

Chapter 1

X-Ray Free Electron Lasers and Their Applications



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X-ray free electron lasers (FELs) represent the latest generation of X-ray sources, with unique properties and capabilities that present novel opportunities in the study of matter in unique forms as well as the study of interactions and dynamics on ultrafast timescales. For the purpose of this book focused on the use of X-ray FEL beams for the study of biological materials, the story begins with the availability of these novel sources to the scientific community as user facilities. Let us however take a quick step back and provide a brief historical background on what has led to the advent of X-ray FEL sources. This will be followed by a short description of the principles of operation of X-ray FELs and the breadth of their scientific use.

1.1 X-Rays and Their Applications

When Wilhelm Conrad Röntgen discovered X-rays in 1895, despite scientists all over the World not immediately knowing their true nature, there was a rapidly growing excitement in the scientific community and the general population regarding the potential uses of these new particles, this new form of radiation. It became quickly well known across the globe that X-rays have the power to see inside matter, inside the body of patients requiring medical care, for example. This became the first

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obvious application for these unknown rays. In this particular case, the particle-like behavior of X-rays is exploited via the absorption of energy by the material, allowing shadow images representative of how absorbing, or equivalently, how dense a material is.

Following two decades of intense scientific research, discovery and debate about the apparent dual nature of X-rays, at times seen to behave as particles and at times as waves, an increased understanding of X-rays eventually improved both the methods by which they are generated and the ways to utilize them for probing matter. In the early 1910s, the seminal works of Max von Laue, William Henry Bragg, and his son, William Lawrence Bragg led to the realization that X-rays are ideal tools to study the atomic structure of matter due to their electromagnetic wave nature, which allows them to probe features at scales similar to or longer than their wavelengths. Electromagnetic waves, including the visible light we see, can in principle exist at any wavelength. Visible light interacts with structures of size comparable to the wavelength of the light or larger, allowing us to see things. Similarly, X-rays can “see” objects as small as atoms due to their wavelength approaching atomic scales. In the continuum of wavelengths of the electromagnetic spectrum, X-rays such as those discovered by Röntgen now define a range of wavelengths spanning roughly from 0.1 to 100 Å, with the typical spacing between atoms in solids and liquids in the middle of this range, making them ideal probes of the atomic structure of matter.

Today, X-rays are recognized to possess a dual nature, as all matter does according to quantum mechanical theory. X-rays are electromagnetic waves with discrete energy units behaving as particles under some interactions with matter. Both aspects of this dual nature of X-rays are widely exploited by scientists around the World today. X-rays are used to understand the fundamental structure of matter and what happens at the atomic and electronic levels in the universe we live in, not only from a fundamental point of view but also with very practical applications. The study of biological systems represents an important aspect of the many uses of X-rays in scientific research. The reader new to the field of X-ray methods is referred to the excellent introduction by Jens Als-Nielsen [5].

1.1.1 X-Ray Methods

X-ray methods have been broadly developed over the last century and offer many diverse scientific communities a variety of tools optimized for particular samples or questions to answer. Many texts and general reviews of X-ray methods exist [5, 32, 73] and we will here only briefly discuss the evolution of the key methods now employed at X-ray FEL facilities for the study of biology.

1.1.1.1 Scattering

The natural match between the wavelength of X-rays and the typical spacing of atoms in solid and liquid matter has made the use of X-rays as a tool for research a rapidly growing field in the twentieth century. X-rays primarily interact with the electrons in matter. The simplest interaction of X-rays with matter is via elastic scattering, where X-rays essentially “bounce off” the electronic structure of matter without losing energy but their direction of travel is changed. The directional dependence of the elastic scattering from these electrons can be measured and primarily reveals the location of concentrated electronic density, typically located around the nuclei of atoms. Elastic scattering extracts information on the correlation between the location of atoms, that is the likelihood of an electron being located at a certain distance or direction from another, which can be used to deduce the detailed structure of the material or sample at hand [5].

Solid matter often arranges itself naturally in a crystalline structure where the atoms or molecules self-organize into a repeating pattern. This creates a repeating pattern of electrons where the correlation between their positions also becomes periodic. Shining an X-ray beam on a crystalline material will lead to X-rays elastically scattered from this repeating electronic density pattern to produce a corresponding repeating diffraction pattern of sharp bright spots in the measured scattered intensity. Following the first observation of X-rays diffracted by the periodic atomic arrangement in a crystal by Walther Friedrich and Paul Knipping in 1912, at the suggestion of von Laue, X-rays were soon used to map the structure of the majority of naturally occurring crystalline materials [3] as well as most man-made materials. Crystallographic methods of various forms are now regularly used to understand the structure of novel materials and some of their more unique properties such as superconductivity. The foundations of X-ray crystallographic methods are thoroughly discussed in the International Tables for Crystallography [32] for the interested reader.

