategies, improved algorithms, and more images, then the resolution will improve even further.

For X-ray spectroscopy, a similarly wide array of liquid jet technologies is available that can optimise the measurement using XAS and XES.[19,20] An important motivation for high repetition rate is that very dilute samples, for example those consistent with the concentrations in naturally occurring biochemistry, can be studied; optimised sample environments that minimise noise in the detection channel must be further developed.

Solid state samples of importance in materials science face a limitation due to sample damage (both pump beam and X-ray induced). This effect has hitherto limited data acquisition to relatively low repetition rates. To fully exploit the capabilities of the XFEL it is important to develop sample growth facilities to provide a ready supply of high-quality samples, moving sample holders that allow a fresh region to be probed even at a high repetition rate, and in situ sample cooling to ameliorate damage. Solid samples for high energy density (HED) science, and diamond anvil cells transparent to X-ray probing, will also need to be developed. HED science has traditionally been performed at low-repetition rate, high energy laser facilities (with repetition rates below one per minute) and, as the sample must be replaced for each shot, this has become the low throughput working mode. It is reasonable to move towards faster sample refreshment that could see a step change in data quality, enabled by far higher repetition rate X-ray pulses (for directly creating WDM) and the rep-rated high energy laser. To achieve the higher-rep rate objective, developments in target fabrication and presentation to the beams will be required.

For solid crystalline samples, the ultrafast excitations of interest are often at low temperatures requiring cryostats. This is challenging for pump-probe applications because two vacuum windows are needed, one for the pump and one for the X-ray probe, and few materials are transparent to both. Availability of cryostats at existing XFEL facilities is patchy and the choice of samples or facilities is often constrained by this. "Cryostream" gas jets are often used with nitrogen or helium cooling gas to avoid the window problem, but these lead to icing and sample stability issues. Sample vibration is a second, related issue in the implementation of a cryostat. The UK XFEL will benefit from expertise at existing neutron and X-ray facilities, as well as the national presence of the Oxford Instruments company to strive to deliver innovative solutions. For example, fixed window, feedthrough-based solutions have been proposed and are under development at Diamond's I-16 beamline.

9.2.5 Advanced X-ray detectors

X-ray imaging detectors of high sensitivity and dynamic range, and operable at high repetition rate, are essential for all X-ray scattering measurement, and also for momentum-spectrum resolved RIXS and spectroscopy measurements. This has been an area of dedicated progress across a number of organisations over a long period of time (including RAL UK, PSI Switzerland, DESY Germany and SLAC USA) and excellent detectors for the current range of repetition rates are available (see **Table 9.1**). For

anticipated higher repetition rates (> 50 kHz) new detectors are under development, but approaching the near future 1 MHz rates are still seen as a major challenge.

The development of hybrid technology detectors, with charge integrating front-end electronics instead of photon counting, has been critical for XFEL sources, where many photons arrive at the detector in a very short period of time due to the pulsed nature of the source. These detectors need to have single photon sensitivity (i.e. the detector equivalent noise charge must be smaller than the charge released in the sensor by a single photon event) and they also need to be able to detect a large number of photons at one time (up to 10^6 photons/pulse) without going into saturation. Hybrid integrating detectors are in use at existing XFEL sources, such as LPD, AGIPD, and DSSC developed for the European XFEL, ePix detector developed for LCLS at Stanford, and the JUNGFRAU detector developed for the SwissFEL. The JUNGFRAU detector can run at a frame rate up to 2.4 kHz, and the development team is planning further improvements of the chip that aim to bring the maximum frame rate to around 4 kHz. At SACLA, CITIUS, an integrating detector with a frame rate of 17.4 kHz, is under development.

Further initiatives are currently underway to meet the challenges that are posed by the next generation of XFELs, such as LCLS-II or the upgrade of the European XFEL. These new sources will require detectors running at a frame rate of 100 kHz and above, expected to be in routine operation within the next 10 years. For instance, at LCLS the plans are based around the ePIX detector family with ePIXHR (5 kHz) now being rolled out for LCLS II, and future models ePIXHR2.5D (25 kHz) and ePIXUHR (100 kHz – 1 MHz) in the development pipeline. Nevertheless, at SLAC it has been recognised that no single detector solution will satisfy all future applications. There remains an urgent need for innovation and continuing R&D in this arena, but on the timescale of 10 years, off-the-shelf solutions likely up to the 100 kHz rate will be ready for UK XFEL.

9.2.6 Electron and charge particle detection

Many measurement modes utilise emitted electrons and ions that carry the signatures of dynamical changes, e.g. in X-ray photoelectron spectroscopy (XPS), angle resolved electron spectroscopy (ARPES), and coincidence-based momentum imaging. Favoured techniques, such as velocity map imaging (VMI) and electron/ion time-of-flight (TOF) measurements, can still be used at higher rep-rates, but there will be limits placed at high repetition rates (on readout speeds in the case of VMI and flight times in the case of TOFs). Technical developments to provide efficient high throughput analogues to TOF and VMI will be required to optimise instruments at a number of end-stations. ARPES using standard hemispherical analysers is, in principle, compatible with high repetition rates, but, unless integration over many shots is required, upgraded fast readout detectors will need to be used to access single-shot data. Momentum imaging techniques, such as COLTRIMs, are intrinsically designed for high data rate acquisition, and the REMI instrument at the European XFEL and the soon to be commissioned DREAM instrument at LCLS are already able to handle the higher repetition rates.

9.2.7 Data infrastructure and management for operating at high rep-rate

Along with the massive scientific advantages associated with the high data rate from a high repetition rate XFEL comes a heavy cost in terms of data transfer, storage and management. At the existing high repetition rate facilities, it has been realised that the cost of proceeding without significant data compression and intelligent data retention policies is too high to be viable (estimated at around $0.25 billion in the case of LCLS II and would grow further). Analysis of LCLS II suggests that each working end-station operating at 1 MHz will generate in the range of 100 Gb/s – 1 TB/s. In their planning, they account for a factor of 10 reduction through data compression to 10 GB/s – 100 Gb/s. Part of this compression will be in the form of on-chip data reduction using field programmable gate arrays (FPGAs) integrated to the front-end detectors. Compression via feature extraction, vetos, and multi-event reduction must all form part of the strategy. At the same time, it is vital to provide the possibility of fast feedback to the users in real-time during the experiment to ensure efficient use of beamtime. Very large off-line data storage and analysis capability will be essential, requiring multiple 100 PB storage capacity. To manage this will require the implementation of a forward looking set of

policies on data retention. It is important to start planning hardware, software and administrative policies from the outset, to avoid serious problems later.

The advantages of greater coherence and stability of X-rays by going beyond SASE modes (seeding, eSASE, superradiance schemes) is that the required experimental signal may be measured in a greatly reduced number of shots compared to conventional SASE operation. Experience with two-pulse SASE X-ray modes, where spectral/temporal/intensity fluctuations affecting both pulses in the pair requires aggressive data sorting, has shown that a down selection by several orders of magnitude is often required, which would be greatly improved were seeded and stable operation to be available. Moreover, the pulse-to-pulse X-ray diagnostics are very expensive in terms of data volume, especially if they involve detector arrays (e.g. spectral or temporal measurements like XTCAV) – it has been shown that machine learning approaches to X-ray diagnostics can be hugely beneficial in this regard.[21]

A fully integrated controls environment must be developed for the entire facility, including all end-stations and experimental installations. The experience required to do this is available from Diamond, LCLS, European XFEL, etc.

9.2.8 Auxiliary support facilities

To allow the efficient delivery of the science mission, UK XFEL will require an extensive array of state-of-the-art support facilities, as well as excellently equipped end-stations. These facilities need to be accessible easily and in some cases on-site location is desirable.

Capability for sample preparation and fabrication will be central to supporting the best science. Nanofabrication capability on-site, including nanoscribe, fast-ion beam (FIB), sample growth and nano-lithography, will be required. Laboratories for safe preparation of high-quality chemical and biological samples will likewise be required. If the industry demand arises, there may need to be facilities for handling nuclear materials. Additionally, first class machine shop, optical testing and coating, and electronics workshop facilities will be necessary to support both the in-house facility development and the R&D programmes, as well as the user science programme. This includes local testing and measurement labs equipped with sample characterisation capability, such as LEED, TEM, and SEM, as well as standard optical and 2-photon microscopy.

Further measurement modalities, other than X-ray based, can be very valuable in establishing integrative approaches to the science and so stretching the scientific capability; an example of this is co-location of UED capabilities (**Appendix 2.3**). Laser laboratories for optical only time-resolved measurements, Cryo-EM capability for single molecule imaging, and NMR capability might also be integrated into the scientific offer of the UK XFEL, either at the same site or distributed across the STFC facility network.

9.2.9 User support infrastructure

Users are at the core of the scientific success of any facility. A UK XFEL must offer appropriate user support just as any other large-scale user facility, such as the CLF, Diamond or ISIS. In many respects the user support infrastructure in terms of accommodation, transport, catering, safety initiation and training, technical training and data policies will be much the same as at these existing facilities, although attention will be given to ensuring the user experience is as efficient and productive as possible, and that innovations and best practice are applied.

At this relatively early stage in their development, however, the use of XFELs is perceived to be much more challenging than for more established methods and this has presented a significant barrier to the adoption of their use for routine science. A UK XFEL must do all that is possible to support new users and substantially lower this access barrier, both that perceived and the actual one caused by the complexity of end-stations and the rapid development that the technology is still undergoing. Measures to accomplish this are being pioneered at the existing facilities in terms of offering end-station scientist support and transparent to operate end-station controls, and we will adopt all best practice. Some classes of measurement, e.g. diffract-before-destroy CDI, serial nano-crystallography,

time-resolved X-ray spectroscopy and RIXS, should be made far more routine and fully supported, so that in the future in many instances users need only send a sample and collaborate with the staff scientists on the data analysis. Where this is not practical, standard end-station configurations should be developed that minimise facility staff and user time in swapping between experiments, thus making high quality data taking more certain and efficient.

Whilst most end-stations should be configured with a dedicated set of high calibre instrumentation, to ensure high quality data and high scientific productivity. Nevertheless, some provision for “roll-up” user supplied end-stations should be retained, to ensure operational flexibility and future-proofing through the development of new experimental concepts.

Finally, an extensive training support programme will need to be offered by the facility to provide new users with the necessary skills: this ought to be mirrored by university-based academic training actions.

9.3 Synergies with other national facilities and capability: Synergistic technology transfer among XFELs, synchrotrons, and electron microscopy / diffraction

No single method can solve all scientific problems, so it is essential that a UK XFEL is fully integrated into the wider UK science infrastructure. In life sciences several complementary methods exploiting X-rays and electrons will yield atomic level structural and functional insights with increasing temporal resolution, which can be applied to individual macromolecules through to whole cells and tissues. In physical sciences, methods to probe spectroscopy, chemistry and physics will impact materials characterisations and industrial catalysis. By enhancing critical interactions and cooperation between e.g. Diamond-II, the Central Laser Facility, electron imaging centres for physical (ePSIC) and life sciences (eBIC), and the UK XFEL, there will be a large multiplying impact upon the science and upon each facility, as synergistic technologies are developed and shared between each of them.

9.3.1 Fostering relationships with other institutes and facilities

The UK XFEL will not "operate in a vacuum" but rather will leverage the significant opportunities for in-depth cooperation with as many national facilities and research organisations as required, and certainly including: the Diamond Light Source upgrade (Diamond-II), the Electron Physical Science Imaging Centre (ePSIC), the Electron Bio-Imaging Centre (eBIC), the Central Laser Facility (CLF), the Rosalind Franklin Institute (RFI), the Francis Crick Institute, the Henry Royce Institute and the wider university sector. Indeed, the diverse set of capabilities and expertise at these facilities and organisations altogether enable a large cross-section of the science community, thereby making a unique situation in the world.

The Science and Technology Facilities Council's CLF carries out research using lasers to investigate a broad range of science areas, spanning physics, chemistry and biology. It provides a broad spectrum of laser facilities, from high intensity laser systems to ultrafast sources and laser microscopy techniques. The CLF instruments are enabling capabilities that underpin time-resolved spectroscopy and structural biology with pump-probe strategies, computational plasma physics to target micro-fabrication, and laser tweezers. Some of these efforts already include close cooperation with Diamond Light Source to enable time-resolved dynamic structural biology and spectroscopic studies. Artemis is a leading ultrafast XUV research facility, based upon high harmonic generation with a strong programme on time-resolved ARPES and CDI, and will be strongly connected to part of the science mission of a UK XFEL. Indeed, pump-probe optical laser-based capabilities are also common and critical at all XFEL facilities around the world. The world-leading expertise in ultrafast lasers available at the CLF will be an essential asset for the new facility, as will the synergistic R&D being carried out for the nascent EPAC project.

In early 2020 and within the framework of the HiBEF user consortium, STFC and the CLF delivered a 10 Hz repetition rate, high-energy laser, D-100X, to the High-Energy Density (HED) instrument at the European XFEL. The experimental set-up at the HED instrument will enable scientists to generate and study extreme temperatures and pressures in materials that are similar to the interior of exoplanets, with temperatures of up to 10,000°C, and pressures of up to 10,000 tons per square centimetre. Without question, the UK XFEL project will include very close interactions with the CLF, as reflected in the plans here to incorporate the DiPOLE technology into the proposed end-stations.

The RFI is a new national institute, funded by the UK government through UK Research and Innovation, dedicated to bringing about transformative changes in life science through interdisciplinary research and technology development. It will bring together academia and industry to solve the most pressing problems in the life sciences (Industrial Biotechnology, Pharmaceutical, Agrichemical). The RFI has a Hub at Harwell and currently ten university partners (Spokes). The RFI has five interlinked scientific themes; structural biology, next generation chemistry, imaging with sound and light, mass

spectrometry and next-generation electron microscopy. A new building for the RFI is under construction on the Harwell Campus and is already interacting with Diamond Light Source, the CLF, and the Research Complex at Harwell (RCaH). There is every expectation that it will also interact with the UK XFEL project, especially within the structural biology and next-generation chemistry thrusts.

Diamond-II is a co-ordinated programme, funded by the UK government and the Wellcome Trust, for a major machine upgrade.[22,23] In April 2020, the project cleared CD1 status and is currently in the design, baseline scope, cost, and schedule phase, with an anticipated start of user operations in early 2027. Diamond-II will be a diffraction limited, fourth-generation synchrotron source based upon a novel multibend-achromat (MBA) storage ring lattice and electron beam accelerator operating at 3.5 GeV to provide dramatic gains in photon brightness (especially at high energy) and coherence. The project includes complementary improvements to optics, detectors, sample delivery, and computing, as well as integrated and correlative methods. As a result, Diamond-II will be transformative in speed and resolution, and will offer scientists streamlined access to enhanced instruments for life and physical sciences. Diamond-II will enable a wide range of science at its > 34 beamlines as well as a suite of complementary facilities – eBIC,[24] ePSIC, the MPL (Membrane Protein Lab),[25] the XChem Fragment Screening service[26-31] and the XFEL Hub at Diamond,[32,33] which develops technology for sample delivery and data analysis for XFELs for life sciences. In addition, the world-recognised strengths of the collaborative computing projects (CCP4,[34] CCPN,[35] CCPEM[36,37]) in structural biology based at the RCaH and the Diamond structural biology software groups, provide an excellent environment for future software developments. More information about these opportunities is detailed in **Appendix 2**.

ePSIC and eBIC are national user facilities operated by Diamond Light Source to provide access to state of the art transmission electron microscopes for physical and life sciences. ePSIC is equipped with two aberration corrected microscopes for studying materials at the atomic scale. eBIC already offers high-end Titan Krios instruments equipped with direct electron detectors and automated data collection software for single particle cryo-electron microscopy. It also supports molecular cryo-electron tomography, cellular cryo-electron tomography, focused ion beam milling and imaging and will soon offer electron crystallography. More information with respect synergistic relationships between the UK XFEL, cryo-EM, and eBIC is detailed below and in **Appendix 2**.

9.3.2 Examples of synergistic efforts in structural biology

Structural biology is experiencing parallel step-changes in X-ray crystallography and cryo-EM methods.[16,38-44] The former is related to XFELs and emerging opportunities in SFX, time-resolved SFX, and time-resolved single particle imaging. The latter impact is highlighted by the 2017 Nobel Prize in Chemistry awarded to Dubochet, Frank, and Henderson for "developing cryo-electron microscopy (cryo-EM) for the high-resolution structure determination of biomolecules in solution."[45,46] Because methods and microscopes are improving rapidly,[47-49] and national centres supporting the high-end instruments are more common, more high resolution structures of smaller macromolecules are being released on a daily basis. Facilities like eBIC at Diamond provide scientists with state-of-the-art experimental equipment and expertise, for both single particle analysis and cryo-tomography.[24] It is part of the UK infrastructure that overall fields more than 20 high-end microscopes. Similarly, three US NIH-funded national electron microscopy centres are operational in New York, Oregon and California. There are also analogous initiatives in many European countries and Asia.

