1

Introduction

How does nature create a living thing from simple chemical components? How is a complete human being constructed nine months after the unique mixing of its parents’ genetic material contained in a single fertilized egg?

When I was a young child, these questions were only just beginning to be answered. Indeed, just five months before my own birth, the Nobel Committee announced that the 1962 Prize in Physiology or Medicine would be awarded to James Watson, Francis Crick, and Maurice Wilkins for their elucidation of the structure of deoxyribonucleic acid (DNA) [1] ‘and its significance for information transfer in living material’.

DNA resides permanently within the nucleus of a living cell. How then is its information conveyed to the rest of the cell and elsewhere in the organism; how is new living material subsequently synthesized; and how do initial (‘stem’) cells in the blastocyst differentiate into specialized cells as diverse as ganglions, muscle cells, or skin? Major steps towards answering these questions were made in research that would result in Nobel Prizes in Chemistry in 2006 and 2009.

The first step in carrying out the commands encoded in DNA is its transcription into so-called messenger-RNA (mRNA), which then leaves the confines of the nucleus to the protein-producing parts of the cell. How mRNA is synthesized and carries the genetic information with high fidelity, via a very special macromolecule called RNA-polymerase, was reported by Roger Kornberg and co-workers in 2001 [2], for which he received the 2006 Nobel Prize in Chemistry.

The following step, protein synthesis, uses the blueprint of the mRNA, plus raw material in the form of amino acids attached to small transfer-RNA (tRNA) molecules in a chemical factory called the ribosome. The detailed description of the mechanisms by which this highly complex biomolecular process occurs won Ada Yonath, Thomas Steitz, and Venkatraman Ramakrishnan the Nobel Prize in Chemistry in 2009 [3, 4].

As should be apparent from its title, this textbook is not a treatise on molecular biology. It is, however, concerned with diverse aspects of a tool now considered indispensable to molecular biologists – synchrotron radiation. The thematic link between the above trilogy of Nobel Prizes is that of structure, and its inherent importance in determining biomolecular activity. Although the structure of DNA was determined to a large extent by a combination of model building, biochemical know-how (including the application of Chargaff’s rules), and some guesswork, it

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1 Wilkins’ contribution to this work was minor, the crucial crystallographic data being recorded by his King’s College colleague, Rosalind Franklin, and her student Raymond Gosling. Controversially, Wilkins showed the now famous ‘photograph 51’ to Watson and Crick without Franklin’s knowledge or permission. Its characteristic cross-motif provided the Cambridge pair with the last key information about the precise helical nature of DNA, from which they swiftly deduced the detailed structure. Sadly, Franklin was to die of ovarian cancer (possibly caused by exposure to x-rays) in 1958, four years before the prize was announced.
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Figure 1.1 The three central biostructures associated with the ‘Nobel trilogy of life’. Left: a DNA dodecamer; centre: the yeast RNA polymerase subunit; right: the 80S ribosome from *Tetrahymena cerevisiae*. Rendered from the pdb files 1bna, 1i3q, and (4v5o + 4v8p), respectively.

was x-ray diffraction data which provided the last key information in solving the puzzle\(^2\). The latter two discoveries of the ‘Nobel life trilogy’ depended intimately on x-ray diffraction (see Figure 1.1 and Table 1.1).

The relevance of these studies goes well beyond pure academic understanding – the detailed description of DNA transcription and the difference in this process between eukaryotic organisms (with intracellular nucleus) and prokaryotic organisms (without intracellular nucleus), as well as a knowledge of the biochemical function of the ribosome, are already having a huge impact on the design of novel antibiotic substances and other drugs, and provide a deeper understanding of how some cancers arise and how they might be tackled.

The year that Yonath, Ramakrishnan, and Steitz were awarded their Nobel Prize also saw first light at the pioneering hard x-ray free-electron laser (XFEL), the Linac Coherent Light Source (LCLS) at the SLAC facility in California. The first report of a new biological structure (to a resolution of 2.1 Å) determined using the LCLS was reported a little over three years later [5] (see Figure 1.2). XFELs provide x-ray beams with unique properties regarding pulse duration, peak pulse intensity, and beam cross-section. Using a technique coined ‘diffraction-before-destruction’, crystals with sizes orders of magnitude smaller in volume than hitherto possible can be investigated. As the growth of sufficiently large and well-ordered crystals has to date been the major bottleneck in biomolecular-structure studies using x-rays from synchrotrons, the application of this technique at XFELs represents a sea change in this field of research.

The above examples beautifully illustrate that, since their discovery in late 1895 by Wilhelm Röntgen, x-rays have played a pivotal rôle in society, particularly in medicine, pharmacy, physics, and chemistry. Whereas research using x-rays was originally the dominion of physicists, x-rays are now a ubiquitous tool for research in almost all branches of scientific endeavour (see Figure 1.3). They allow us, among many other things, to determine the internal architecture of cells and other biological structures; to identify the chemical composition, fabrication techniques, and provenance of archaeological artefacts; and even to examine the previously hidden earlier artistic efforts of one of the foremost influential post-impressionist painters.

\(^2\) In the same year that Watson, Crick, and Wilkins won their Nobel Prize, two of their colleagues at the Cavendish Laboratory, John Kendrew and Max Perutz, won the Nobel Prize in Chemistry for their structural studies of myoglobin and haemoglobin, respectively, also using x-ray diffraction, thereby demonstrating this technique could be used to determine structures of hitherto unimagined complexity.
Table 1.1 Nobel Prizes awarded in the field of x-ray research.