Crystallographic methods, which will be featured prominently in this book, were eventually adapted to the study of biological molecules. Life is supported by a multitude of molecules with specific roles and tasks to perform for each organism. To begin to understand the details of life, and perhaps to help enhance it by, for example, curing diseases, requires an understanding of the interactions of these molecules with each other and with their environment. This is a very daunting challenge that first involves obtaining a detailed understanding of the structure of these molecules—that is the 3D arrangement of the atoms comprising them. The initial demonstration of macromolecular crystallography on the protein myoglobin took place in 1958 [35]. Since then, macromolecular structure determination using X-rays has become a very important scientific method, with wide-ranging impact in the medical and life science fields. Today, many thousands of three-dimensional structures of biological molecules are determined each year using X-ray diffraction and this trend is still increasing as shown in Fig. 1.1. X-ray FEL facilities have

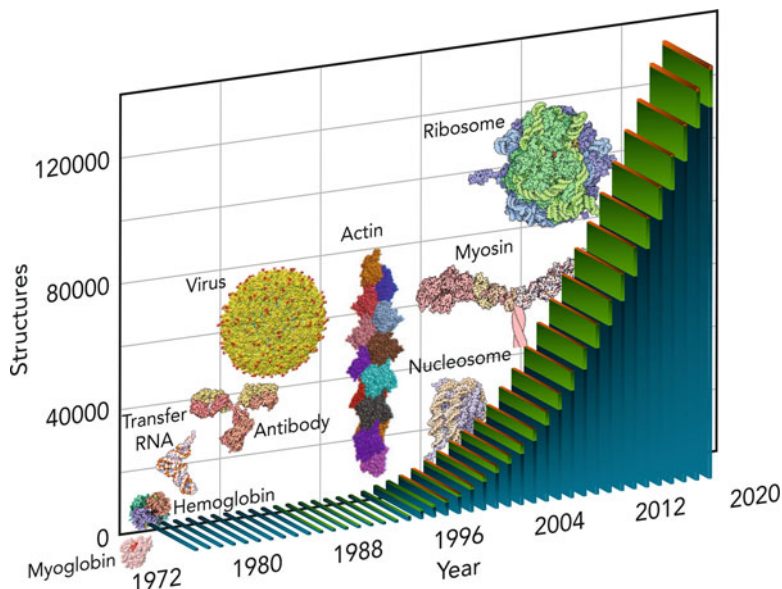


Fig. 1.1 Cumulative number of structures in the Protein Data Bank [6] used by different techniques. The Protein Data Bank is an international repository of macromolecular structures used to disseminate structural information. Figure adapted from [1]. Modified by Gregory Stewart and Terry Anderson with permission of the International Union of Crystallography

begun using their unique capabilities to contribute to the wealth of structural knowledge available. Chapter 2 of this book offers a thorough review of the current state of crystallographic methods using X-ray FELs. However, for the majority of macromolecules, a crystalline state is not a naturally forming state. The challenges of producing crystals of biomolecules of sufficient quality to allow interpreting their diffraction patterns to yield a structure exist no matter what X-ray source is used. The challenges to crystal preparation specific to X-ray FELs will be presented in Chaps. 3 and 4.

In principle, it is possible to use elastic scattering to obtain an image of a nonperiodic or noncrystalline sample to a high resolution that is only limited by the wavelength of the X-rays used. Such a possibility would obviate one of the biggest challenges in structural biology, the need to grow high-quality crystals of a molecule of interest. These relatively new imaging methods can be grouped together under the umbrella of coherent diffractive imaging (CDI) methods that were extensively reviewed recently [47].

In the case of coherent diffractive imaging, a coherent X-ray illumination, where the X-ray wave field illuminating the sample has a well-defined phase relationship across the illumination, is necessary. In simple terms, this means that the X-rays

illuminating the sample look more like a long single-break wave hitting the shore rather than be composed of multiple waves colliding, leading to areas of the beach with a big surf and others more calm. Coherent diffraction methods form an image of the sample by combining the measured angle-dependent scattering amplitudes with computationally retrieved phases of the scattered waves. Mathematically, the amplitude of the elastic scattering pattern from a single object under such coherent illumination will be proportional to the amplitude of something called a Fourier transform of the illuminated electron density. The interested reader is referred to optics and X-ray physics textbooks for a detailed mathematical treatment [5, 26].

The phases of the scattered waves must be known to form an image, but these phases cannot be measured by X-ray detectors, which only sense the deposited energy in a pixel and cannot resolve the extremely rapid oscillations of the electromagnetic waves. This leads to the so-called phase problem in both imaging and crystallography, where the phases are unknown from the measurement itself. In the CDI method, iterative calculations under specific boundary conditions, by applying constraints to the image or solution based on some previous knowledge of the sample, are performed to retrieve the phase. Compared with conventional imaging methods using lenses, CDI methods can improve the resolution, because they are free from the limitations of X-ray imaging optics. Solutions to the phase problem in X-ray FEL crystallography will be discussed in Chaps. 8 and 9. The use of coherent beams recently available with brighter X-ray sources, and especially X-ray FELs, opens the door to new capabilities in the study of single particles via imaging and will be the subject of Chap. 14.