There is, however, still room to improve cryo-EM technologies especially with respect to the quantum efficiency of detectors, recovering all of the high-resolution signal in the presence of various types of noise, selection of the appropriate electron energy, sample preparations methods and data analysis algorithms. Improvements in all of these areas will bring the method closer to its theoretical limits. Together, MX and cryo-EM have the potential over the coming decade(s) to provide the necessary tools to establish the structural basis of nearly every functional aspect from any type of cell.

With such large global effort and many important biological targets (see also **Table 7.1**), progress across all of biology has been profound and will continue with increasing pace.[50] This is reflected in the recent PDB statistics (**Figure 9.3**) indicating that the ratio of X-ray to cryo-EM in 2019 was 6.8;

compared to a few years earlier when the ratio was greater than 100. It is very likely that parity will be reached soon. Although cryo-EM does not require a crystal lattice, the data is collected under cryo-conditions that are far from physiological and do not allow for dynamic conformational changes. However, freeze-quench methods are being developed to enable time-resolved cryo-EM with about ms time resolution.[51-53]

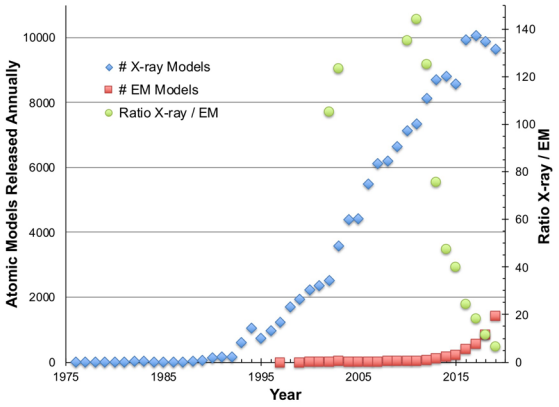


Figure 9.3: ***Growth of the PDB archive from X-ray and cryo-EM methods*** *(compiled 27 Feb 2020). The tally algorithm does not account for thousands of models related to fragment screening results (at Diamond and elsewhere), consequently the numbers for MX are still increasing.*

Sample preparation and delivery are unmet challenges in both serial MX and cryo-EM methods. This offers significant opportunities for technology transfer between the fields. They each must manipulate on-demand nano- to picoliter volumes of either macromolecules in solutions or as a slurry of micro-crystals.[13,52-58] Freeze-quench methods in cryo-EM will likely be limited to about 100s µs to ms time range because of constraints linked to sample grid preparation; however, this is an active area of R&D. High-quality SFX and time-resolved SFX data collected at XFEL facilities already approach fs time resolution for light-triggered reactions. For mixing strategies, it is likely that enzyme reactions will be studied from 100s of µs through seconds. With more XFEL facilities, some running with MHz repetition rates, scientists will be able to significantly improve the correlations between the electronic and atomic structures, even potentially on a crystal by crystal basis.

Scientists working at the forefront of biology will use many of tools available to them in an increasingly integrative approach (**Figure 7.2**). For structural biology, some frontier challenges for synchrotrons, XFELs and cryo-EM / electron diffraction (ED) are summarised in **Table 9.2.** In **Section 7** and **Appendix 2**, several areas of common synergistic overlap are identified. Consequently, R&D effort in one area is very likely to transfer rapidly to other areas.

Table 9.2: Frontier challenges in structural biology and some approaches for progress

Goal	Synchrotrons	XFELs	cryo-EM & ED
To determine time-resolved structures directly from systems engaged in catalysis at physiological temperature and pressure	• RT serial µ-crystal methods • focused µ-beams • µs – ms datasets to dose limits • kinetics within µ-crystals correlated w/ spectroscopy	• on-demand sample delivery methods • mixing injectors • kinetics within n – µ-crystals correlated w/ spectroscopy • SFX processing pipelines	• automated, time-resolved sample grid preparation • high resolution from smaller targets • RT serial & time-resolved ED
To determine structures from single molecules in native-like conditions (in solution or membranes, in pure complexes)	• continuous diffractive imaging from n – µ-crystals with coherent sources	• single particle imaging & sample delivery methods • continuous diffractive imaging	• imaging processing & better detectors • low-energy electron holography
To understand structure/function/dynamics in native context	• X-ray microscopy with correlated imaging of metals and/or labels	• *in-situ* SFX of n – µ-crystals • imaging processing	• liquid / whole cells • high resolution microscopy

Exciting future challenges lie in the ability to observe dynamic enzymes and macromolecular complexes at high spatial and temporal resolution, both in purified/reconstituted forms and *in situ/in vivo*, and the ability to correlate these dynamics with physiological changes from the cell to the tissue and organism. There are clear opportunities to exploit the synergies between all of the current structural biology techniques including but not limited to:

- synchrotron- and XFEL-based MX including serial methods
- cryo-EM single particle techniques
- cryo-electron tomography
- serial and time-resolved electron diffraction from sub-micron macromolecular crystals
- NMR
- other spectroscopic methods.

9.4 Options Analysis

To guide the decision-making as to the way forward, with the objective to deliver all or most of the scientific opportunities identified in this Science Case, we have looked at a range of options. These span from the recommended option, as determined by the science opportunities identified in this case, of building a world-leading machine to simply building on the status quo. A discussion of the pros and cons of each option is offered.

Given the science and technology opportunities highlighted in this Science Case, we must now address how best to realise these opportunities in the fullest form, whilst being mindful of other considerations and constraints (cost, timescales, etc.). We have developed the following preliminary analysis of different classes of options to guide us in this process. No rigorous quantification of cost is as yet available to us, so the analysis is necessarily only qualitative. Nevertheless we can assert that the most ambitious options (A and B) carry the highest cost, but also provide the greatest benefits for the UK science base and potentially the wider economy. In contrast, the latter options (C – F) are relatively cheaper, but will return progressively less gain to the UK science base and the economy.[1]

A. Build a unique UK XFEL optimised for new capability

This option would deliver a unique UK XFEL, fully optimised with some of the most advanced X-ray capabilities in the world with, for instance, high repetition rate across a significant portion of the photon energy range. In this category are both *Concept outline 1* and *Concept outline 2*, overviewed in **Appendix 1**. Seeding would be available up to at least 1 keV, narrow bandwidth modes through the entire X-ray range, and attosecond pulse pairs also across the entire photon energy range from soft to hard X-rays. It would offer a farm of end-stations equipped with the most advanced lasers, THz radiation sources, electron beams and other auxiliary equipment, and have the highest specification high energy and high-power laser integrated into the facility. A high repetition-rate end station for X-ray photolithography could be part of the facility. It would also provide science access to the electron beam for plasma wakefield and other accelerator technology research, as well as a high brightness gamma ray source. The fully superconducting *Concept outline 1* would be the most expensive, but it would deliver high repetition rate across the entire photon energy range at full power and so, in this respect, be directly as capable as LCLS II HE. The hybrid superconducting/normal conducting accelerator in *Concept outline 2* would be more restricted in having high repetition rate X-rays at full power only to 2 – 3 keV, but with lower power harmonics (3^{rd} and 5^{th}) into the hard X-ray range, however it could still have the full range of other unique features as *Concept outline 1*. Pushing the repetition rate of the normally conducting linac for the hard X-rays could deliver repetition rates as high as 5 kHz at full power, although R&D is required to ensure that this is delivered.

The overwhelming advantage of this option is that it will provide the UK with a world-leading XFEL capability, giving maximum scientific reach and the largest potential impact (see **Sections 8.1** and **8.7**). Such an international flagship facility would attract some of the world's best scientists across the physical, chemical, material and life sciences to our shores as users and staff scientists, and into the UK university sector. There would be maximum benefit to the UK skills pipeline, and the high-profile activity would attract young people in STEM subjects and foster growing public appreciation of science. Such a facility would likely attract an exciting array of partners from around the world, including EU, USA, Japan, Korea and China along with nations not yet invested in this technology, such as India, Australia, Canada, Latin American nations, Israel, Middle Eastern & African Nations, and emerging economies in the Pacific rim, perhaps contributing financially to running costs and governance. Nevertheless, the UK would be in control of all major decisions and strategic directions. Sovereign

[1] Although we caution that the time and resources available to us did not permit a quantitative comparison of relative costs, timescales and economic impact between options, such an exercise should be undertaken in any next stage.

capabilities would be safeguarded for the long-term. The facility would signal global scientific and technical leadership.

On the other hand, the cost of such an option would be the highest and the timescale to delivery would be the longest, necessitating other measures to be taken in the interim. As new features and new combinations of features would be combined into the facility, there are moderate technical risks to manage, although no completely new technology needs to be developed for this option.

B. Build a UK XFEL providing capacity well beyond 10 years

This option would be focused on providing national capacity in XFEL science and technology for the long-term. It could include still some novel features and combinations of capabilities that would make it a world-competitive facility, but not the full array envisioned under Option A. It would be in the character of a class of option referred to in the 2016 panel exercise as "SwissFEL+". *Concept outline 3* presented in **Appendix 1** is in this category. We would still anticipate it addressing the majority of our needs for time-resolved X-ray science from soft to hard X-rays, and could have seeding and/or attosecond modes over a moderate photon energy range. It would not, however, provide high-repetition rate (> 500 Hz) over any of the photon energy range. Scope for a full array of lasers and other light sources would still be open, and future upgrades could provide a very exciting array of end-station capabilities.

As the technology for this option is already fully developed, and the scale of the infrastructure significantly smaller than Option A, both cost and delivery time are reduced. We estimate a cost of around 70% of *Concept outline 2*, and delivery time may be appreciably shorter (two-thirds). It would still safeguard a wide range of scientific, technological and sovereign capability. The impact on the UK skills pipeline would still be strong, and it would still be a national flagship for attracting students into STEM subjects. The UK would be in full control of all decisions and strategy, including the nature of future upgrades. There would be some scope for international partnerships, to assist in running costs for instance.

This option would not deliver a comparable level of kudos to the UK as Option A and would signal that, whilst the UK is a competitive environment for X-ray science, it is not a global leader in science and technology. Options to attract scientists from overseas would also be possible, but more likely restricted into specific areas where the facility proves itself especially effective. Some of the UK's XFEL science would likely as not still need to be carried out at more capable overseas facilities. Project risks would be less than in Option A, but it would still require rigorous project management.

C. Invest more in dedicated UK facilities at existing XFELs

As partners in European XFEL, and users of the other main XFELs globally, we would be in a strong position to influence and invest in upgrades. Exactly which of these are most attractive, and/or available to our investment, would require further analysis. There would be scope for doing this at LCLS, SwissFEL, SACLA or PAL FEL (Korea) if an upgrade opportunity matching our aspirations were to become apparent. At European XFEL there are already two unfilled tunnels that could house two undulators dedicated for particular performance ranges, for which input in their development is actively being sought at the current time and in which the UK could become a strong partner. It is thus this option that is analysed specifically here.

This approach could provide end-stations tailored to the needs of a significant fraction of the UK user community with, presumably, some arrangement for preferred access (although unlikely to be exclusive access). As the superconducting electron linear accelerator already exists, the extra costs are much lower than Options A or B (estimate 10 – 20% of Option A cost). Delivery time could be on the order of five years, but we would need to move rapidly to stake our intentions and to bring along like-minded partners. This could certainly be flagged as a national or shared (e.g. German/UK) end-station, politics permitting, which would bring moderate kudos and may attract some star players in the relevant areas to locate at UK universities.

The impact on the UK science and technology base would be modest. As the construction would be overseas, there would be restricted direct benefits to the UK economy. The limited space available in the European XFEL end hall will lead to significant restrictions on what can be done. Additionally, the pulsed nature of the European XFEL RF, leading to a complex temporal structure in the electron bunches, has a restraining impact on the science that can be planned. A small impact on UK skills may ensue from additional UK staff scientists and technicians seconded to European XFEL, but the volume would likely be relatively small compared to Options A or B. Some training opportunities might be created, but again nothing like on the scale of Options A or B. Moreover, we would not have full long-term control over the arrangements, and, although doubtless we would have a say, we could not solely determine the future strategy. UK sovereign capability would not be secured and, in the long-term, access to this capability might still be subject to, as yet, unforeseen geopolitical uncertainties (as well as those already all too apparent). There is thus some risk to the UK science and technology base in pursuing this option.

D. Increase investment to support users in exploiting existing opportunities (e.g. long-term grant funding schemes, CDTs, "UK XFEL Institute")

This option is concerned with building the UK XFEL scientific community so that it has a competitive size, comparable to those in Germany or the USA where the existence of a national facility has greatly accelerated growth. The UK user community is very dynamic and has led many important developments in the early years of XFEL science, but it is still relatively small although growing steadily. To better position UK science to exploit the numerous scientific benefits offered by XFELs, a coordinated programme of community development and training ought to be undertaken urgently. Such a measure is equally important if we decide to build our own facility, as we will need a community ready to take full advantage of all the science opportunities. Large-scale community building, aimed at bringing new groups into XFEL activity that would at the same time allow existing groups to be more effective, should be part of this. These could support the growth of the community by funding research fellows and technicians, networking activity, travel and the required equipment at the home base for preparing XFEL experiments across a wide range of disciplines. Building of specific instruments to be permanently stationed at end-stations might also form an important part of this activity (akin to the contribution of the DiPOLE laser in the HIBEF project at the European XFEL). In parallel, PhD training support is urgently needed. This could be delivered through a set of inter-related CDT doctoral training programmes. Several of these, for instance, centred on serial nanocrystallography, chemical dynamics, HEDs, quantum materials, time-resolved imaging and X-ray physics, could support the science mission whilst providing a high-quality multidisciplinary training environment. Establishing a Scientific Institute (or several Institutes) to promote ultrafast X-ray science could be an additional highly-effective measure, such as the very effective PULSE Institute at Stanford and CFEL at DESY.

The advantage of these measures is that they would accelerate the growth of the science base in the relevant areas, whilst also making a modest contribution to the broader skills pipeline. The cost of such activities would be modest compared to Options A – C, and could be spread across the research councils. We would estimate costs in the range £10 – 30M over five years, depending on the scale of activities undertaken. It could catalyse actions by the universities to recruit academic staff in the area. It would help to make the UK better able to benefit from the world XFEL infrastructures by being more competitive at winning beamtimes and delivering high quality science.

This option, however, offers limited additional economic benefit to the UK and will have only a modest impact on skills outside of the PhD training actions. For instance, it does nothing to support the UK accelerator science capability. Neither does it add significant new scientific capability or capacity to any of the XFELs that would be used. We would still be reliant on access to the facilities hosted by other nations and so fully subject to the rules and strategies of external agencies. UK sovereign capability would not be secured and, in the long-term, access to the scientific capability would still be subject to uncertainties. There is thus some risk to the wider UK science and technology base in pursuing this option.

E. Dedicated R&D effort towards a future XFEL ("test facility")

An action that could have significant value is an XFEL test facility for dedicated R&D. This could support in the longer term an ambitious future XFEL. Already such an action is partly underway in the form of the CLARA facility at Daresbury Laboratory.[59,60] That project might be built upon to satisfy some of these long term R&D needs. This would also play an important role in supporting critical R&D if we go ahead to build an XFEL (Options A or B) on a faster time-line. A detailed analysis of the essential R&D steps that are required to achieve the aims of the preferred XFEL option is required. These essential steps could include proving of novel FEL schemes and pre-production accelerator system demonstrations, such as a very high repetition rate photoinjector, an optimised superconducting RF cryomodule, and high gradient-low repetition rate/low gradient-high repetition rate normal conducting linac systems. Following this analysis a test facility would be proposed which would be optimised for achieving these R&D milestones. This might be an upgraded CLARA or a completely new test facility.

This option would be a stepping-stone to a future facility and would carry only a moderate cost over the next five years (£15 – 30M), of similar scale to Option D. It would at least maintain and modestly grow UK skills in accelerator science, and maintain the UK in a position to be competitive in the required technology. It would be possible to test some very advanced concepts not yet mature enough to be incorporated on the critical path for design of Options A or B (e.g. plasma wakefield acceleration mediated by dielectric or metallic structures).

This option, if carried out alone, would not contribute to the health of the wider science base in the UK in the short or intermediate terms. It would require a recurrent budget and a long-term commitment (~ 10 years) to the activity for it to be effective. If carried out in isolation, it would also not deliver any of the economic, national or skills benefit of a larger-scale facility. It would thus carry with it a moderate risk to UK science and innovation, and embed lost opportunities for at least the intermediate term. The motivation for doing this, if it is not to be seen as part of a long-term strategy to build a UK XFEL, would need to be carefully considered.