Other scattering methods are broadly used in many areas of science. For example, inelastic scattering uses the difference in the energy of incident and scattered photons to extract information on the dynamics in materials. Incident X-rays can transfer energy to the sample via inelastic interactions, where excited states with energy levels lower than the incident photon energy can be produced by absorption of X-ray photons and instantaneous reemission of photons at a lower energy. This inelastic scattering process couples incident X-rays to available excited states of the system and can therefore probe the available energy levels within the sample. Measuring inelastic scattering spectra as a function of scattering angles can reveal the dispersion relation of many dynamic processes such as phonons (lattice dynamics), magnons (spin dynamics), plasmons, and excitons (electron dynamics). Inelastic scattering methods are used more broadly in materials research than in biology and have seen limited use in biology at X-ray FELs to date. The topics covered in this book exploit elastic and coherent scattering techniques exclusively, and inelastic scattering methods will therefore not be discussed further. It is however expected that higher repetition rate X-ray FELs in the near future will make inelastic scattering methods more practical and this will benefit the biological sciences. Such potential future applications and the future of X-ray FELs will be discussed in the last chapter of this book.

1.1.1.2 Spectroscopy

Beyond the use of scattering methods to probe the primarily static structure of matter, spectroscopic methods that utilize the particle-like behavior of X-rays are commonly used. It was realized early after the discovery of X-rays that specific X-ray energies were emitted by specific materials and these differed for different materials. This is directly equivalent to the different colors emitted by neon light signs in the visible range, where different gases produce different colors. It is now known that atoms can emit X-rays when an unoccupied electronic orbital (typically an inner shell orbital for X-ray emission) gets filled by an electron from a higher orbital or by a free electron within the system, such as in metals, for example. The energy of the emitted X-ray is representative of the binding energy of the core electron orbital that got filled and its difference in energy compared to the previously filled orbital or the free electron. High atomic number elements emit harder X-rays (shorter wavelength) due to the higher energy of their core electrons, which are more tightly bound to a more highly charged atomic nucleus.

Not only does the wavelength of typical X-rays match interatomic spacings, but the energy of these X-rays also match well the energy levels of electronic orbitals of core electrons. Therefore, X-rays represent a probe capable of element sensitivity, differentiating between different atoms in the sample. Since the energy levels of electrons are perturbed by their local environment, the occupancy of valence electronic levels, as well as spin states, accurate measurements of the spectrum of emitted X-rays from a sample can be used to deduce accurate information on the electronic states of specific elements in a sample. Crystallographic and imaging techniques are not very sensitive to the finer details of the electronic structure of the samples being measured, making spectroscopy a powerful complementary tool.

X-rays of sufficiently high photon energy can be used to excite atoms by knocking out core electrons, which can be followed by X-ray emission from this core electronic level being filled shortly afterward. Methods of X-ray emission spectroscopy (XES) are powerful tools to understand, for example, oxidation states, which is particularly relevant in biocatalysts. Many important biological functions involve the binding of oxygen to one or many metal atoms in a molecule or the exchange of electrons from the molecular environment to the metal atom (oxidation). For example, the molecule Photosystem II is critical to the photosynthetic process of splitting water molecules to produce the oxygen (O_2) molecules we all breathe to maintain life on Earth as we know it. X-ray emission spectroscopy can probe the oxidation state of such a metal center by measuring the spectrum of emitted X-rays and how this is modified by small changes in the electronic state of a particular atom and its local environment. Additionally, X-ray absorption spectroscopy (XAS), where electronic energy levels are probed by directly measuring the absorption (comparing an incident and transmitted spectrum), is also broadly used in X-ray science in general and beginning to find applications using X-ray FELs. Spectroscopic applications will be discussed at length in Chap. 13.

1.1.2 The Evolution of X-Ray Sources

For the first two thirds of the twentieth century, the method to generate X-rays changed little. Of course, technological improvements made sources brighter and more easily usable for experiments as X-ray generation became better understood. However, the generation of X-rays remained fundamentally the same for decades. X-ray tubes use high voltages to accelerate electrons from a cathode to an anode. As the electrons interact with the anode, a deceleration leads to emitted X-rays in a broad spectrum known as Bremsstrahlung radiation. Beyond this broad spectrum, high-energy electrons can remove core electrons from the atoms in the anode. As previously discussed, the core holes get filled rapidly and can generate emitted X-rays of a particular energy. This leads to a relatively narrow band (small range of wavelength centered around the emission line of the material) radiation emitted by the X-ray tube, however, with a high divergence and polychromaticity set by the bandwidth of the emission process. This limits the achievable brightness of the beam. Most of the energy used in generating X-rays in this fashion results in heat in the anode and cooling limitations set a limit to how much X-ray energy can be generated from an X-ray tube.

The 1970s brought the first revolution to X-ray sources. Decades of development of particle and especially electron accelerators led to more powerful machines such as cyclotrons and synchrotrons dedicated to particle physics or high-energy physics applications. It was known that such machines, with their mostly circular design, would generate emitted photon beams as the electrons are accelerated inward by the magnetic fields keeping them within a defined, mostly circular, orbit. With higher energy machines, the range of energies of the emitted photons reached the X-ray regime and a few places around the world built the capabilities to exploit, parasitically at first, this unavoidable radiation. The great initial successes of these parasitic operations, due to the very large increase in brightness compared to X-ray tubes, was rapidly sufficient to justify investment in dedicated electron storage rings built specifically for the production of X-ray beams to be used for photon science. These facilities are known as second-generation synchrotron sources, and starting in the early 1980s they provided dedicated user facility access to high-brightness X-ray beams produced from the circular trajectory of electrons through the bending magnets.

The so-called third-generation synchrotron radiation facilities made their appearance in the 1990s. These facilities are distinguished from second-generation facilities by their design specifically intended to make use of the straight sections between bending magnets to generate even brighter X-ray beams. In these straight sections, long arrays of magnets of alternating polarities called undulators are installed to send the electron beam on a rapidly oscillating sinusoidal path. The oscillating motion around a straight path leads to a much more intense, more collimated output of radiation compared to the fan of radiation from a bending magnet and this leads to much brighter sources of X-rays. These sources allow more challenging experiments and measurements, studying smaller or more dilute samples for spectroscopy, for

example. Third-generation light sources are now prevalent across the globe, with hundreds of beamlines with dedicated instrumentation for a broad set of scientific fields. The contribution of these facilities to scientific knowledge and technical developments is undeniable, certainly in the life sciences but also across many fields of science. Many of the third-generation sources are now undergoing upgrades to further improve their brightness by reducing their beam emittance, a measure of the size and angular spread of the electron beam, to values approaching the theoretical minimum possible for a diffraction-limited light source. This is achieved via the use of multi-bend achromat magnets to replace double magnet benders per cell. The gentler bend in the electron beam thus afforded reduces the horizontal spread of the electron beam, increasing the beam brightness.

Following on the rough trend of a new generation of X-ray sources every decade, the 2000s saw the beginning of the X-ray FEL era, with the construction of the first FEL user facilities culminating with the start of the first ever hard X-ray FEL. The next section will describe X-ray FELs in more detail. More detailed information about the history of synchrotron sources can be found here [7].

1.2 X-Ray FELs as User Facilities

Free electron lasers have only recently become well known to the broad scientific community with the construction and start of operations of facilities open to use by scientists. Free electron lasers have, however, been around for a few decades, starting with an initial theoretical conceptualization by Madey in 1971 [44]. This was followed by a demonstration of the principles a few years later, where an optical cavity was used to generate infrared radiation [15]. The concepts and technologies eventually leading to the feasibility of FELs in the X-ray regime were developed during the 1980s and 1990s, culminating with the realization of linear accelerator-based single-pass machines dedicated to the production of short-pulsed photon beams of wavelength approaching, and eventually reaching, interatomic spacings of a few Ångströms or less. The first such machine built specifically to be made available to users was the Free electron LASer in Hamburg (FLASH) starting in 2005 [2, 65], followed by the SPring-8 Compact SASE Source (SCSS) [61, 74]. Both of these sources operated in the ultraviolet regime, approaching the soft X-ray range. A few years later, hard X-ray FELs became a reality with the Linac Coherent Light Source (LCLS) in the USA in 2009 [16] and the SPring-8 Angstrom Compact free electron LASer (SACLA) in Japan [31] shortly after. As of 2018, the European XFEL in Germany, SwissFEL in Switzerland, and PAL-XFEL in South Korea have joined the ranks of operating X-ray FELs. For the interested reader, the history of FELs is beautifully recounted by Pellegrini [54]. Below, the physics behind free electron lasers will be briefly described.

1.2.1 The Physics of Free Electron Lasers

Many excellent articles and reviews describe in great detail the technology and physics behind X-ray FEL radiation generation [27, 51, 59, 60]. Of particular interest should be the recent review article by Pellegrini *et al.* [55]. For the purpose of this book, we will only briefly summarize FEL physics in the hopes of stimulating the curiosity of the reader.

X-ray FELs are at times classified as fourth-generation synchrotron sources. This nomenclature is not universal due to the noncircular design of FEL facilities and other developments such as diffraction-limited storage rings and energy recovery linacs sometimes being also referred to as fourth-generation sources. Nevertheless, X-ray FELs take previous technologies from third-generation sources a large step further. Third-generation sources were based on the intended use of undulator technologies and X-ray FELs entirely rely on extending the use of undulators to devices more than one order of magnitude larger. The linear design of an X-ray FEL is not by choice since a circular design allowing multiple FEL sources would be much more desirable. It is required by the electron beam quality needed for the lasing process, which cannot be accomplished with a circular design.