F. Extend activities of existing Life and Physical Sciences Hubs

The life science XFEL Hub at Diamond has proven a great success in promoting UK FEL activity in the structural biology subject area (**Figure 9.4**). The Hub is a first in the world. It was formed with grant support from the Wellcome Trust, MRC and BBSRC awarded to Jim Naismith *et al.* in late 2013. The Hub scientists were recruited in 2015, reside at a synchrotron, develop technologies for XFELs and look to take advantage of synergies between XFELs, synchrotrons, and electron microscopy and diffraction to better enable users to solve biomedical questions. There is a special focus on accessing the time domain with high resolution macromolecular crystallography. To these ends, the Hub has established the *Dynamic Structural Biology at XFELs and Diamond* beamtime allocation group at Diamond. This provides valuable training to new users, enables scientist to collect important preliminary data for XFEL beamtime applications across the global XFEL market, and also generates results that stand on their own. The Hub scientists also pursue specific in-house science driven projects in close collaboration with users and other synchrotron and XFEL scientists. The Hub has helped grow the community, especially with travel awards initiated in Oct 2016 that have now enabled more than 250 UK life scientist visits to all five XFELs for their experiments.

The Physical Science hub hosted by the CLF has just begun and is an opportunity to similarly promote the growth of UK XFEL users in other areas of science. These activities must at least be maintained and, for a modest investment, could be expanded and made more effective. Other community actions are currently being discussed, e.g. Oxford/Imperial plus others are looking at better co-ordinated post-graduate training for XFEL science in the chemical/life sciences area, as a step towards a university hosted CDT. Although these activities are only a modest growth from the status quo, they are welcome and of value far exceeding their cost.

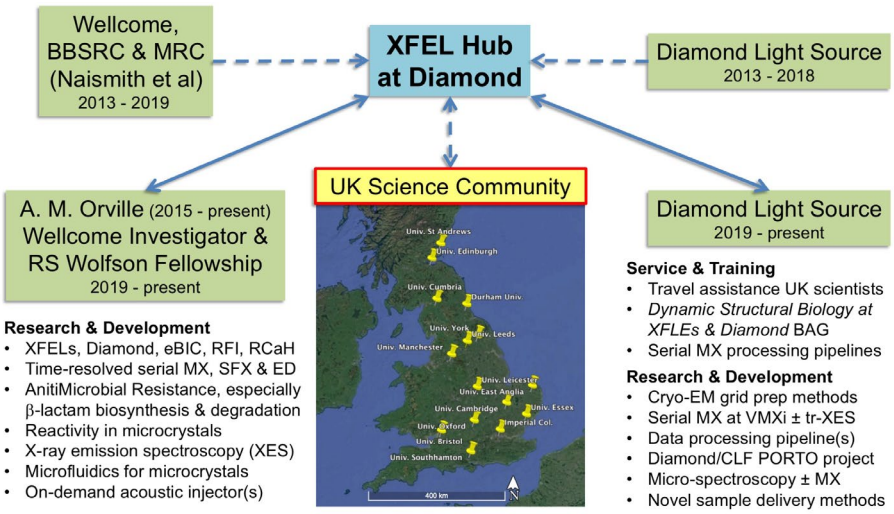


Figure 9.4: Relationships between the XFEL Hub at Diamond and the UK life science communities. The Hub interacts with scientists from around the UK as well as internationally. To date, they have participated in more than 40 XFEL experiments across all five hard X-ray FEL facilities.

To grow these activities, perhaps by guaranteeing long-term funding and a couple of additional staff positions, would be the cheapest option towards delivering on the science opportunities. It would at least support a modest growth in some parts of the UK community and would help a number of additional groups to integrate XFEL-based measurements/experiments into their research programmes. If properly promoted, it could encourage universities to consider creation of new academic positions in this area.

Even with some net growth in the UK XFEL user community under this option, we are likely to fall back steeply against international competitors in relative terms as their community growth accelerates. As this would be widely perceived as doing nothing much new, there is a risk of a brain-drain from currently active university researchers who will see better prospects in overseas universities and institutes perceived to be more favourable to their science. As a "user" only nation, we would have little or no influence on future policies and strategy at the overseas XFELs. There would be a serious risk of lost access due to geopolitical circumstances and changes in access policy (e.g. it has been mooted that at least one major XFEL may bring in charging for access at market rates). No substantive general economic or skills boost would ensue from this option, although some of the individual research projects may create impact. Overall this would carry the highest risks to UK science, innovation and industrial competitiveness.

9.4.1 Summary of options analysis

In summary, the options that involve least cost and sit closest to the status quo are least able to deliver all the science and technology opportunities, and so carry the highest risks to the UK science base and economy. Nevertheless, a combination of Options D, E and F needs to be considered in some form, as they are required steps towards building a machine – which will necessarily benefit from expanding the UK scientific user community and the technical capabilities of UK accelerator science. Option C could also sit efficiently in conjunction with Options A and B, as a way of bridging the capability required over the next ten years and effectively filling any gap not readily satisfied by the planned machine (e.g. very high repetition rate serial nano-crystallography) in the longer term.

"Do nothing" or "do little" strategies are now the riskiest options and could potentially damage national competitiveness, technology and sovereign capability, and international scientific standing. The more ambitious the machine the lower the future risks to UK science and technology.

We thus, based upon the science and technology criteria, strongly recommend that Option A is adopted, supported by the required R&D activities and components of Options D, E and F to continue to build the UK community in the interim.

9.5 Next steps

Building a UK XFEL with a unique array of capabilities is our recommended option to support future science and technology. This will require a structured plan that develops a concrete technical and civil construction design for the infrastructure, addresses costs and economic impacts, identifies a suitable site and builds further a science community. Accounting for construction and commissioning, we could then anticipate an operating facility at the end of the decade.

9.5.1 Community building and continuing engagement

This report was initially publicly released as a "Draft Science Case", and an opportunity was given for further engagement with the community which resulted in the current revised Science Case. We anticipate continuing to engage with individual scientists, the wider community of scientists and technologists, and the research funding agencies and institutes. A high priority is a wider engagement with industry and industry-facing research organisations. It is fully the intention to continue to evolve and refine the science, and identify new areas not as yet covered in this process.

A necessary next step to optimise the UK position in the science areas identified is to continue to engage with the scientific community. The objective will be to encourage a wider participation in the science as we are mindful of the perceived, and real, barriers to access that need to be overcome. Actions such as the Life and Physical sciences Hubs at Diamond and the CLF, respectively, are very important in this regard, but these must expand significantly and other actions must be promoted within the universities and national research institutes. Development of synergies with other UK capabilities will be essential in developing the required scientific leadership (see for example the plans for Life Sciences sketched in **Section 9.3** and **Appendix 2**). An essential objective is to build an effective cohort of scientists who can drive the science forward, both at the existing international facilities over the next decade, and at a UK XFEL too in the longer term.

Targeted funding, in the form of Programme and Project grants and Centres for Doctoral Training, established in a coordinated way across UKRI would be very important to achieving this. The universities must also be encouraged to step up and support new academic positions in the area, and explicitly recognise XFEL science as an element of their strategy. The establishment of XFEL Science-related research institutes would clearly be beneficial in shaping the intellectual leadership and the training infrastructure that is required: examples of significant success in this regard are CFEL at DESY, Hamburg and the PULSE Institute at Stanford that have greatly contributed to the standing of this new science in Europe and the USA, respectively.

9.5.2 Technology assessment and conceptual design

The conceptual designs presented in **Appendix 1** have already undergone expert analysis and a broad feasibility assessment. In a next step a full *Conceptual Design Study* will need to be implemented over a period of around two years, to develop a fully coherent machine design that will deliver the science at a competitive cost. This will require development of a cost model to allow the cost benefit analysis of different scenarios, as well as detailed simulations and analysis of all technical aspects of the facility. A *Business Case* will also be prepared for the facility. The Conceptual Design team will need to remain in continuous discourse with the scientific community to ensure that the evolving scientific demands are matched to the developing design.

Certain key elements of R&D, already identified, will be more fully defined and initial work begun. These could include work on the photoinjector, RF accelerator modules (both super-conducting and high-rep rate normally-conducting) and other critical systems, superconducting undulators, timing and synchronisation systems, the possibility of an ERL system or return loop system for soft X-ray generation, high power laser and high energy laser systems, high rep-rate lasers for facility end-stations and for seeding, designs of a gamma ray source based upon inverse Compton scattering from a ~ 1 GeV electron beam, feasibility and configuration studies for X-ray oscillator or regenerative

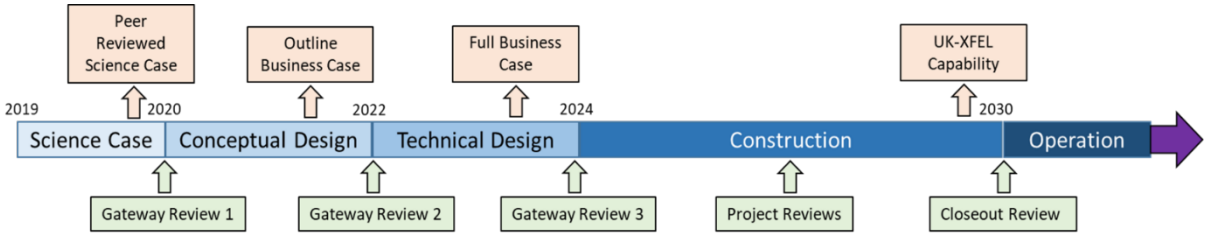
amplifier options, synchronised MeV guns for THz and auxiliary e-beam capabilities, etc. Once the conceptual design is completed the critical path R&D can be fully defined.

This step has been costed and the timescale assessed. In order implement it effectively will require ~ 20 FTE over a period of two years, at an approximate cost of £3M.

9.5.3 Technical design, R&D and pathway to construction and commissioning

The main part of the required R&D would take place over the period 2021 – 2024, using dedicated facilities and synergies with CLARA and other projects within the STFC accelerator science landscape, as well as extensive modelling and simulation work. Close collaboration with the existing XFEL facilities will ensure an accelerated process and benchmarking of all of the R&D. This and an accompanying site selection exercise will inform a full Technical Design.

A feasible time-line for the full project is shown below.



It is reasonable to suppose that a Technical Design could be ready by 2025 and, if funding were available at that point, construction could start with a likely completion in 2028/29. With such a timeline, an operating UK XFEL infrastructure could be delivering science by 2029/30.

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Appendix 1: An Outline of a Technical Solution

To consider the various technical options for a UK XFEL facility requires a dedicated conceptual design phase, beyond the scope of this Science Case. Nevertheless it is important to consider some of the ways in which a UK XFEL could be optimised to meet the ambitious requirements of the science. This section details preliminary work to outline technical solutions for different scenarios, each of which would feature world-leading capabilities, customised to the needs of the UK.

A1.1 Introduction

Section 9.4 sets out the different options for UK FEL science, including option A – to build a unique UK XFEL optimised for new capability and option B – to build a UK XFEL providing capacity well beyond 10 years. This section details two different technical solutions for option A: *Concept outline 1*, which would be a fully superconducting accelerator with maximum capability, including up to MHz repetition rate at all photon energies; and *Concept outline 2*, a hybrid superconducting/normal conducting accelerator, expected to be somewhat less expensive by operating at kHz repetition rate for hard X-rays but otherwise featuring a full complement of capabilities. A technical solution for option B: *Concept outline 3*, is also described – this would be the least expensive option, with reduced repetition rate and possibly lower photon energy reach, but it would be a world competitive facility with capabilities optimised for UK science. The rationale behind the technology choices is also described.

A1.2 Key parameters for facility design

As shown in **Figure A1.1**, some of the most significant factors that influence the facility design are repetition rate, photon energy and energy per pulse:

- **Repetition rate is a driving factor behind the choice of accelerator technology.** As described in **Section 2.3**, the majority of existing XFELs use normal conducting linacs, which deliver pulses at ~100 Hz; however, advanced designs and reduced gradient may enable higher (~1 kHz) repetition rates in a future facility. Superconducting linacs deliver significantly higher repetition rates, e.g. the European XFEL utilises superconducting linacs to deliver 27,000 pulses per second in a pulse train structure, while superconducting linac facilities presently under construction (LCLS-II, SHINE) will deliver a continuous train of pulses at ~1 MHz. For even higher repetition rates, energy recovery linacs (ERLs) may reach ~100 MHz by transferring energy from used bunches to subsequent bunches. Very advanced concepts such as plasma acceleration are not yet considered to be mature enough to be on the critical path.
- **Photon energy and energy per pulse strongly affect the required electron beam energy.** Typically, facilities producing extreme ultra-violet (EUV) light have electron beam energy of 1 – 1.5 GeV (e.g. FLASH, FERMI). Soft X-ray (SX) output (up to a few keV) requires electron beam energy of 2-3 GeV, hard X-rays (HX) up to ~15 keV can be produced with an electron beam energy of 6 – 8 GeV, while there are proposals to extend the photon energy reach of European XFEL to 100 keV, utilising its very high electron beam energy (17.5 GeV). UK XFEL could utilise novel short period undulators (e.g. superconducting) to access higher photon energies for a given electron beam energy, together with advanced low-emittance photoinjectors to provide suitable electron beam quality. All else being equal, the energy per pulse strongly scales with the electron beam energy.

Figure A1.1 shows the clear diagonal trade-off between repetition rate and photon energy in the science requirements as highlighted in **Section 9.1**, relative to the facility design considerations. It is clear that a high electron beam energy (~10 GeV) facility is needed to deliver the required photon energies. The requirement for high pulse energy at high photon energy is also a key driver that directs the design to high electron beam energy. There are two options to meet the majority of the repetition rate requirements – either a fully superconducting linac to deliver MHz pulses across all photon energies, or a hybrid approach – partially superconducting to deliver MHz pulses at lower photon

energies, with an advanced normal conducting linac to provide kHz bunches for the higher photon energies.

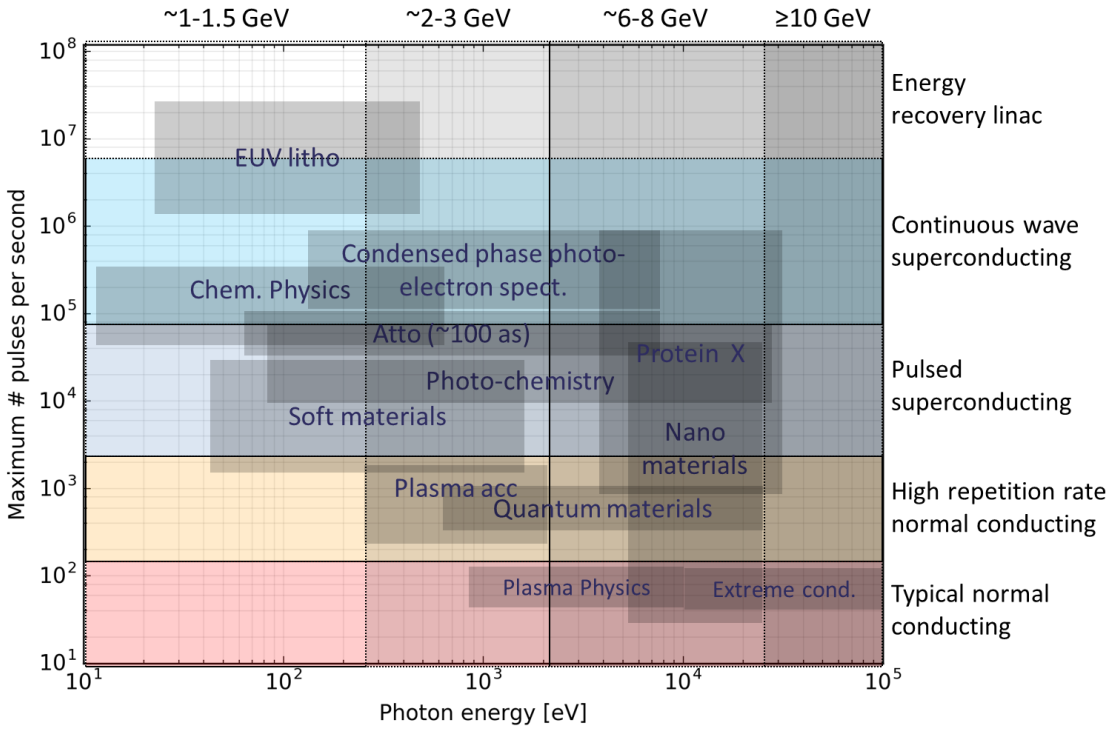


Figure A1.1: How the repetition rate and photon energy requirements of the science case map onto the choice of accelerator technology (right labels) and approximate electron beam energy (top labels)

A1.3 Other key features

While the parameters already described provide the basis of the technical solutions, there are numerous additional features that could be incorporated to provide a UK XFEL with unique capability. As described in **Section 2.4**, some of the most promising features for world-leading capability matched to UK needs are:

- High repetition rate laser seeding
- High spectral purity X-rays
- Attosecond pulses across all photon energies
- Combining X-rays with other advanced capability
- High average power for EUV/gammas.

All of these features could be incorporated into *Concept outlines 1* and *2*, and some could feature in *Concept outline 3*, as described below.

A1.4 Concept outline 1: Superconducting accelerator

Concept outline 1 is a high energy (~10 GeV) superconducting accelerator operating with MHz repetition rate, as shown in **Figure A1.2**. By combining high energy and high repetition rate, it covers the full repetition rate-photon energy parameter space required by the science case. High electron energy and advanced (e.g. superconducting) undulators provide access to very high energy per pulse up to very hard X-ray. Fast kickers can be used to distribute bunches between different FEL lines, with the ability to deliver lower repetition rates where required. The linear (i.e. single-pass) layout shown in **Figure A1.2** would be broadly similar to LCLS-II HE and SHINE; however a recirculating option (i.e. a shorter linac used, for example, two to three times) could also be considered to reduce cost.

High repetition rate seeding would be incorporated to as high a photon energy as possible. Beyond this, other high spectral purity techniques would be used, such as HB-SASE, and oscillator FELs including XFELO are an option due to MHz repetition rates. Techniques for attosecond pulses could be incorporated at all photon energies. End-stations would be equipped with the most advanced lasers, THz radiation sources and electron beams, for use in combination with the X-rays.

A feature under consideration for both *Concept outlines 1 and 2* is to have a second photo-injector towards the end of the main linac. While it is not essential in this case, it offers the opportunity to provide lower energy electron beams to serve the soft and hard X-ray undulator lines independently – or in combination for multi-colour experiments with widely separated photon energies. Soft X-rays with high pulse energy could be generated from the 10 GeV beam if required. A second injector also provides the option of upgrading this region to even higher repetition rate by introducing an energy recovery linac, which could support a high average power EUV FEL and a high brightness gamma ray source.

Concept outline 1: Superconducting accelerator

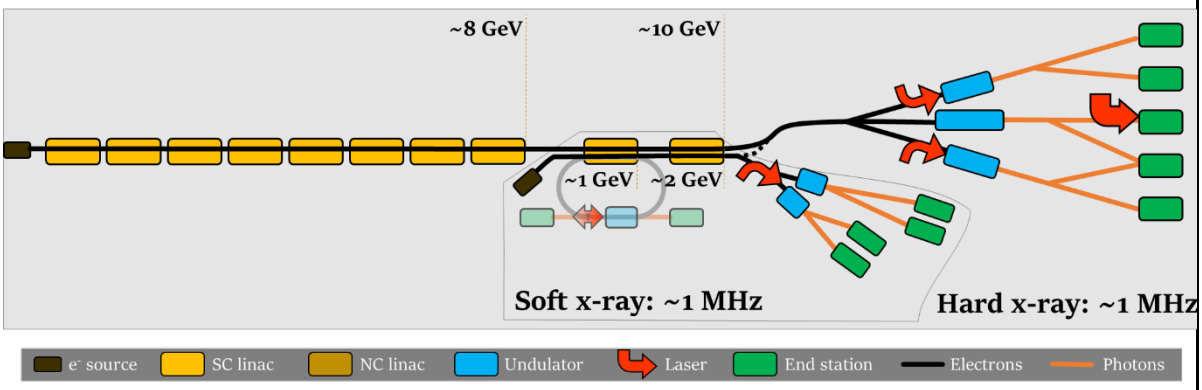
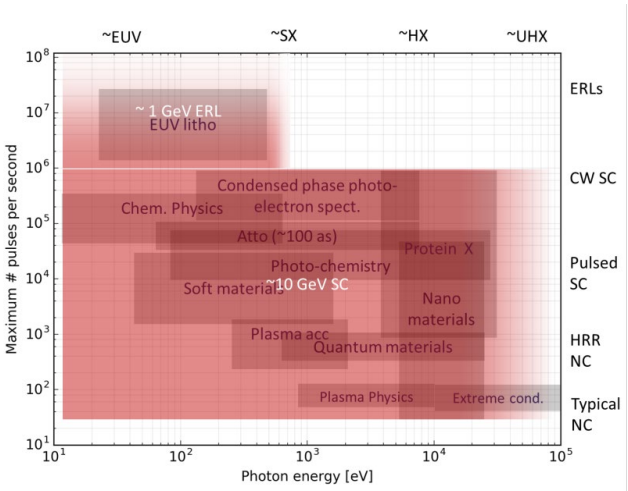


Figure A1.2: UK XFEL Concept outline 1: superconducting accelerator.

The above schematic shows the layout for a ~10 GeV superconducting accelerator facility proposed to meet the science requirements.

The plot to the right shows how such a technical solution would cover the repetition rate-photon energy requirements of the science case.



A1.5 Concept outline 2: Hybrid accelerator

Concept outline 2 is a high energy (~10 GeV) hybrid of two accelerator types as shown in **Figure A1.3**. It features a ~2 GeV superconducting linac, operating to provide MHz repetition rate up to a few keV photon energy. This is coupled to an ~8 GeV advanced normal conducting linac, to provide kHz repetition rate for up to very hard X-ray photon energies.

Concept outline 2: Hybrid accelerator

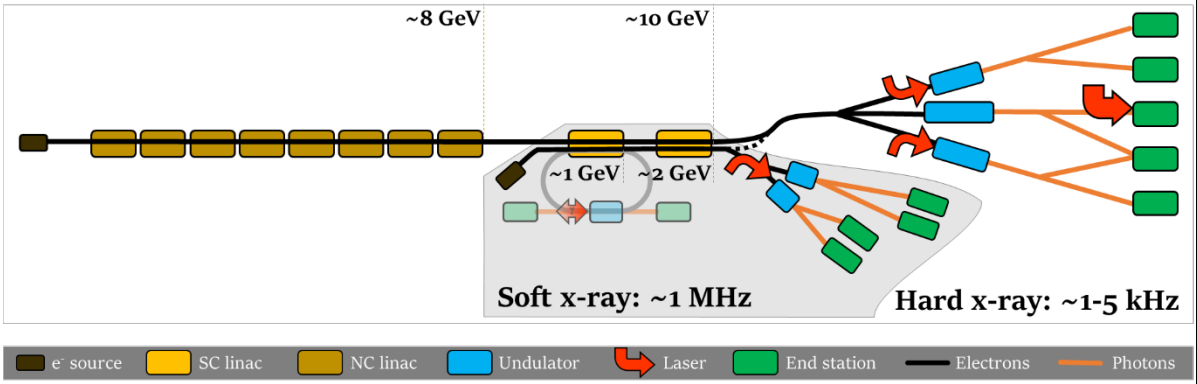
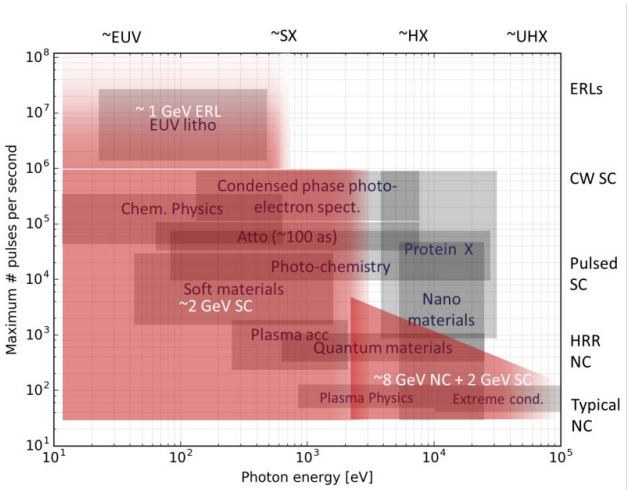


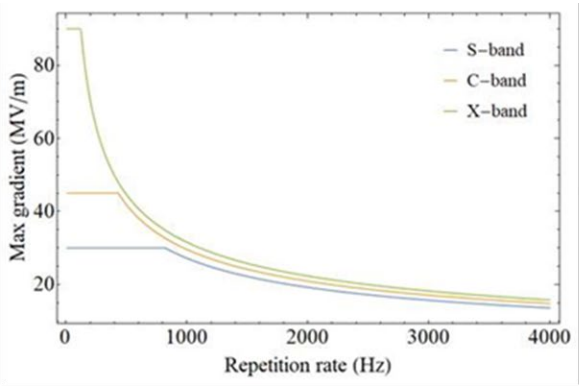
Figure A1.3: Concept outline 2: hybrid accelerator.

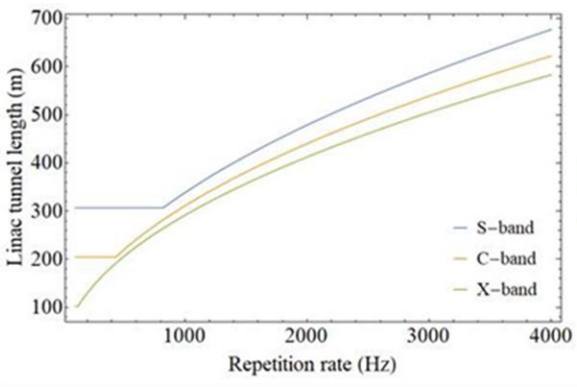
The above schematic shows the layout for a ~10 GeV hybrid accelerator facility proposed to meet the science requirements.

The plot to the right shows how such a technical solution would cover the repetition rate-photon energy requirements of the science case.

The plots below show the trade-off between repetition rate and gradient (left) and corresponding linac length for an 8 GeV NC linac (right), with estimated peak field limits imposed at lower repetition rates.







Operating in this way provides a more targeted approach to covering the repetition rate-photon energy requirements of the science case, as shown in **Figure A1.3**. While it cannot deliver MHz repetition rates at high energy as per *Concept outline 1*, the hybrid option would likely be more flexible for trading off gradient against repetition rate (as shown in **Figure A1.3**), meaning it could more efficiently target the very high photon energies required by some areas of the science, albeit at low repetition rate. Preliminary work is ongoing around a baseline of 8 GeV at 1 kHz for the normal conducting section, potentially scaling up to 5 kHz at lower gradient, or to higher energy at lower repetition rate. Again, advanced undulators would be used for maximum reach in terms of photon energy/pulse energy, and fast kickers would distribute bunches between different FEL lines.

Two electron injectors would be essential in this case: an ultra-low emittance, low repetition rate injector for hard X-rays, together with a high-repetition rate injector for soft X-rays. This would also provide opportunity for multi-colour experiments with widely separated photon energies. Soft X-rays with high pulse energy could be generated from the 10 GeV beam if required, albeit at lower repetition rate. A second injector again provides the option of upgrading this region to an energy recovery linac to support a high average power EUV FEL and a high brightness gamma ray source. Alternatively, recirculation around the superconducting section would be a promising future upgrade to extend MHz repetition rates towards hard X-ray.

As for *Concept outline 1*, high repetition rate seeding, attosecond pulse generation, and high spectral purity techniques could be incorporated, although the use of oscillator FELs would be limited to photon energies where MHz is available (i.e. up to a few keV). An oscillator FEL could potentially be used to seed to higher photon energy. Again, end-stations would be equipped with the most advanced lasers, THz radiation sources and electron beams, for use in combination with the X-rays.

A1.6 Concept outline 3: Normal conducting accelerator

Concept outline 3 is a proposed technical solution for option B of **Section 9.4** – to build a UK XFEL providing capacity well beyond 10 years. It is therefore less ambitious than *Concept outlines 1* and *2* but it would be a world competitive facility, with capabilities optimised for UK science.

As shown in **Figure A1.4**, it features a fully normal conducting accelerator, operating with a repetition rate of approximately 500 Hz. This is lower than the normal conducting section of *Concept outline 2*, but higher than the present generation of normal conducting XFELs. An electron beam energy of ~8 GeV would be internationally competitive, and advanced undulators could be employed to extend the photon energy reach beyond comparable existing machines. Trading off gradient against repetition rate could potentially be employed to increase to kHz repetition rate at lower photon energies. This is not shown in **Figure A1.4**, but in any case the coverage of the repetition rate-photon energy parameter space is limited compared to *Concept outlines 1* and *2.* An extraction line at ~3 GeV could serve the lower photon energy undulator lines, or soft X-rays with higher pulse energy could be generated from the 8 GeV beam.

Seeding, attosecond pulses and high spectral purity methods could be incorporated, although oscillator FELs would not be an option. End-stations could be equipped with the most advanced lasers, THz radiation sources and electron beams, for use in combination with the X-rays.

Concept outline 3: Normal conducting accelerator

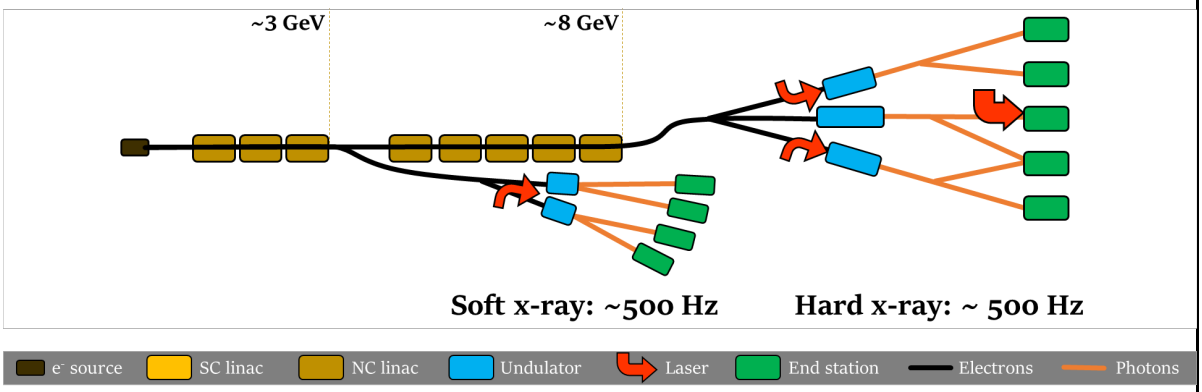
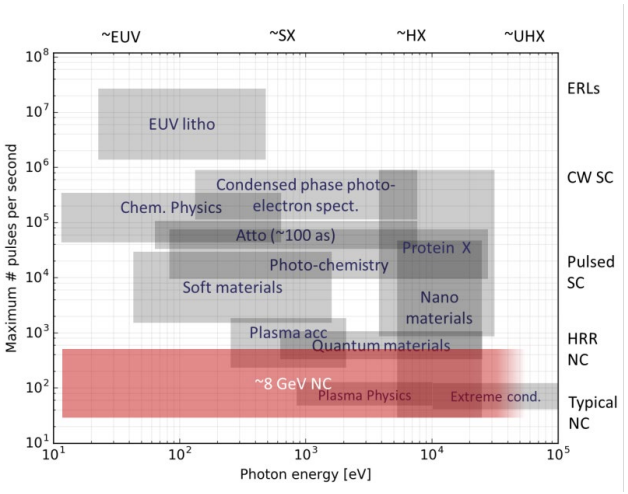


Figure A1.4: Concept outline 3: normal conducting accelerator.

The above schematic shows the layout for an ~8 GeV normal conducting accelerator facility proposed to provide world competitive national capacity

The plot to the right shows how such a technical solution would cover the repetition rate-photon energy requirements of the science case.



Appendix 2: Complementarity of Techniques

A2.1 Cryo-electron microscopy (cryo-EM), tomography (cryo-ET), and diffraction (cryo-ED)

Cryo-EM, with the recent resolution revolution, is trending towards becoming a major method for macromolecular structural studies. An active R&D area includes time-resolved studies with samples trapped by freeze-quench methods at the ms and longer timeframe. Current challenges in cryo-EM include a) the development of new approaches towards cryo-EM sample preparation, reaction triggering, and delivery in order to b) improve efficiency and reduce the time required from pure proteins to structures, and c) the ability to assign structures to functional states during a dynamic process. Cryo-ET provides structural detail within context, such as whole cells, albeit without as high a resolution. Cryo-ED yields atomic resolution models from sub-micron size crystals and time-resolved methods are a very active R&D area. These all complement macromolecular crystallography (MX), currently the major technique in structural biology. Time-resolved serial MX data collected at physiological temperatures at XFELs probe fs and longer, whereas studies at microfocus synchrotron sources probe reactions from ~ns to µs and longer. Together, these complementary approaches share R&D efforts in sample delivery, reaction triggering strategies, and data analysis algorithms.

For decades macromolecular crystallography (MX) has been the main technique in structural biology.[1-5] An unavoidable issue of MX is the need to obtain well-ordered crystals, which remains a trial and error process. Although often automated and using nL volumes per condition, crystallisation trials can consume large amounts of samples and take significant time to optimise. In addition, the crystallisation process requires a homogenous macromolecular conformation, which poses challenges for large, dynamic and transient complexes that play key roles in mediating many biological processes.