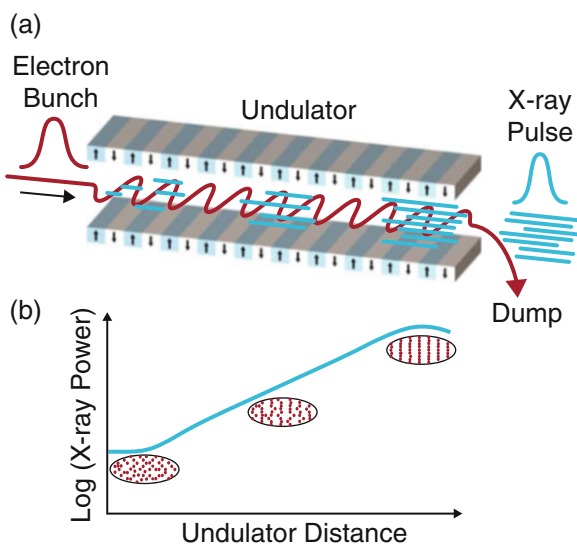
An undulator causes an electron beam with energy γmc^2 to oscillate in a nearly sinusoidal fashion leading to emitted radiation of wavelength:

$$\lambda_r = \frac{\lambda_u}{2\gamma^2} \left(1 + \frac{K^2}{2} \right) = \frac{2\pi c}{\omega_r} \quad (1.1)$$

where $K \equiv eB_0\lambda_u/(2\pi mc)$ is the undulator strength parameter, B_0 is the peak magnetic field strength, λ_u is the undulator period, e is the electron charge, c is the speed of light, m is the electron mass, and ω_r is the fundamental undulator frequency. This equation holds true for the radiation emitted from any undulator system including those at conventional synchrotron sources. What distinguishes X-ray FEL radiation from synchrotron radiation is the brightness of the electron beam required, along with the length of the undulator, which allows for self-amplified spontaneous emission (SASE), an exponential growth in the radiated intensity via the interaction of the electron bunch with the previously emitted X-ray field as they co-propagate along the undulator. Achieving SASE is quite challenging and requires the electron beam to be of sufficient quality, *i.e.*, a low emittance, high peak current, and a small energy spread that are only achievable with a linear accelerator. The parameters basically control how similar all the electrons are. The lasing process is an enhancement of emitted energy by placing as many electrons as possible in the same state so that they emit in harmony (in phase).

The electron trajectory in the undulator must be sufficiently straight (on the order of $5 \mu\text{m}$ deviation over the $\sim 100\text{-m}$ -long undulator path) to maintain the spatial overlap of the electron beam and the co-propagating X-rays. If these conditions are met, it leads to a microbunching process in the electron beam in which the X-ray field slows down the faster electrons and speeds up the slower ones. The

Fig. 1.2 In the self-amplified spontaneous emission (SASE) process, microbunching increases as the electron beam travels down the undulator length causing the radiation power to grow. Reproduced with permission from [10]



microbunches created behave like a single massive charge since the electrons in the bunch oscillate in phase, leading to an increased X-ray emission by a factor of N^2 along the axis of the electron beam, where N is the number of electrons in the microbunch. The process is schematically illustrated in Fig. 1.2. It eventually reaches saturation when space charge effects (electrons becoming too close and repelling each other) and the same forces that cause the microbunching in the first place eventually start to rip the microbunches apart. The SASE process also generates higher harmonics, integer multiples of the fundamental energy, at the roughly 1% intensity level of the fundamental.

The end result for an optimized accelerator and undulator system is a highly transversely coherent X-ray beam. However, the electron beam is typically comprised of many microbunches for a SASE FEL. These microbunches are uncorrelated and there is a natural spread of energy within the bunch, leading to only moderate longitudinal coherence and a typical bandwidth of the beam on the order of 0.2%. The amplification starting from random fluctuations in the initial electron beam gives rise to appreciable fluctuations in essentially all relevant parameters including pulse energy, average wavelength, and the photon energy spectrum [30, 67, 78], as well as the spatial and temporal profiles [25]. The SASE process produces short pulses, typically on the order of the few tens of femtoseconds (fs), with the potential longer pulses in the few hundred fs range or shorter pulses in the attosecond range. The X-ray pulse duration is controlled by the length of the electron bunch that possesses sufficient “quality” to produce lasing. This can be achieved by simply controlling the overall electron bunch length or possibly by intentionally producing an electron bunch where only a small part possesses the characteristics required to produce lasing. The interested reader is again referred to the review of Pellegrini for more detail [55]. The amplification process produces radiation in