The 2017 Nobel Prize in Chemistry was awarded to Dubochet, Frank, and Henderson *"for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution."* This reinforces the recent revolutionary advances in cryo-EM.[6-14] These include microscope instrumentation, detector developments and image processing algorithms. An advantage of cryo-EM is that it only needs a relatively small amount of sample at a significantly lower (100 – 1000x) concentration compared to MX. Consequently, structural determination by cryo-EM is an attainable goal for many large proteins and complexes that are difficult to produce, purify or crystallise. The method allows fast structural determination for many proteins, as demonstrated by the recent structures of COVID-19 spike protein, which were resolved within weeks of genes being sequenced (see also **Section 8.5**).[15] Furthermore, since each particle is imaged individually, and can be sorted out *in silico* according to their conformation, even dynamic proteins and complexes can now be imaged and their structures determined, provided that their different structural classes are sufficiently differentiated. Stunning cryo-EM results are published frequently in *Science* (13 published in 2020 through 31 March 2020) and *Nature* (14 published in 2020 through 31 March 2020), as well as other high profile journals; a selected subset are listed here.[15-30]

The principal structural methods that use frozen-hydrated samples and a transmission electron microscope apply to macromolecular samples in pure states in solution (cryo-EM) or submicron crystals (cryo-ED) to heterogenous samples in complex environments such as whole cells (cryo-ET) (**Figure A2.1**).[31-37] Current cryo-EM single particle analysis methods focus on biomolecules ranging from ~50 kilo-Daltons (kD) to several mega-Daltons, covering the majority of macromolecules complexes as well as viruses.[35,38-42] Indeed, recent examples demonstrate that even haemoglobin (64 kD) can be studied by cryo-EM and 10 of the 4641 atomic models released by the PDB (29 March 2020) are to better than 2 Å resolution.[34,35,38-45] Cryo-ET provides structural information *in situ* and with the extraordinarily valuable context of whole cells.[6,8,46-53] The technique is very likely to unravel new biology as we start to observe links between different macromolecular complexes inside the cell, track how different macromolecular complexes change in response to environment stimuli and

complexes associate and dissociate. However, samples for cryo-ET must be less than 500 nanometres thick and often require cryo-focused ion beam milling, a laborious and time consuming process. Similarly, cyro-ED requires sub-micron size crystals to reduce or eliminate multiple diffraction events from the sample, but it can provide truly atomic resolution results.[31,32,37,54-59] To date, all cryo-ED structures have been solved by molecular replacement, with the exception of the very high resolution dataset of a prion peptide that enabled direct methods to calculate phases.[36] Analogous to cryogenic X-ray crystallography, most cryo-ED data are collected with continuous-rotation methods. In comparison to X-rays, however, electrons interact much more strongly with matter and thereby yield high resolution diffraction from much smaller samples.

The requirement to use sub-micron size samples also makes cryo-ED synergistic with SFX and serial MX methods at XFELs and synchrotrons. The parallels continue with serial cryo-ED strategies wherein nanocrystals are randomly dispersed on a TEM grid, located with a low-dose exposure, then a still cryo-ED pattern is collected from each sample, and the whole dataset is merged together from tens of thousands of still images.[54,60] The use of nanocrystals also makes serial electron diffraction an attractive and complementary method for time-resolved studies. This still needs significant R&D effort and is likely to exploit freeze quench methods on TEM grids with a minimum time resolution on the order of 100s µs to 10s ms. An alternative is to use a mega-electron-volt (MeV) ultrafast electron diffraction instrument and exploiting pump-probe or mix-inject jets to deliver thin streams or sheets of nanocrystal slurries at room temperature to achieve a temporal resolution of approximately 200 fs.[61-63]

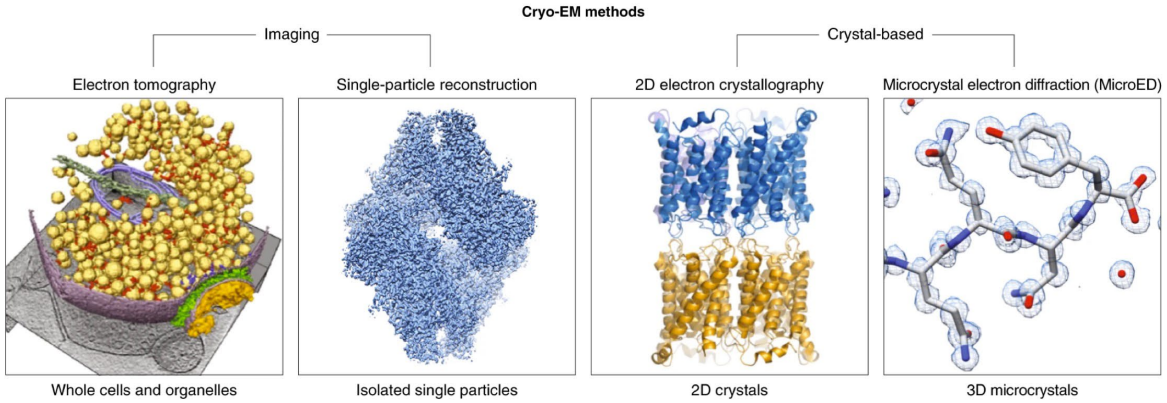


Figure A2.1: The diverse imaging-based and diffraction-based techniques used in cryo-EM can provide structural information from a wide range of samples.
Images acquired with the different techniques are shown here, depicting the synaptosome (electron tomography), a 2.2 Å reconstruction of β-galactosidase (single-particle reconstruction), a 1.9 Å structure of aquaporin-0 (2D electron crystallography) and a 1.0 Å structure of the NNQQNY Sup35 prion fragment (MicroED).

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To achieve the highest resolution in single particle imaging by cryo-EM requires optimum samples and sufficient microscope time. Rapidly improving technologies and high end instruments are becoming more widespread, which in aggregate are producing many new results on a daily basis.[7] All of the 4641 cryo-EM models released by the PDB give an average 5.92 Å resolution; however, for those 485 models released in 2020 as of 29 March the average is 3.9 Å resolution. Fortunately, the trend is to higher resolution. Thus, cryo-EM is becoming the leading methodology for most structural biology projects, including structural studies to characterise ligand and/or inhibitor binding. Cryo-EM methods complement MX, wherein the latter often provides atomic resolution to well beyond 2 Å resolution and sometimes even with direct correlations with spectroscopic data from the same samples. Although time-resolved MX studies at physiological conditions with XFELs is a major use case, time-resolved cryo-EM is also very actively perused by several research groups.[64-67] For instance, the Frank group has recently published freeze-quench cryo-EM studies of the ribosome initiation of translation

with time points at 20, 80, 200 and 600 ms, wherein the rapid formation of the 70S initiation complex transitions into 70S elongation-competent complex.[68]

In addition to resolving multiple conformations and composition heterogeneity within a single sample, cryo-EM is well suited to study dynamic systems, at the milliseconds to seconds time frame dictated by freeze-quench methods, within which many macromolecular assembling, co-factor binding, conformational changes and signalling events, take place. However, in order to track a dynamic process, precise and well controlled sample preparation, triggering and delivery systems are required to capture different functional states or distributions of functional states during a dynamic biological process. Despite these clear advantages and capabilities, there are a number of challenges and limitations that hinder cryo-EM to reach its full potential:

1) *Instrumentation capacity*
   A significant problem for cryo-EM is the limited access and long waits to use extraordinarily expensive microscopes. In the last few years, the UKRI and Wellcome Trust, as well as individual universities/institutes, have invested significantly in high end instrumentation. This includes establishing the national electron bio-imaging centre (eBIC) at Diamond Light Source, a successful model that is now widely adopted in many other countries. However, these instruments are expensive to purchase, maintain and require expertise to operate; they are thus best placed in centres or institutions with sufficient user groups. To best utilise these high-end instruments and to allow more scientists to have access to cryo-EM, samples need to be screened first, which should be assessed locally. There is currently limited access to screening instruments across the whole UK structural biology community. Fortunately, there are a number of current efforts and approaches to address this; for instance, the development of 100 keV instrument that aims to democratise cryo-EM.[69,70]

2) *Sample preparation and delivery*
   Current methods in cryo-EM sample and grids preparation date back to the 1980s. Although blotting works for many samples, it is becoming increasingly a major bottleneck as the numbers of samples and their complexity increases.[71] The difficulty is that many macromolecular complexes dissociate, aggregate, denature or simply do not go into the holes of the cryo-EM grids. A further complication is the lack of rapid and easy quality assessment early in the process, which now happens after the samples have been imaged using a cryo-EM instrument and analysed computationally. The lack of robust and reliable specimen preparations, and the inability to assess sample quality prior to cryo-EM imaging, hinder the overall efficiency of structural determinations by cryo-EM. Fortunately, these areas are experiencing rapid development and have even spawned new product lines (e.g. VitroJet™ by Cryosol, Maastricht, The Netherlands and chameleon™ by SPT Labtech Ltd, Hertfordshire, UK).[72-77] Given that sample delivery is a major area of development required for successful XFEL experiments, as detailed in **Section 7**, there is significant synergy with the sample delivery systems developed for serial methods at XFELs.

3) *Cryo-ET Development*
   One of the most exciting but least developed areas is the ability to image and recognise macromolecules to high resolution *in situ*. Electron cryo-tomography reconstructs a three-dimensional image from a series of tilted images, which limits resolution to about 15 – 20 Å. Furthermore, the limited penetration power of electrons in the available microscopes (100 – 300 keV, limiting to ~ 200 nM) requires many of the biological samples to be thinned first, currently through focused-ion beam milling.[51] The resolution limitation can be overcome and 3 – 4 Å resolution has been achieved through sub-tomographic averaging in some cases;[78,79] but this is not always possible, due to the small numbers and small sizes of the objects within the biological specimen. There remains a significant technical challenge to develop methodologies to improve the resolution, to increase penetration power and develop new ways to obtain thinner specimens, and to enable particles to be identified in tomograms.

A2.2 Next generation synchrotron light sources

The emerging generation of high-brightness synchrotron sources provides scientific capability that is highly complementary to that of XFELs, particularly in the time domain they cover and the peak X-ray intensity they deliver.

Time Domain

Synchrotrons, such as Diamond and its planned upgrade to Diamond-II, are designed for the study of a wide range of processes under functional conditions, on timescales down to microseconds, and with high spatial resolution. This time resolution can be further enhanced by taking advantage of the electron bunch structure of the synchrotron, and this can facilitate dynamic studies using system snapshots taken in hundreds of picoseconds. One way to achieve this is by operating the synchrotron with distinct separation between the electron bunches to facilitate stroboscopic measurements with fast pulses of X-rays, as is the case of the hybrid or single bunch mode available at Diamond. Higher time resolutions have been achieved at synchrotrons using novel time schemes such as laser-electron slicing[80,81] or by producing shorter, more intense X-ray pulses with crab cavities[82] or low alpha optics.[83] In all these cases, the higher time resolutions are attained at a large cost in flux. Of these options, the low alpha mode is currently the high time resolution mode offered at Diamond achieving time resolutions of the order of 10ps.[84]

The development of Diffraction Limited Storage Rings (DLSR) or fourth generation synchrotrons, with reduced horizontal emittance values by between one to two order of magnitude, offers the scientific community the opportunity to exploit much brighter photon beams and an increased coherence. These beam characteristics are being exploited for the study of materials with nanometric spatial resolution. From the perspective of time-resolved studies, the ultralow emittance sources are in conflict with the optimum requirements for the timing schemes usually used for pump-probe experiments, as these require highly charged electron bunches. In general, these new low emittance machines will make use of longer electron bunches, that in turn reduce the time resolution achievable. Some of the upgrades being planned are consequently considering implementing two different operation modes: a brightness mode and a timing mode. In the case of the APS upgrade, APS-U,[85] the timing mode maximises the brightness of a single bunch, at the expense of the attainable vertical emittance. Forty-eight bunches of approximately 4 mA will be used in that mode with a bunch length larger than 200 ps. Petra IV,[86,87] on the other hand, is planning to operate the timing mode with eighty bunches, approximately 150 ps long, separated by 96 ns, each with a current of 1 mA. In the case of Diamond-II,[88,89] it is expected that the bunch length will be of the order of 100 ps, and advanced timing modes such as the low alpha will not be available.

The hundreds of picoseconds time resolution offered in synchrotrons and diffraction limited machines are suitable for increasing our understanding of chemical and biological process mechanisms, by solving the electronic and geometrical structures of the transient states on the time scales of ns to hours. XFELs, on the other hand, with photon pulse lengths more than 10,000 times shorter than those on fourth generation synchrotron sources, enable the study of complex systems on femtosecond timescales with high flux, opening the door to the study of electron and nuclear dynamics under system conditions that are far from thermal equilibrium. These very high time resolutions can also provide access to transient states of matter that can be induced, for example, by the application of extreme pressures, electric or magnetic fields by shockwave methods.

Peak intensity

Synchrotron sources and XFELs are also complementary in the peak intensity they deliver. These intensities can be different by up to 10 orders of magnitude. The high peak intensity delivered by XFEL sources is enabling novel experiments that cannot be performed at synchrotron sources. For example, XFELs are used to study the atomic structures of delicate biological systems from micron to submicron size samples and before radiation-induced effects damage the samples, and their high peak power is also well suited to the study of high energy density systems.

Many examples of applications of the use of the high time resolutions and high peak intensities achieved at XFEL sources can be found in the present Science Case in many different areas, from chemistry and energy materials, to life sciences, quantum chemistry and matter under extreme conditions.

The complementarity of synchrotrons, including diffraction limited sources, and XFELs is increasingly being recognised by the scientific community, and one can find many examples of co-location of these sources, such as Petra III and the European XFEL, the SLS and the SwissFEL, Elettra and FERMI, and SPring-8 and SACLA. By combining the capabilities of both sources, studies of the dynamics of complex materials can be investigated over the full range of timescales, from below femtoseconds to minutes and even hours, and also across a large energy range.

A2.3 Ultrafast electron diffraction

Ultrafast electron diffraction (UED) with a relativistic electron gun is an emerging method in structural dynamics. We discuss the synergy with an XFEL facility and point to unique scientific possibilities if a UED apparatus were synchronised with the XFEL.

The use of monoenergetic electron beams for atomic scale structure determination by diffraction has a long history, stretching back to the Nobel Prize winning work of Thompson, Davisson and Germer in 1926. Electron diffraction is a natural complement to X-ray diffraction, as it has different sensitivities and characteristics. Electrons have $10^4 - 10^6$ higher scattering cross-sections than X-rays, making them more suitable for thin or diffuse samples. In 1930, Mark and Wierl realised that diffraction patterns for the molecule CCl_4 in the gas phase could be acquired in a fraction of the time required for X-rays.[90] A few short years later, the structure of 146 molecules in the gas phase had been determined[91] and structural determination of gas phase molecules using electron diffraction became an important technique that remains in use.[90] Electrons scatter from both the electrons and the nuclei in the target, in contrast to X-rays that scatter only from the electrons, making electron diffraction more sensitive to low Z atoms. In principle, it can be used to detect H atoms, which are effectively invisible to X-ray diffraction. The possibility of using diffraction of ultrafast electron pulses to image structural dynamics has therefore caused substantial interest in the chemical dynamics and materials communities in recent decades. Not unexpectedly, the impact has been greatest for probing dynamics in gas phase molecules and thin films of crystalline material. Early work by Zeweil[92] and Miller[93] and others on ultrafast electron diffraction (UED) demonstrated what is possible. There is a strong consensus that UED is, along with time-resolved X-ray diffraction, a powerful route to access structural dynamics in molecules undergoing chemical reactions[94] and in crystalline materials undergoing phase changes.[95]

Despite this promise, there are severe limits to temporal resolution set by space-charge repulsion between electrons in an electron bunch. Unless the number of electrons in the bunch is kept unrealistically low, the time-resolution becomes badly degraded (although single electron "attosecond" experiments are possible when sampling periodic dynamics[96]). This has limited the temporal resolution in most UED experiments to picoseconds, despite efforts to design optimal electron optics. A big improvement is gained by using relativistic electron guns that rapidly accelerate the electron bunch to > 1 MeV. In this case, relativistic Lorentz contraction reduces the effective space-charge by an enormous factor so allowing simultaneously very short pulses (< 100 fs) and high bunch charges that enable good signal to noise measurements. A UED facility based upon a relativistic electron gun operating at 2 – 4 MeV with ~100 fs pulses has been established at SLAC,[97,98] and this has been running as a user facility alongside LCLS for the last 18 months. The SLAC facility has achieved significant scientific impact in this short time with measurements in photochemistry[99,100] and condensed matter physics[101] among prominent recent results. The high scattering cross-section and small de Broglie wavelength of the electrons is likely to enable time-resolved pair-distribution function retrieval in liquids in the future.

A relativistic UED instrument of the type operating at SLAC, or the REGAE system being developed at DESY, is arguably two orders of magnitude cheaper than a hard X-ray FEL and far more compact. It can be synchronised with external pump lasers to enable a wide range of pump-probe studies. It can deliver a range of structural dynamics information in gas phase, thin films and in liquid samples (**Figure A2.2**) with temporal resolution < 100 fs. In particular, liquid samples are constrained to thickness < 20% of the electron mean free path (approximately 1 µm in water for electrons at 3.7 MeV). To this

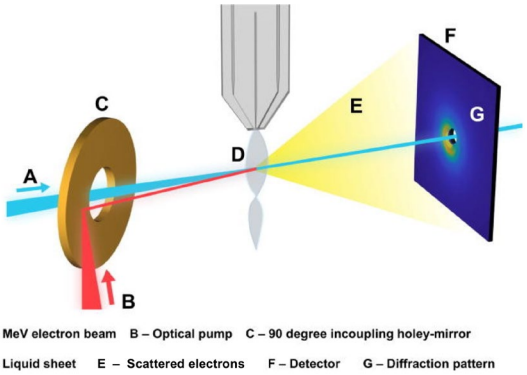

Figure A2.2: Schematic representation of the liquid-phase MeV UED experimental setup

*Figure reproduced from J.P.F. Nunes et al. Struct. Dyn. **7**, 024301 (2020) DOI: 10.1063/1.5144518 licensed under Creative Commons Attribution 3.0 Unported license.*

end, Nunes *et al.*[61] exploited a water sheet using with a microfluidic chip to produce a 20 µm cylindrical liquid jet that was flatted with gas flow into a sheet with a profile that decreases from 700 nm near the top to < 100 nm at the bottom. As discussed in **Section A2.1** above, the requirement to use nanocrystals also makes time-resolved studies well-suited to serial electron diffraction with biological macromolecules. Although the present SLAC gun is operating at 180 Hz, higher repetition rate upgrades are foreseen to reach > 1 kHz repetition rate. The pulse duration at SLAC has recently been reduced, e.g. using THz driven electron beam compression, to around 35 fs in development experiments and so higher temporal resolution is expected to be achievable.

Overcoming space-charge broadening in relativistic electron pulses has seen significant success, however isn't without side-effects that need careful consideration. MeV electron pulses can transport much higher fluxes as compared to non-relativistic pulses over the range 40 – 100 keV. The study of thin, high-Z or, particularly, biological samples can undergo knock-on or polarisation damage when high bunch charge and energy are combined. In some cases, with a carefully controlled electron beam, longer exposure can be possible with lower energies, as advocated by the SALVE Consortium for conventional electron microscopy. Longer exposure and less damage can result in higher contrast and resolution. Furthermore, non-relativistic pulsed electron instruments can be operated without RF acceleration, rather making use of highly stable DC acceleration, reducing the uncertainty in bunch charge and energy distribution, hence duration. A consequence is that THz/IR compression has higher shot-to-shot stability at non-relativistic energies, hence a temporal resolution down to around ten fs is possible. Considering linear electron-EM field interactions, transient fields as driven by a laser E-field or intensity envelope scatter lower energy electrons more effectively, therefore non-relativistic electron pulses are well-suited to observing diffraction from, for example magnetic devices. Practically, implementing a non-relativistic UED is cheaper as RF infrastructure is not required, and is far more compact. With careful design, such an instrument could also be operated as a conventional transmission electron microscope, albeit with limited performance as compared to the current state-of-the-art, however routine sample monitoring and characterisation would be invaluable.

The complementarity with XFELs is best understood by considering the limitations, as well as the strengths, of UED. First and foremost, the penetration length, due to the inherent high scattering cross-section, is much less than hard X-rays and so precludes the study of bulk material properties, buried structures and 3D biological samples such as whole cells. The temporal resolution is currently two orders of magnitude worse than that achieved with eSASE modes of an XFEL and is only likely to see modest improvements in the foreseeable future. Moreover, whilst electron diffraction can retrieve crystalline structures, there is no method equivalent to X-ray CDI that permits the time-resolved retrieval of irregular structures, limiting the application mainly to macroscopically crystalline samples and gas phase molecules. Likewise, there is no equivalent to inelastic scattering currently stimulating powerful new notions in X-ray scattering measurement (see discussion of coherent mixed scattering and quantum imaging (see **Section 3.2**)). The strong interaction of electrons with electric, magnetic and electromagnetic field is also a significant limit when investigating interactions with field dressed materials, whereas X-rays are immune to any perturbation. Finally, the argument has been advanced that new high-flux X-ray photon sources can achieve higher spatial resolution than UED during realistic exposure times, due to significantly lower noise in the large momentum-transfer data where UED suffers from much stronger quenching than X-ray scattering.[102] Ultimately, the greatest strength of electron scattering is as a structural technique and we will still need the power of X-ray spectroscopy, XES, RIXS and XPS, plus the emerging non-linear techniques, to address the electronic quantum state dynamics that accompany, and drive, structural changes. A state-of-the-art relativistic UED facility would be far less versatile and scientifically pervasive than an XFEL, but would still likely find an enthusiastic user base.

In view of this it is reasonable to propose the development of a UED facility alongside a UK XFEL, to complement the capabilities and increase capacity for users who are addressing questions of structural dynamics that the more limited temporal resolution of UED can deliver. This model of co-location has been effective at SLAC and has led to significant extra scientific productivity and reach for that laboratory. We do not, however, advocate merely co-location of UED and XFEL capability. Instead

we would consider developing a more synergistic model, where an end-station for time-resolved X-ray diffraction and X-ray spectroscopy can also be equipped with a UED gun that delivers electrons close to collinearly with the X-ray beam. In this way some common installations and equipment can be shared and the end-station can maintain productivity even when X-rays are not available. Sharing of the pump beam capabilities, including a wide spectral range of advanced femtosecond laser and THz sources, which will be established at a UK XFEL, can thus be used with significant scientific benefit for UED studies.

Further there is then the possibility of interrogating the dynamics of the same systems via multiple channels, e.g. XES, UED and time-resolved X-ray diffraction, thus exploiting the strengths of each method in an integrative methodology. Additionally, this configuration will open-up new scientific possibilities where an electron or an X-ray pulse is used as a pump and the other synchronised, but controllably delayed, X-ray or electron pulse is used as a probe. One possible scientific application is touched on in Chemical Dynamics, **Section 6.2**, where the possibility for research into fast radiolysis processes will be enabled by such a configuration. The chemical and physical effects of an electron ionisation can thus be probed by X-ray spectroscopy and allied X-ray methods. We would foresee a wide range of other scientific possibilities with this dual XFEL/UED capability.

A2.4 Life Sciences Hub and roadmap

The options available to the life sciences community (**Table A2.1**) are broad and range from the currently active (e.g. the XFEL Hub at Diamond) to long-term developments (e.g. this UK XFEL project) with additional opportunities in between (e.g. partnerships with existing XFEL facilities). For instance, the XFEL Hub at Diamond is a first in the world and was formed with grant support from the Wellcome Trust, MRC and BBSRC awarded to Jim Naismith *et al.* in 2014. The three full-time Hub scientists reside at a synchrotron, develop technologies for XFELs, and look to take advantage of synergies between XFELs and synchrotrons to better enable users to solve biomedical questions, especially by accessing the time domain with high resolution structural biology. The Hub helps users compete for beamtime on the global XFEL market. Because XFEL beamtime is massively oversubscribed, we take it as a measure of success that the Hub has participated in more than 45 XFEL experiments at all five operating XFELs worldwide since October 2015. The Hub has also provided travel assistance to more than 250 UK-based scientists for their participation in XFEL experiments. The overwhelming majority of these were given to students and Post-docs to participate directly in XFEL experiments. Staff at the XFEL Hub at Diamond also pursue science driven projects in close collaboration with users and other synchrotron and XFEL scientists. To these ends, the Hub has active R&D projects with Diamond beamline staff at I04, I24, VMXi and VMXm, as well as with eBIC.

Table A2.1: Some options for life sciences in XFEL research and development

Time frame	Main objectives and/or goals	Relative cost
Short term (0 – 2 years)	• Full support &/or expansion of the XFEL Hub at Diamond and XFEL Hub for physical sciences • CDT / DTP PhD studentships in life and physical sciences dedicated to XFEL research • Sample delivery collaboration between Diamond and SwissFEL for time-resolved SFX ± XES	0.005 – 0.02
Medium term (3 – 5 years)	• Partnership with SwissFEL &/or European XFEL to construct hard X-ray beamline(s) within existing accelerator tunnel for dynamic structural biology & imaging • Institute for XFEL Science	0.1 – 0.25
Long term (> 10 years)	• Build UK XFEL with hard X-ray capability for dynamic structural biology and imaging • Develop time resolved and single molecule imaging capability	1.0

Although the XFEL Hub at Diamond is much smaller in scale, there are parallels between it and BioXFEL (https://www.bioxfel.org/), a Science and Technology Center funded by the US National Science Foundation. BioXFEL is a multi-institutional and international centre established with a $25M grant in 2013, which was awarded a five-year renewal in 2018 with a $22.5M grant. The BioXFEL does not have a specific user support role.; rather they are mandated to address education, outreach, research and development with aims to develop biological applications for XFELs. As a result, BioXFEL has extensive collaborations throughout the global SFX community.

The XFEL Hub at Diamond has established a "*Dynamic Structural Biology at Diamond and XFELs*" beamtime allocation group. It introduces and brings serial MX capabilities to users, advances dynamic structural biology, and helps reduce the barrier to access to XFELs for SFX and time-resolved studies of reactive intermediates generated *in situ*. This provides valuable training to new users, enables scientist to collect important preliminary data for XFEL beamtime applications, and also generates results that stand on their own. Judging from the increasing access of UK to XFEL sources, the XFEL Hub has already had a useful catalytic role, despite its modest scale. There is strong consensus in the UK that the XFEL Hub at Diamond should be fully supported by the STFC/UKRI and expanded to increase its impact across a larger cross-section of structural biology R&D.

Mid-term options to life sciences include partnerships with existing facilities to build out their infrastructure. For instance, two unoccupied tunnels are already drilled at the European XFEL. One of these could be developed to support dynamic structural biology with an intra-train pulse rate of 4 MHz over up to 600 µs that repeats at 10 Hz. Eventually the European XFEL may strive to achieve CW-like operations. SwissFEL also has room for another hard X-ray beamline that will deliver X-ray pulses at 100 Hz and at lower flux density. Finally, an Institute for XFEL Science would bring research groups into a coordinated space similar to Center for Free-Electron Laser Science – CFEL on the DESY campus in Hamburg Germany (https://www.cfel.de/). These options all have significant merits and will be considered further in **Section 9**.

Long-term options include building the UK XFEL. For life sciences, the desired machine will deliver 5 – 25 keV X-ray pules at about 100 kHz or faster, of 0.1 – 25 fs duration, in a well-focused beam (~0.02 – 2 μm^2) with at least 10^{12} photons per pulse. There are strong incentives to tightly integrate the science programmes of UK XFEL with Diamond II, cryo-EM and serial electron diffraction, RFI in the Life Science area. Further details of a potential machine are detailed in **Appendix 1** following the demands of the analysis in **Section 9**.

A2.5 References for Appendix 2

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Appendix 3: Complementary Technologies

A3.1 Complementary pulsed X-ray technologies

Two nascent compact pulse X-ray source technologies based upon electron pre-bunching and radiation either in an undulator or via inverse Compton scattering are discussed. These hold promise of short X-ray pulses, albeit at much lower peak powers and repetition rates than a full scale XFEL. These ideas are being developed at UCLA and Arizona State University, where demonstration systems are being built. If these demonstrations are successful, we recognise synergies with a UK XFEL in providing additional X-ray pulse pumping/probing capability and the possibility of use as sources for hard X-ray seeding in a future enhancement of the XFEL.

Only a multi-GeV facility can cover the full range of FEL user requirements, in particular the requirement for high photon flux and mJ pulse energies. This is because the FEL is a device for converting electron beam kinetic energy into photon beam energy and, while it may be possible to produce HXR photons with significantly lower beam energies, there are two fundamental factors which compound one another to limit the flux. First, to obtain the required wavelength with a low energy beam, the undulator period must be very short. Technologies are available, or under development, to achieve this, but the efficiency of the FEL, i.e. the fraction of electron beam power converted to photon beam power, scales with undulator period so will always be low. Second, the electron beam power is itself proportional to the beam energy. Taken together these two factors prohibit the production of high photon flux and mJ pulse energies from a low energy facility. To obtain FEL pulses appropriate for high energy density science, multi-GeV electron beams are essential.

Proposals are, however, under development for compact, university scale, accelerator-based HXR sources. Such sources can be seen as complementary, offering pulse energies only a few percent of that available from a full-scale facility, but which may be appropriate for some science applications, as discussed below. By co-locating such sources at a large facility, they could provide additional pump-probe capability and potentially be used as HXR seed sources.

Table A3.1 shows the main parameters of two well developed proposals. The first is from UCLA[1] (UC-XFEL). It features high gradient cryogenically-cooled accelerating sections and a short period cryogenically-cooled undulator. The electron bunch is modulated with a laser and converted into a train of microbunches – by doing so the beam quality in each low charge microbunch can be conserved, and the peak current in each microbunch is high enough that FEL saturation is reached in a few metres. The micro-modulated beam is less susceptible to wakefield degradation in the undulator than a conventional bunch, allowing a very small gap of 2 mm, so that the undulator period can be made very short while maintaining sufficient on-axis field. For this reason 8 keV photons can be produced with a beam energy of only 1.6 GeV. The pulse energy is around 12 µJ. The second proposal is by Arizona State University[2] (CXFEL), with funding secured for construction and experimental verification. Beam tests are now ongoing. The method is to generate a pre-bunched electron beam by translating the transverse diffraction pattern of the electron beam incident on a nano-patterned silicon crystal into a longitudinal modulation. The photons are then emitted through coherent Inverse Compton Scattering off an incident laser, demonstrating good temporal coherence with a pulse energy of 0.13 µJ. This source could potentially be used as a direct HXR seed for an FEL amplifier driven by a multi-GeV beam, because the peak power is sufficient to dominate the noise from the SASE process.

Table A3.1: Performance parameters (simulated) of the UCLA and Arizona State University compact light source projects

Performance parameter	UC-XFEL [1]	CXFEL [2]
Beam Energy	1.6 GeV	35 MeV
Photon Energy	7.8 keV	8 keV
Peak Power	8 GW	2 MW
Pulse Energy	12 μJ	0.13 μJ
Bandwidth	0.1%	0.01%
Repetition Rate	100 Hz	1 kHz
Facility Length	40 m	10 m

A3.2 Plasma and laser wakefield acceleration

Plasma and laser wakefields are novel concepts for electron acceleration that are likely to have considerable technology impact in the future. Although the technology remains insufficiently mature for the foreseeable future to replace the conventional linear accelerator in the UK XFEL, we see strong synergies with the facility. These are in: incorporation of laser wakefield capability at some end-stations, and for a plasma wakefield accelerator test end-station integrated into the facility design.

Plasma wakefield accelerators utilise the huge electric fields generated within plasma waves driven by intense laser pulses or particle beams. These fields are of order 100 GV m^{-1}, or around one thousand times greater than those possible with conventional radio-frequency (RF) technology. In addition to being extremely compact, plasma accelerators generate electron bunches with several highly desirable properties. These include: few-femtosecond bunch duration; multi-kA peak current; sub-micron normalised transverse emittance, with prospects for reaching emittances in the nanometre range; and, for laser-driven or hybrid plasma accelerators, tight synchronisation with an ultrafast laser system. To date, plasma accelerators have accelerated electrons to tens of GeV energies in accelerator stages only a few tens of centimetres long[3-7]. The electron bunches they produce have been used to generate radiation from 100 eV to 1 MeV in magnetic undulators,[8,9] via betatron oscillations in the plasma accelerator,[10,11] and by Compton scattering.[12-14] They have also been used to generate positron beams,[15] positron-electron plasmas,[16] and pions,[17] and have been employed in fundamental physics tests.[18,19]

The UK is a world leader in the development of both laser-driven and electron-driven plasma wakefield acceleration (laser wakefield accelerators (LWFA) and plasma wakefield accelerators (PWFA), respectively). This work is coordinated by the Plasma Wakefield Accelerator Steering Committee (PWASC, http://pwasc.org.uk/), which represents UK universities, ASTeC, the CLF, and the two Accelerator Institutes. In 2019, the PWASC summarised the rapid developments in plasma wakefield accelerators, and published a roadmap[20] for research and development to 2040. The potential of plasma wakefield accelerators, and the applications they enable, has proved a major driver for significant investments, such as: the £81.2M Extreme Photonics Application Centre (EPAC) at RAL; the Compact Linear Accelerator for Research and Applications (CLARA) at Daresbury Laboratory; and university-centred initiatives, including the Scottish Centre for the Application of Plasma-based Accelerators (SCAPA), and upgrades to several university-based systems across the UK. The importance of novel accelerator science has also been recognised by STFC, which selected the UK Novel Accelerator project as a “priority project”.