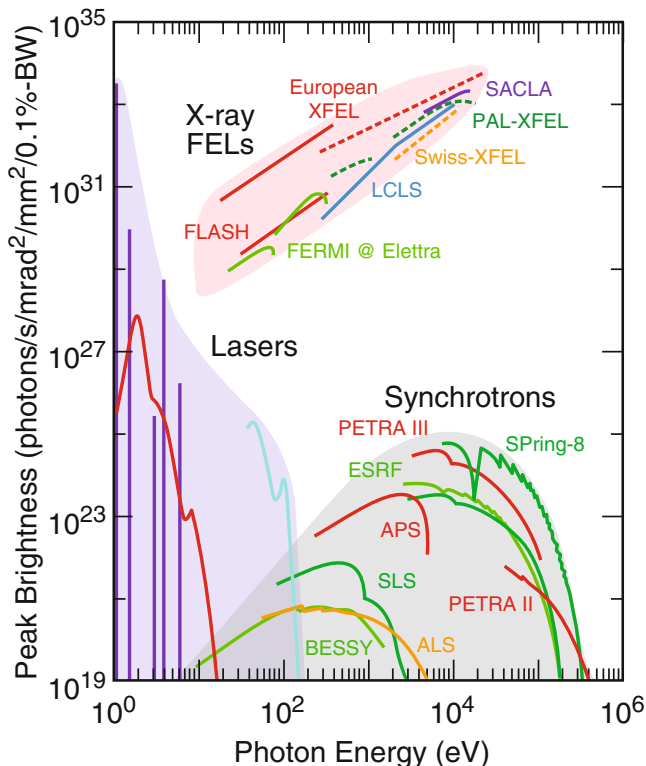


Fig. 1.3 Comparison of peak brightness as a function of photon energy between conventional lasers and higher harmonic generation sources, synchrotron sources, and X-ray free electron lasers. Modified by Gregory Stewart and Terry Anderson from [69]

a very narrow cone, with lower divergence than spontaneous radiation and with a narrower bandwidth. This ultimately results in a peak emitted brightness 9 to 10 orders of magnitude higher than the spontaneous radiation from third-generation sources. A comparison of typical performance of FELs and synchrotron sources is shown in Fig. 1.3.

The fluctuating nature of X-ray FEL beams creates a need for diagnostics to measure the pulse-to-pulse fluctuation of beam parameters that could influence the scientific measurement. For example, the technique of absorption spectroscopy, where the changes between the transmitted spectrum and the incident spectrum can reveal information on the fine details of the electronic structure of the sample, requires an accurate knowledge of the spectrum on a single pulse. Such requirement, among others, has led to the creation of single-shot spectrometer diagnostics based on bent crystal concepts where the X-rays are spatially dispersed based on their energy and measured by an area detector [78]. Other methods such as time-resolved diffraction require the measurement of very fine changes in intensity between a

sample in its ground and excited states, or in the case of a sample excited via an optical laser, the ground (unpumped) and pumped state. Accurate, single-shot capable, nondestructive intensity monitors were required to achieve better than 0.1% accuracy in time-resolved measurements. These intensity measurements are based on Compton backscattering from thin targets [19, 66]. Diagnostics on the properties of any beam used to probe a sample is key to a quantitative scientific understanding. Most X-ray sources prior to X-ray FELs have stable beams that do not require constant monitoring and measurement. X-ray FELs, by their fluctuating nature, have required creativity in developing the required diagnostics, with many highlighted in the proceedings of a recent conference dedicated to photon diagnostics [14].

Beyond diagnostics, the instantaneous nature of the arrival of all X-rays at a detector and the relatively high repetition rates of even the first X-ray FELs creates a need for novel detector technology. A review of detector technology in use at LCLS is recommended as a starting point to the interested reader [9].

As of mid-2017, five FEL user facilities are in operation at or near the X-ray range. The first two, FLASH in Hamburg, Germany and FERMI in Trieste, Italy [4], operate in the ultraviolet to the low-energy end of soft X-rays. The other three, SACLA in Harima, Japan, LCLS in Menlo Park, California, USA, and the European XFEL in Hamburg, Germany are the first X-ray FELs in operation capable of operating in the hard X-ray regime above 10 keV. They are also capable of soft X-ray FEL generation down to the water window (slightly below the oxygen K-edge of 533 eV and above the carbon K-edge of 282 eV). The FEL-based results presented in this book will be entirely from four of these operating facilities, with the European XFEL being too recently operational to present results.

Other FELs have now demonstrated lasing and are undergoing early commissioning or are very near completion and will begin user programs in the late 2017 or in 2018. These include the PAL-XFEL in Pohang, South Korea and the SwissFEL in Villigen, Switzerland. Upcoming and potential new facilities as well as the novel science they will allow will be discussed more thoroughly in Chap. 16.

1.3 The Scientific Applications of X-Ray FELs

X-ray FELs produce beams of X-rays that have properties unseen before and the most successful use of these beams is via the exploitation of these unique capabilities, which can provide information unobtainable via other methods. Along with the many unique opportunities afforded by FEL beams come equivalently unique challenges. We will briefly explore the breadth of scientific exploration using X-ray FELs from the perspective of their unique capabilities and highlight how these were exploited with a few examples, ultimately leading into how X-ray FELs are valuable tools for biological studies.

1.3.1 Using the Time Resolution

The typical duration of an X-ray FEL pulse is roughly three orders of magnitude shorter than a typical shortest pulse from a synchrotron (but contains approximately the same number of photons that a synchrotron would produce in 1 s). With pulse lengths typically shorter than 30 fs, this opens a new area of ultrafast science. X-ray FELs combine these very short pulses with short wavelengths, allowing simultaneous high spatial and temporal resolution like never before. Many of the fundamental interactions in matter involving electrons and nuclei happen on the few tens of femtosecond timescales and X-ray FELs are ideal tools to study these interactions. Such fast dynamics must be triggered in a controlled and reproducible manner to extract information on these ultrafast timescales. This trigger is a brief stimulus applied to the sample, with optical pumping with an ultrafast laser being the main tool to initiate dynamics to be probed by the X-ray FEL beam. Light stimulation is currently the only reliable method to initiate dynamics with a few tens of femtosecond accuracy or better.