The repetition rate, energy gain and bunch properties of plasma accelerators continue to improve at a rapid pace,[21] and the number of applications they enable continues to grow. Current laser technology is limiting the repetition rate of laser-driven, GeV-scale plasma accelerators to around 10 Hz, but a variety of approaches for increasing the repetition rate of LWFAs is being pursued. One approach is the development of more efficient, higher-repetition rate lasers, such as the CLF’s DiPOLE technology. A complementary approach is the use of different methods for driving the plasma wave; for example, in the multi-pulse approach,[22,23] the drive energy is delivered over many plasma periods, which allows the use of novel lasers, such as thin-disk lasers, that can deliver picosecond-duration, joule-class laser pulses with high wall-plug efficiency and at multi-kHz repetition rates.

To improve the quality of the electron bunches, potentially transformative prospects are being pursued through projects such as the STFC PWFA-FEL, H2020 EuPRAXIA and NeXource. One prospect, the use of plasma photocathodes (“Trojan Horse”), offers the potential to improve the stability, energy spread,[24] emittance and brightness[25] by orders of magnitude, and reached LCLS-level emittances in the first proof-of-concept.[23] If optimised, these electron beams could become orders of magnitude brighter than even those used in state-of-the-art hard X-ray facilities today. It is worth noting that laser-plasma accelerators and hybrid plasma wakefield accelerators[26] offer intrinsic time-synchronisation, for example, for pump-probe experiments.

Although very promising, this new accelerator technology is not yet at a point that would allow a coherent X-ray light source facility to be planned around it. The levels of energy spread, emittance and shot-to-shot stability, although improving, remain inferior to conventional linac technology by a significant factor. Moreover, the requirement, for laser wakefield accelerators, of relativistic intensity laser pulses, is limiting realistic repetition rates to around 10 Hz at the current time. In contrast the "first generation XFELs" operate at ~ 100 Hz and the "second generation" at 1 – 1000 kHz. As reflected in this Science Case, there is a demand for these higher repetition rates across the majority of the proposed applications. While the quality and repetition rate of beams from plasma accelerators obtained experimentally are currently far below those from conventional linac technology, prospects for improving both could add unique opportunities for the UK XFEL in future upgrades.

Synergies between plasma wakefield acceleration and XFEL output and performance are strong. Consequently, it appears opportune to integrate laser- and electron-beam driven plasma wakefield acceleration capabilities and capacities into the design of a future, cutting-edge XFEL machine, although significant R&D would be required. Auxiliary compact betatron[9,10] or inverse Compton scattering-based secondary light sources[12,13] (e.g. for poly-X-ray beam illumination), with tight synchronisation to ultrafast visible lasers, could complement these features, as discussed in **Sections 3** and **4**. Plasma wakefield accelerators and laser-driven plasmas and are already employed in XFELs, such as the Matter at Extreme Conditions station at LCLS and the HIBEF beamline at the European XFEL. Attempts to drive FELs directly with LWFAs are being pursued by several groups worldwide. Furthermore, in view of the superior emittance and brightness offered, programmes have been initiated at Daresbury Laboratory and SLAC (for example, via the STFC PWFA-FEL project), and at DESY, to integrate plasma accelerators into existing and future (X)FELs.

Using PWFA at the UK XFEL facility would enable additional capabilities, including the use of plasma stages to boost the bunch energy (by a factor of two to five), and the use of plasma photocathodes as compact electron brightness afterburners (up to 100,000 times). Such an approach would open pathways to higher photon energies at reduced electron energies and/or sub-femtosecond, higher brilliance photon pulses, and intrinsically synchronised pump-probe multi-colour experiments. Such hard-X-ray flashes may even allow imaging of electronic motion inside atoms and molecules on their natural timescales.

Plasma wakefield accelerators are compact and highly flexible, and could also be implemented after the FEL undulator stages, to provide energy and brightness afterburners, and exploitation of novel XFEL in compact undulators instead of wasting the electrons in (conventional or plasma[27]) beam dumps. Such dedicated research stations could also be used for related applications, such as high-field science.[18,19] Bringing together researchers with expertise in conventional accelerators, plasma accelerators, and XFELs is likely to promote advances at the interface of these disciplines, such as the development of novel laser and XFEL diagnostics.

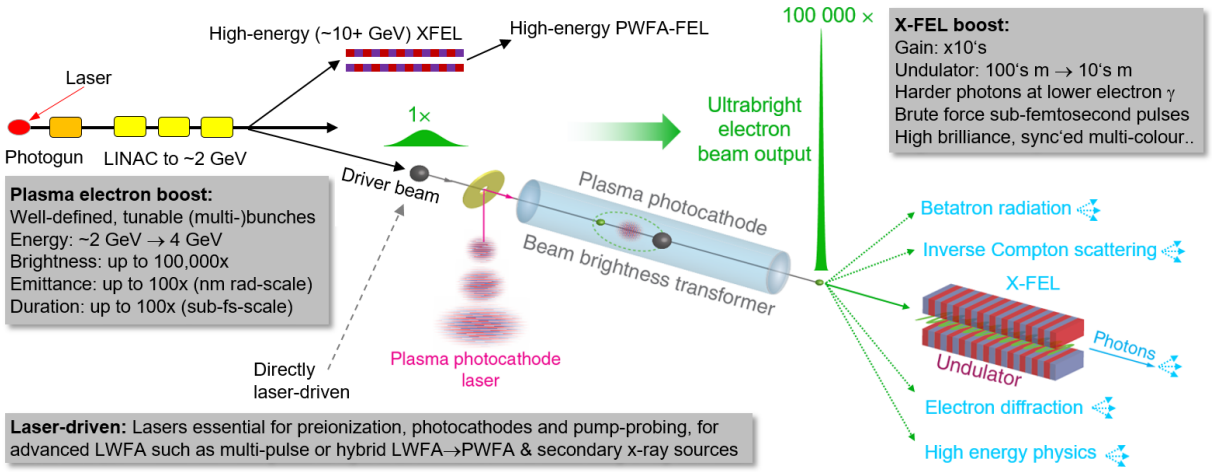

Figure A3.1: Schematic diagram of the capabilities enabled by combining XFEL beamlines and plasma accelerators

A3.3 High Harmonic Sources

High order harmonic generation (HHG) driven by high power ultrashort pulse optical lasers is a standard technique for generating short wavelength coherent radiation in the 10 – 500 eV photon energy range. It was, until the recent eSASE demonstration, the only way to generate attosecond pulses and remains the workhorse for attosecond science. Although pulse energies are low, it is a compact and versatile method that naturally offers itself for incorporation into XFEL pump-probe experiments.

Both HHG-based attosecond sources and XFELs are now established methods for generating light of unique characteristics. They are both sources of short wavelength (VUV to X-ray), ultrashort light pulses with durations in the range from 100 fs to < 0.5 fs (500 attoseconds). This is having an impact through the rich scientific applications so far achieved. In the scientific sphere, both have proved extraordinary in enabling things not possible before. Both are unique tools that are finding growing applications in science, technology and medicine. For HHG sources, the brightness in the spectral range from 10 – 100 eV has proved sufficient to enable a wide range of applications, for example in time-resolved photoelectron spectroscopy, coherent diffraction imaging and time-resolved absorption spectroscopy in a wide variety of settings including surface science, photochemical reaction dynamics, time-resolved band structure imaging, nanostructure and biological structure imaging.

A significant number of facility scale beamlines have been developed at institutions around the world and some made available to a wider user base (e.g. Artemis in the UK, various LaserLab Europe facilities, and the nascent ELI facilities) and a number of commercialisations are now being made available. The importance is reflected in a significant level of public investment in these facilities, amounting to hundreds of millions of Euros globally. There has been a steady stream of applications, and it is clear that this capability is firmly established in the repertoire of ultrafast probing methods available to science and technology. HHG has been widely applied as a short pulse (femtosecond domain) source of coherent X-rays for imaging and time-resolved spectroscopy applications.[28-30]

The unique selling point of HHG sources has, however, been the potential to do something hitherto no other source could – to provide sub-femtosecond time domain pulses for directly measuring and controlling electronic dynamics in matter. This latter possibility termed *attosecond science* has generated a great deal of excitement and effort over the past two decades. This is not surprising as HHG is an enabling tool to probe the most fundamental events of electronic dynamics in matter. There have been remarkable developments and insights obtained over the years from laboratories all around the world. The first unambiguous confirmation of the production of attosecond pulses (a pulse train) in HHG was carried out using a side-band modulation (RABBIT) method by Agostini's group at Saclay.[31] The sideband method has now been widely used with considerable success in characterising ionisation (phase) delays at the attosecond level in atoms and molecules, with work progressing in a number of groups around the world. The first demonstration of isolated attosecond pulses was, however, made in Garching using the streaking idea. Isolated pulses are an essential measurement tool for the most general implementation of attosecond science.[32-37] More recently attention has also turned to attosecond electron control concepts in condensed phase systems,[38,39] new concepts in ultrafast field metrology[40] and applications towards photochemistry.[41,42] The field continues to flourish and expand backed by accompanying technical work pushing HHG attosecond sources deeper into the soft X-ray range.

A large-scale European investment to establish the ELI-ALP (Attosecond) facility in Szeged, Hungary, illustrates the maturity of the technology and the confidence for impact. This facility will concentrate on delivering XUV attosecond capability (up to 100 eV) with (for HHG sources) unprecedented brightness. Pulse energies of 100s nJ are likely in the lower photon energy range of operation, below 30 eV, with pulse energies approaching the microjoule range have been demonstrated using high power drive lasers. Potentially this is an excellent complement to the soft-X-ray ESASE capabilities being developed at XFELs such as Fermi, Flash and LCLS, and which we anticipate also being an integral part of any UK XFEL. HHG is now reaching into the soft X-ray range,[43] but above 100 eV the

demonstrated efficiency of HHG falls rather rapidly[44] (see **Figure 3.6**). This is due to scaling limits placed on efficiency when the required longer wavelength lasers are used,[45] so that pJ pulses are likely to remain the norm in the soft X-ray range. In contrast, eSASE has so far shown exceptional brightness between 500 – 1000 eV (> 20 µJ pulses across this range with no fall off with photon number).[46] SXR HHG research will still continue to be an important area for the time being and even in the long term, especially where perfect synchronisation to optical fields is required and for exploratory and complementary studies in collaboration with XFELs. Future eSASE developments are likely to extend this range down towards 100 eV and upwards into the hard X-ray range. Although currently eSASE pulses are somewhat longer than the best HHG-based sources (by around a factor of five), we should anticipate continued improvement in pulse duration especially as harder X-rays are developed. Current HHG sources, nor none currently predicted, can compete with the eSASE FEL attosecond pulse brightness in the X-ray range.

Nevertheless, high repetition rate drive lasers based on OPCPA and fibre laser technology are now making an impact, even on attosecond generation.[47] These are pushing towards the MHz repetition rate with moderate pulse energies sufficient for reaching the XUV via HHG. We can therefore expect significant improvements in average flux performance in the XUV. Therefore, we anticipate XFEL-based sources to be dominant in attosecond applications above 100 eV photon energy, whilst HHG-based systems will continue to be competitive and probably the source of choice up to around 100 eV. For non-linear X-ray interactions, diffract-and-destroy and other single shot measurement schemes and probing hot plasmas XFELs will dominate across the XUV – X-ray range.

An alternative route to HHG, based upon the relativistic acceleration of particles at surfaces, has excited substantial interest over the last decades.[48] Development at various laser facilities has proceeded to improve the performance and to establish attosecond capability.[49-51] These sources promise to be high brightness with significant energy conversion efficiency from the laser pulse to the HHG. Currently proven performance is limited to the soft X-ray range. Moreover, a relativistic laser intensity (> 10^{18} W cm^{-2}) is required, which limits the repetition rate to around 10 Hz at current laser technology. Efforts to develop these sources continue at facilities such as ELI-ALP and through laser development programmes and so, in the longer term, they may prove more competitive, although they cannot form the basis of a facility plan at the current time.

Importantly the availability of XUV pump sources based on HHG alongside higher photon energy XFEL based eSASE sources at a facility end-station is an exciting and so far untapped opportunity that should add considerable additional attosecond and ultrafast measurement capability. It is thus likely that there will be substantial synergy with HHG sources at future XFEL facilities, especially as techniques for synchronisation and time stamping improve to the sub-femtosecond range. We would plan to make such capability an integral part of the facility at some end-stations, as the incremental cost of setting this up beyond the already installed high-repetition rate femtosecond lasers is on the order of just £100k.

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Appendix 4: Community Engagement, Case Authorship and Development of User Community

A4.1 Workshops and community engagement events

Table A4.1: Workshops and numbers attending

Event	No. of attendees
Launch Meeting (Royal Society, London, July 16th 2019)	72
Matter at Extreme Conditions (University of Edinburgh, Oct 2nd 2019)	27
Life Sciences (Crick Institute, London, Nov 5th 2019)	160
Frontiers in Physical Sciences (Imperial College, London, Nov 13th 2019)	102
Quantum and Nanomaterials (University of Southampton, Nov 27th 2019)	40
Applications to Industry (University of Warwick, Dec 4th 2019)	29
Chemical Dynamics and Energy (University of Newcastle, Dec 11th 2019)	50

A website was established dedicated to community engagement with presentations from workshops and opportunity to input:

https://www.clf.stfc.ac.uk/Pages/UK-XFEL-Scientific-Case-Consultations.aspx

A number of discussion meetings were organised for the science and technical teams; these were arranged to facilitate the development of machine specification and construction of the science case:

- Meeting of Science and Technical teams 27th September 2019, Kings College London
- Meeting of full Science team 15th – 16th January 2020, Cosener's House, Abingdon

A4.2 Science team

Project Lead Jon Marangos, Imperial College

The team was organised into sub-teams (with some cross-over between members) to tackle the different science topics featured in this case:

- **Physics and X-ray Photonics** Jason Greenwood (Queens University, Belfast), Adam Kirrander (University of Edinburgh), Jon Marangos (Imperial College London), Amelle Zair (Kings College London)
- **Matter at Extreme Conditions** Andrew Comley (AWE), Marco Borghesi (Queens University, Belfast), Andrew Higginbotham (University of York), Malcolm McMahon (University of Edinburgh), Sam Vinko (University of Oxford), Justin Wark (University of Oxford)
- **Quantum and Nanomaterials** Marcus Newton (University of Southampton), Anna Regoutz (University College London), Ian Robinson (University College London / Brookhaven National Laboratory), Simon Wall (ICFO, Barcelona / University of Aarhus)
- **Chemical Sciences and Energy** Andrew Burnett (University of Leeds), Sofia Diaz-Moreno (Diamond Light Source), Russell Minns (University of Southampton), Thomas Penfold (University of Newcastle), Julia Weinstein (University of Sheffield)
- **Life Sciences** Allen Orville (Diamond Light Source), Jasper van Thor (Imperial College London), Xiaodong Zhang (Imperial College London)
- **Applications for Industry, Society and Defence** Andrew Comley (AWE), David Dye (Imperial College London), David Rugg (Rolls-Royce), Sven Schroeder (University of Leeds)

A4.3 Full authorship team for the Science Case

Initial	Surname	Affiliation	Project role
M.	Altarelli	MPSD	Science advisor
F.	Alves Lima	Eu XFEL	Science advisor
M.	Attallah	University of Birmingham	Industry advisor
S.	Awan	University of Plymouth	Science advisor
S.	Bartlett	Diamond Light Source	Science advisor
J.	Baxter	Imperial College London	Science advisor
U.	Bergmann	SLAC	Science advisor
T.	Blackburn	Chalmers University, Sweden	Science advisor
R.	Boll	Eu XFEL	Science advisor
S.	Bonetti	University of Stockholm	Science advisor
M.	Borghesi	Queens University Belfast	Science team
C.	Bressler	Eu XFEL	Science advisor
B.	Brocklesby	University of Southampton	Science advisor
C.	Brown	AWE	Science advisor
W.A.	Bryan	Swansea University	Science advisor
P.H.	Bucksbaum	University of Stanford	Science advisor
T.	Burge	Central Laser Facility, Rutherford Appleton Lab	Technical Author
A.D.	Burnett	University of Leeds	Science team
C.R.A.	Catlow	University College London	Science advisor
R.	Chantrell	University of York	Science advisor
J.	Clarke	ASTeC, Daresbury Laboratory	Technical team
A.	Cohen	SLAC / LCLS	Science advisor
S.J.	Coles	University of Southampton	Science advisor
J.	Collier	Central Laser Facility, Rutherford Appleton Lab	Project Champion
A.	Collins	UKRI – Science and Technology Facilities Council	Senior Graphic Designer
A.	Comley	AWE	Science team
L.	Cowie	ASTeC, Daresbury Laboratory	Technical team
J.	Cryan	SLAC / University of Stanford	Science advisor
G.	Dakovski	SLAC	Science advisor
M.P.	Dean	Brookhaven National Laboratory	Science advisor
S.	Dhesi	Diamond Light Source	Science advisor
S.	Diaz-Moreno	Diamond Light Source	Science team
P.	Dowding	Infineum	Industry advisor
D.	Dunning	ASTeC, Daresbury Laboratory	Technical Team
D.	Dye	Imperial College London	Science team
J.	Dyke	University of Southampton	Science advisor
D.	Eakins	University of Oxford	Science advisor
G.	Evans	Diamond Light Source	Science advisor
M.	Foerst	Max Planck Institute for Structural Dynamics, Hamburg	Science advisor
L.J.	Frasinski	Imperial College London	Science advisor
J.	Green	Central Laser Facility, Rutherford Appleton Lab	Physical Sciences Hub
J.	Greenwood	Queens University Belfast	Science team
G.	Gregori	University of Oxford	Science advisor

Initial	Surname	Affiliation	Project role
M.	Guehr	University of Potsdam	Science advisor
F.	Habib	University of Strathclyde	Science advisor
D.	Hall	Diamond Light Source	Science advisor
S.	Hasnain	University of Liverpool	Science advisor
T.	Heinzl	University of Plymouth	Science advisor
B.	Hidding	University of Strathclyde	Science advisor
A.	Higginbotham	University of York	Science team
S.	Hooker	University of Oxford	Science advisor
N.	Huse	University of Hamburg, Germany	Science advisor
O.	Johansson	University of Edinburgh	Science advisor
D.	Keen	ISIS / University of Oxford	Science advisor
A.	Kirrander	University of Edinburgh	Science team
P.	Kolorenc	Charles University Prague	Science advisor
A.	Mancuso	SPB / SFX Instrument, Eu XFEL	Science advisor
S.	Mangles	Imperial College London	Science advisor
J.P.	Marangos	Imperial College London	Science team/ Lead
M.	Marklund	Chalmers University, Sweden	Science advisor
P.	Martin	AWE	Industry advisor
S.	Matthews	Imperial College London	Science advisor
S.	Mc Williams	University of Edinburgh	Science advisor
M.	McCoustra	Heriot Watt	Science advisor
P.	McKenna	University of Strathclyde	Science advisor
M.I.	McMahon	University of Edinburgh	Science team
B.W.J.	McNeil	University of Strathclyde	Technical team
C.	Milne	Paul Scherrer Institute, Switzerland	Science advisor
R.S.	Minns	University of Southampton	Science team
H.	Mueller-Werkmeister	University of Potsdam	Science advisor
S.	Mukamel	University of California, Irvine	Science advisor
J.	Naismith	RFI / University of Oxford	Science advisor
K.	Nelson	Massachusetts Institute of Technology	Science advisor
M.C.	Newton	University of Southampton	Science team
A.	Orville	Diamond Light Source	Science team/Life science HUB
A.	Ourmazd	University of Wisconsin-Milwaukee	Science advisor
R.	Owen	Diamond Light Source	Science advisor
T.	Penfold	University of Newcastle	Science team
F.	Perakis	University of Stockholm	Science advisor
P.	Radaelli	University of Oxford	Science advisor
A.	Randewich	AWE	Industry advisor
A.	Regoutz	University College London	Science team
D.	Riley	Queens University Belfast	Science advisor
I.	Robinson	University College London	Science team
A.	Robinson	Central Laser Facility, Rutherford Appleton Lab	Science advisor
J.	Rodenberg	University of Sheffield	Science advisor
N.	Rohringer	University of Hamburg, Germany	Science advisor
K.	Rossnagel	University of Kiel, DESY	Science advisor
M.	Ruberti	Imperial College London	Science advisor

Initial	Surname	Affiliation	Project role
D.	Rugg	Rolls Royce	Science team / Industry advisor
C.	Russo	MRC-LMB, Cambridge	Science advisor
C.	Sanders	Central Laser Facility, Rutherford Appleton Lab	Science advisor
M.	Scheck	University of West Scotland	Science advisor
P.	Scherkl	University of Strathclyde	Science advisor
C.J.	Schofield	University of Oxford	Science advisor
S.L.M.	Schroeder	University of Leeds	Science team
R.	Scott	Central Laser Facility, Rutherford Appleton Lab	Science advisor
E.	Snell	SUNY Buffalo, BioXFEL	Science advisor
J.T.	Spencer	UK NNL	Industry advisor
E.	Springate	Central Laser Facility, Rutherford Appleton Lab	Science advisor
D.	Stuart	Diamond Light Source	Science advisor
N.	Thompson	ASTeC, Daresbury Laboratory	Technical team
G.	Thornton	University College London	Science advisor
J.	van Thor	Imperial College London	Science team
S.M.	Vinko	University of Oxford	Science team
J.	von Zanthier	University of Erlangen, Germany	Science advisor
S.	Wall	ICFO, Barcelona	Science team
M.	Walsh	Diamond Light Source	Science advisor
J.S.	Wark	University of Oxford	Science team
M.R.	Warren	Diamond Light Source	Science advisor
P.	Weber	Brown University, USA	Science advisor
J.	Weinstein	University of Sheffield	Science team
P.	Wernet	University of Uppsala	Science advisor
P.W.	Williams	ASTeC, Daresbury Laboratory	Technical team
P.	Withers	Henry Royce Institute / University of Manchester	Industry advisor
J.	Yano	Lawrence Berkeley National Laboratory	Science advisor
A.	Zair	Kings College London	Science team
X.	Zhang	Imperial College London	Science team

We are grateful to the **external reviewers** who provided feedback on the 1st draft of this Science Case:

- **Massimo Altarelli**, Max Planck Institute for Structural Dynamics, Hamburg
- **Bridget Carragher**, New York Structural Biology Centre, NY
- **Andrea Cavalleri**, Max Planck Institute for Structural Dynamics, Hamburg
- **Eaton Lattman**, University of Buffalo / BioXFEL Centre
- **Keith Moffat**, University of Chicago
- **Philippe Wernet**, University of Uppsala
- **Linda Young**, Argonne National Laboratory, IL

A4.4 Development of user community

The UK has a strong and growing community of scientists who use existing operational XFEL facilities, such as the European XFEL, LCLS or SACLA, to conduct research in a broad range of areas from protein structural dynamics to matter at extreme conditions and ultrafast electron dynamics. UK users have been benefiting from beam time since first operations on most facilities, either through FAP awarded beamtime or collaborative commissioning campaigns. For the most established facilities, LCLS and SACLA, there is already a clear record of increasing engagement from the UK community. A survey of research groups in the UK (across the Life and Physical Sciences) indicates that over 500 UK scientists have had active involvement in XFEL science in the last decade. This is a conservative estimate, as our survey was partial and many university groups working with XFELs were likely missed. In STFC alone, there are currently over 150 people across multiple departments working to both upgrade the capabilities of existing XFELs and explore new and ambitious technologies that could pave the way for a UK XFEL.

The UK research community is made up of a diverse range of academics consisting of university staff, post-doctoral researchers and post-graduates, who have either attended beamtime or undertaken theoretical and computational analysis. In a 10 year period, the UK's research groups have established a strong reputation in many areas of activity including, for example, structural biology, protein structural dynamics, matter at extreme conditions, materials, chemical sciences and nanoscience and ultrafast X-ray-matter interactions.

The 2016 STFC FEL Review identified that the existing potential XFEL user community should be helped to grow, especially following construction of, and UK investment in, the European XFEL. The Life and Physical Sciences Hubs (based at Diamond and the Central Laser Facility, respectively) serve to support and grow the UK community through various initiatives. Activities include funding travel for experimenters, development of hardware and sample technologies, joint funding of PhD studentships and support for networking activities. Whilst they operate on different models, both Hubs share the common strategic aim to assist users, some of whom will never have visited an XFEL, in gaining the experience and capability to make the most of these cutting-edge facilities. Since XFEL beamtime is in great demand, it is critical that these programmes continue in order to lower the barriers to access that many UK groups face and enable them to deliver greater scientific impact and foster new international collaborations.

SACLA publication data (see **Figure A4.1**) highlights the growth in UK users at this hard X-ray FEL. This is also reflected in the fraction of UK scientists that make up the total number of domestic and international users at the facility. This relatively small, but emergent UK base at SACLA is already delivering scientific impact, with UK authors featuring on 10% of all XFEL user publications at the facility in the last five years. As the first hard X-ray FEL, LCLS-I has been a draw for the UK academic community since the first year of operations in 2009, with an average of 50 unique UK users using the facility annually over the last five years. Accounting for shutdown periods for the development of LCLS-II, the facility has seen a steady increase in UK engagement over that period, with an approximate growth of 10% per annum.

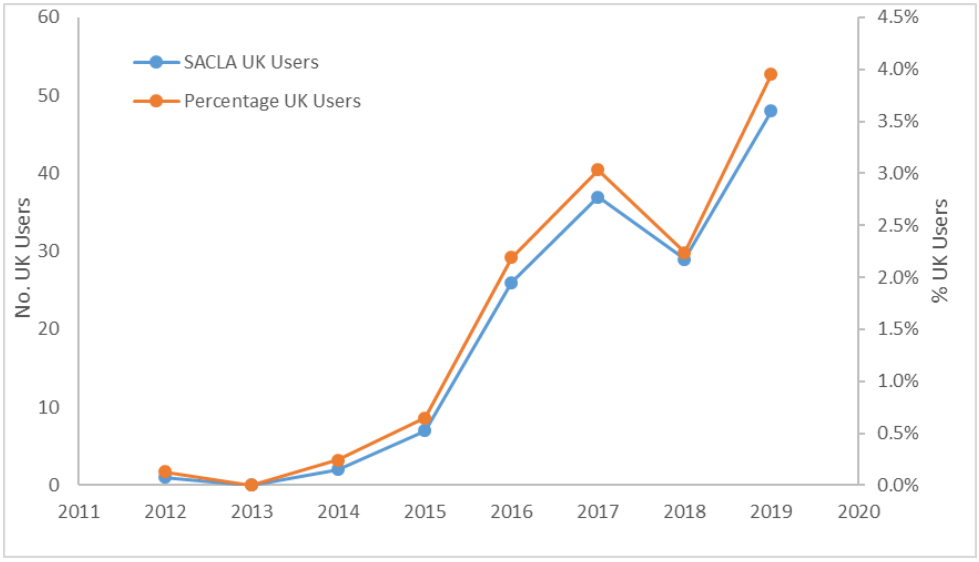

Figure A4.1: Number of UK team members on experiments at the SACLA XFEL. The relative percentage that UK users made up of the total number of users from all countries is also shown.

The UK community is currently moderate in number (in 2018 there were 98 users at LCLS and SACLA), and it is still smaller compared to the communities in Germany, Japan and the USA. Whilst increasing international capacity is welcome by UK scientists to meet immediate needs (especially with the European XFEL recently coming online), output from existing host countries shows how domestic user communities rapidly grow to build and exploit new capabilities. As the geographically closest XFEL facility to the UK currently, as well as offering state-of-the-art capability, the European XFEL is an attractive destination to address a range of scientific challenges for UK scientists. Although it has only been operational for a couple of years, in 2019 there were 891 unique users at the facility overall, 31 of which were from the UK. Although we anticipate UK participation in the European XFEL will grow significantly over the coming years, this number is dwarfed by the number of domestic users at the facility who totalled 303 (34%) unique users. The presence of large domestic user communities is also reflected at established FELs like LCLS and SACLA, the latter of which had 1214 user visits in 2019, with 58% of these consisting of Japanese academic and industrial sectors. A UK XFEL would undoubtedly be extremely valuable in guaranteeing UK access to an ultra-fast X-ray facility and importantly, lowering the barriers to access. In addition, as international demand increases, competition for beamtime on existing facilities is only likely to grow over the next 5 – 10 years.

The cutting-edge nature of the research performed at XFELs is reflected in the quality of the publications produced from the facilities. As the most established hard X-ray facility, and the one most in demand by UK users in over the last five years, LCLS provides useful statistics in this regard. **Figure A4.2** shows how publication numbers from X-ray beam time have increased since first user operations began in 2009, as scientists discovered how the new capability could be used to answer significant scientific questions and developed new experimental techniques to make the most of their limited beamtime. In the last five years, LCLS averaged almost 100 publications per year. LCLS, like many other XFELs, produces significant numbers of high impact publications across a range of fields. Almost one-third of all LCLS X-ray science publications have been in published in high impact journals (Impact Factor > 10). The facility as a whole averaged 186 publications in the same period, owing to additional FEL and accelerator science, as well as publication of scientific work performed by LCLS scientists at other facilities. A UK XFEL would also be expected to produce significant output from these additional activities as the facility developed new techniques, including novel acceleration techniques, X-ray beam characterisation, detector development, sample delivery, and data analysis. As a world-leading facility, we would expect to attract a high calibre of facility scientists, who would also pursue their own scientific programmes at the UK FEL and facilities worldwide.

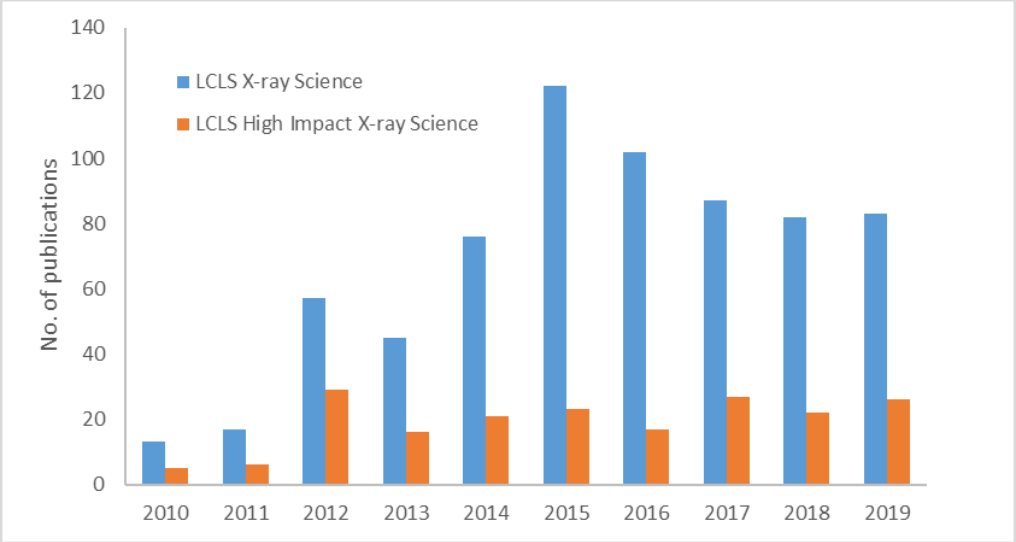

Figure A4.2: Number of LCLS publications based on X-ray science performed at the facility over the last 10 years. The number of high impact publications (impact factor of 10+) is also shown. Note – FY17 and FY19 had limited beam time (6 months and 3 months respectively) due to LCLS-II development work, hence we would expect this to have negatively impacted publication rates from 2017 onwards.

It should be noted that whilst the average number of publications per year from an XFEL such as LCLS is lower than many established X-ray synchrotron facilities, there are a number of key differences. Most synchrotrons are able to operate with multiple end-stations in parallel (typically 20 – 30), significantly boosting the quantity of scientific output. For most currently operational XFELs, only a single end-station can operate at any one time, which has been a limiting factor. However, next-generation XFELs (including LCLS-II, the European XFEL and a UK XFEL) will be capable of multiplexing in order to utilise multiple end-stations simultaneously. In addition, as a mature technology, synchrotrons use established techniques to produce their scientific results, so most beamtime results in a publication of some sort. As a new technology, not only are experimental techniques on XFELs in their relative infancy, but the nature of experiments is often testing the capability of the machine rather than utilising known methods to measure certain material parameters. Whilst these early experiments can yield high impact publications from the first application of cutting-edge techniques (as demonstrated on machines like LCLS), the overall publication rate that results will be lower initially, especially when additional facility development is often continually ongoing in parallel.

As use of XFELs becomes more established across a range of physical and life sciences, and additional capacity is unlocked through the use of multiplexing and higher repetition rates, it is anticipated that the degree of scientific productivity from these facilities will increase significantly.

Whilst we cannot precisely predict how long the current XFEL capacity will sufficiently meet scientific demand, we highlight two important trends. Firstly, everywhere the number of users is steadily growing. Secondly, already at all XFELs beamtime is heavily oversubscribed by typically high-quality proposals, so that of proposals deemed competitive only about one in four receive beamtime. Extra capacity will alleviate this, but demand will also grow as more scientists recognise the benefits of XFEL measurements to their research. Moreover, new capabilities, such as those that will be offered by UK XFEL, will create new areas of demand. It is therefore our anticipation that within the next decade the demand will drive the need for additional XFELs and new capabilities. A UK XFEL would be well placed to satisfy this demand from both national and overseas scientists.

Science and Technology Facilities Council

Science and Technology Facilities Council
Polaris House
North Star Avenue
Swindon
SN2 1SZ

stfc.ukri.org