Pump-probe methods are ubiquitous in X-ray FEL experiments with the majority of experiments employing a laser illuminating the sample to study its dynamics. These methods are applied to all fields of science. In material science, optical pump X-ray probe methods are used to study lattice vibrations and phonon dynamics [68], material properties [33], strongly correlated systems and quantum materials [38], spin dynamics [37] as well as catalytic interfaces [53], to name just a few examples. In chemistry, ultrafast bond breaking and formation initiated by an optical laser can be observed to create a molecular movie of a reaction [36, 49]. Various scattering and spectroscopic methods can also be used to better understand charge transfer in metal complexes [12, 43, 77], eventually helping us to understand systems with potential energy-harvesting applications.

In high energy density (HED) research, it is of interest to create warm or hot states of matter that have thermal energy well beyond what is typically found on Earth but with high density typical of solid matter. These states can be created with very powerful lasers impinging on the sample and depositing a lot of energy in a short time. These states are very short lived as they will expand and cool rapidly after laser illumination. This allows, for example, conditions found in the center of planets, where high densities are sustained at high temperatures and pressures, to be reached under laboratory conditions. X-ray FEL beams are ideal to penetrate the dense material and probe the transient structure of these states of matter [18]. It is also possible to use longer pulsed lasers to initiate a shock in materials and study material failure, among other things [11, 22, 48, 63, 76].

Other variations of pump-probe techniques can involve using the X-ray beam as the pump, for example, to heat materials evenly throughout their volume (isochorically) [72]. In this case, an optical laser probe or the two-pulse capabilities

of X-ray FELs [24, 46] can be used to probe the X-ray-induced dynamics in the sample. A few examples of X-ray pumped dynamics are referenced for the interested reader [17, 28, 40]. Two-pulse applications of X-ray FELs are increasing in use in many fields, including biology, to study the ultrafast processes that lead to radiation damage in the sample.

Measuring time-resolved dynamics with such high temporal resolution is a challenging endeavor due to the nature of the FEL beam. The amplification from noise that gives rise to SASE pulses causes essentially every beam parameter to fluctuate, including the arrival time of the X-rays. Diagnostics to measure this arrival time relative to the pump laser are necessary. Such diagnostics were developed with the advent of X-ray FEL beams. The interaction of the intense X-ray pulse changes the optical properties of a target, which is then probed with a small fraction of the pump laser beam intensity. The ultrafast change in the index of refraction of the target material leads to changes in the optical reflectivity and transmission through this target and can provide arrival time information for the X-rays relative to the laser [8, 25, 34]. These arrival time measurements can be used to sort data into more accurate time bins. The fluctuations in the arrival time, combined with a suitable diagnostic, can be utilized to more rapidly sample time points and sort the data in post-analysis. In this way, a challenging aspect of FEL beams can be turned into a useful advantage by just letting the beam jitter to fill the time bins and sorting that data later.

For soft X-ray and UV FEL beams, it is possible to manipulate the electron bunch with laser beams to generate shorter pulses. A device called XLEAP (X-ray Laser Enhanced Attosecond Pulse Generation) at LCLS will bring attosecond-scale dynamics into the realm of possibilities [45]. At the FERMI FEL, the very accurate synchronization between two pulses from the FEL has allowed the measurement of the beam temporal characteristics on the attosecond timescale [70] and the use of these exquisitely timed pulses to measure attosecond dynamics [56].

In biology, the high temporal-resolution capabilities of X-ray FEL is exploited for the study of light-sensitive proteins and enzymes as will be described in Chap. 11. Dynamics can also be initiated by other nonoptical methods such as rapid mixing but with lower time resolution due to the less precise initiation of dynamics. This will be the topic of Chap. 12.

1.3.2 Using the High Peak Intensity

As described above, X-ray FELs will typically produce X-ray pulses roughly three orders of magnitude shorter than conventional light sources, and these pulses will contain roughly as many X-rays as delivered in 1 s at a synchrotron. This leads to the potential for extremely high intensities when the beam is tightly focused. This can be exploited in a few ways.

1.3.2.1 Diffraction-Before-Destruction

Diffraction-before-destruction is a concept described in 2000 by Neutze *et al.* [52]. With sufficiently high intensities and sufficiently short pulses, it is possible to mitigate and possibly overcome conventional radiation damage limits that exist for longer, continuous measurements. Some of the X-rays incident on the sample probe its structure via scattering as described earlier but the majority of the incident X-rays that interact with the sample deposit their energy in the sample via X-ray absorption. This deposited energy eventually damages the sample, but this process is not instantaneous. If the pulse duration can be kept shorter than the damage dynamics, then it is in principle possible to pack more X-rays in this short time than the damage limit would allow at a synchrotron. Probing a mostly undamaged sample with a higher number of X-rays would yield a higher signal and a potentially undamaged higher-resolution structure. Diffraction-before-destruction is critical to the majority of biological applications at an X-ray FEL due to the radiation-sensitive nature of biological samples. It will be discussed further in Chap. 2 as part of the discussion on X-ray FEL crystallography, as well as Chap. 6 where radiation damage will be discussed in detail.

1.3.2.2 Using FELs to Create New States of Matter

As mentioned before, the X-ray FEL beam can be used as a pump to trigger the start of a dynamic process. Here, the very high intensities afforded by a tightly focused FEL beam provide the capability to isochorically heat a solid material to very high and uniform temperature. The penetrating power of X-rays leads to uniform illumination, even for dense samples, compared to mostly surface heating from optical lasers. This capability is of great interest to the fields of warm and hot dense matter, but also fundamental research in the effects of these extreme X-ray intensities is necessary to understand the limitations of the assumptions of the diffraction-before-destruction idea. For the smallest biological samples, a tightly focused beam is required to maximize the illumination of the sample and maximize the signal and some level of damage or structural change may occur during the pulse. Understanding the dynamics involved in short-lived hot dense states of matter during the pulse duration or shortly thereafter is of fundamental and applied interest. Radiation damage and how it affects biological samples in X-ray FEL measurements will be further discussed in Chap. 6.

1.3.2.3 Nonlinear X-Ray Physics

The high X-ray fields produced by focused X-ray FEL beams can open the door to novel methods such as nonlinear optics or nonlinear spectroscopies. A few examples are the observation of anomalous Compton scattering [20], nonsequential two-photon absorption [21, 64] as well as stimulated emission [57, 75]. The interaction

of multiple X-rays with the same molecule over short times leads to novel nonlinear effects only observable using an X-ray FEL. Nonlinear spectroscopies have the potential to be very sensitive probes of the fine details of electronic states and could reveal important details on enzymatic activities, for example. Spectroscopic applications of X-ray FELs in biology will be discussed in Chap. 13.

1.3.3 Using the Coherence

Laser radiation is highly coherent, and X-ray FELs are no exception. The coherence properties of existing X-ray FELs were measured for both soft and hard X-rays at multiple facilities [23, 29, 39, 41, 50, 58, 71]. An increased level of coherence will improve the signal level and the quality of the data for scattering measurements that rely on this coherence. An example is X-ray Photon Correlation Spectroscopy (XPCS), where the intrinsic dynamics of a sample are probed by tracking the correlation of the intensities in the speckle pattern as a function of time [42, 62]. While such a method shows great promise for understanding the dynamics of untriggered processes, it has limited application in biology due to the need to measure the same sample over time, where radiation damage becomes an issue.

Coherent diffractive imaging (CDI) methods greatly benefit from the increased coherence of an FEL beam compared to a synchrotron and these have been put to use in combination with time resolution for pump-probe studies of phonons in nanoparticles, for example [13]. For biological coherent imaging, the small size of a typical reproducible sample leads to weak signals which requires a highly intense focused beam, which in turn leads to rapid damage and complete destruction of the sample on a single pulse. Therefore, biological imaging applications using an X-ray FEL beam must combine the short pulse and high intensity in a diffraction-before-destruction mode to leverage the increase in coherence of the beam. Chapter 14 will expand further on the status of imaging applications for X-ray FELs in biology.

1.4 Summary

X-ray free electron lasers are the latest X-ray sources that arise from over 120 years of X-ray science and development. They are the result of the last five decades of accelerator-based X-rays source development that have provided extremely valuable tools located at centralized facilities available to broad scientific communities. X-ray FELs push X-ray science into new directions of unprecedented peak intensities in short X-ray bursts that can be exploited for research in atomic, molecular, and optical sciences, material science, ultrafast chemistry, high-energy-density matter, and the study of soft matter and its dynamics. As is the subject of this book, they are also proving their worth in biological studies where they can overcome some of the radiation damage limitations that plague some important samples. X-ray FELs

add ultrafast dynamic capabilities, in combination with high spatial resolution, to the tool set for biologists and structural biologists as they aim to understand the mechanisms of life.

X-ray FELs available today and in the near future span a spectral range from UV to soft and to hard X-rays. Hard X-rays are primarily used for seeing where the atomic nuclei are located, either in a static structure or a dynamic structure using time-resolved methods. They are also used to probe the electronic states of metal centers with absorption edges in the hard X-ray range in important metalloenzymes or proteins.

Softer X-rays are used for imaging methods where the higher scattering cross section can be beneficial for an increased signal level. They are also useful tools for spectroscopic studies of the fine electronic structure of lighter atoms with absorption edges at lower energies.

This book, via its multiple chapters on the status of multiple specific aspects of X-ray FEL experiments in biology, is hoped to provide the reader with a general introduction to the field while still providing sufficient details for those looking to contribute to the field.

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