<table>
<thead>
<tr>
<th>Year</th>
<th>Recipient(s)</th>
<th>Research discipline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1901</td>
<td>W. C. Röntgen</td>
<td>Physics; discovery of x-rays</td>
</tr>
<tr>
<td>1914</td>
<td>M. von Laue</td>
<td>Physics; x-ray diffraction from crystals</td>
</tr>
<tr>
<td>1915</td>
<td>W. H. Bragg and W. L. Bragg</td>
<td>Physics; crystal structure derived from x-ray diffraction</td>
</tr>
<tr>
<td>1917</td>
<td>C. G. Barkla</td>
<td>Physics; characteristic radiation of elements</td>
</tr>
<tr>
<td>1924</td>
<td>K. M. G. Siegbahn</td>
<td>Physics; x-ray spectroscopy</td>
</tr>
<tr>
<td>1927</td>
<td>A. H. Compton</td>
<td>Physics; scattering of x-rays by electrons</td>
</tr>
<tr>
<td>1936</td>
<td>P. Debye</td>
<td>Chemistry; diffraction of x-rays and electrons in gases</td>
</tr>
<tr>
<td>1946</td>
<td>H. J. Muller</td>
<td>Medicine; discovery of x-ray-induced mutations</td>
</tr>
<tr>
<td>1962</td>
<td>M. Perutz and J. Kendrew</td>
<td>Chemistry; structures of myoglobin and haemoglobin</td>
</tr>
<tr>
<td>1962</td>
<td>J. Watson, M. Wilkins, and F. Crick</td>
<td>Medicine; structure of DNA</td>
</tr>
<tr>
<td>1964</td>
<td>D. Crowfoot-Hodgkin</td>
<td>Chemistry; structure of penicillin</td>
</tr>
<tr>
<td>1976</td>
<td>W. N. Lipscomb</td>
<td>Chemistry; x-ray studies on the structure of boranes</td>
</tr>
<tr>
<td>1979</td>
<td>A. McLeod Cormack and G. Newbold Hounsfield</td>
<td>Medicine; computed axial tomography</td>
</tr>
<tr>
<td>1981</td>
<td>K. M. Siegbahn</td>
<td>Chemistry; high-resolution electron spectroscopy</td>
</tr>
<tr>
<td>1985</td>
<td>H. Hauptman and J. Karle</td>
<td>Chemistry; direct methods to determine x-ray structures</td>
</tr>
<tr>
<td>1988</td>
<td>J. Deisenhofer, R. Huber, and H. Michel</td>
<td>Chemistry; determining the structure of proteins crucial to photosynthesis</td>
</tr>
<tr>
<td>1997</td>
<td>P. D. Boyer and J. E. Walker</td>
<td>Chemistry; mechanism of adenosine triphosphate synthesis$^1$</td>
</tr>
<tr>
<td>2003</td>
<td>R. MacKinnon and P. Agre</td>
<td>Chemistry; structure and operation of ion channels$^1$</td>
</tr>
<tr>
<td>2006</td>
<td>R. D. Kornberg</td>
<td>Chemistry; atomic description of DNA transcription$^1$</td>
</tr>
<tr>
<td>2009</td>
<td>V. Ramakrishnan, T. A. Steitz, and A. E. Yonath</td>
<td>Chemistry; structure and function of the ribosome$^1$</td>
</tr>
<tr>
<td>2012</td>
<td>R. J. Lefkowitz and B. K. Kobilka</td>
<td>Chemistry; studies of G-protein-coupled receptors$^1$</td>
</tr>
<tr>
<td>2018</td>
<td>F. H. Arnold</td>
<td>Chemistry; the directed evolution of enzymes$^1$</td>
</tr>
</tbody>
</table>

$^1$Work using synchrotron radiation as a primary tool.

This broad range of applications of x-rays has manifested itself since the turn of this century in the diversity of disciplines served and in the broad palette of techniques now available at synchrotron facilities, which represents one of the principal examples of multidisciplinary research [6]. Today, there are more than seventy facilities in operation, or under construction, worldwide, providing services for well over one hundred thousand users from virtually every discipline of the natural sciences. Each year, several thousand articles are published which explicitly mention synchrotrons (see Figure 1.4). Since 1945, in total almost 90 000 papers relating to synchrotrons and synchrotron radiation have been published and have been cited almost 1 200 000 times.

Why are x-rays (and ultraviolet radiation, which bridges the gap between visible light and x-rays) especially important for investigating the properties of materials? There are several reasons. Firstly, x-rays are able to probe deeply and nondestructively into solid materials, with the degree of penetration depending on their energy and on the electron density (and hence the atomic masses and spatial distribution) of the constituent elements of the sample under investigation. Conversely, if the x-ray beam is made to impinge at very shallow angles to the sample...
Figure 1.2  Left: the cathepsin B structure determined using XFEL radiation. This is a potential target in the quest to develop new drugs against sleeping sickness, a disease caused by the parasite *Trypanosoma brucei*, which uses cathepsin to break down proteins within the host cell. Rendered from the pdb file 3mor. Right: a typical nanocrystal used in the XFEL ‘diffraction-before-deSTRUCTION’ experiment grown *in vivo* in insect cells. The scale bar is 1 μm. Reprinted from [5] with permission from the American Association for the Advancement of Science.

surface, the beam will be totally reflected and only a so-called evanescent wave will penetrate the surface to a depth of a few nanometres. In this manner, x-rays can also be used as a highly surface-sensitive probe.

Secondly, x-ray photons with energies of several kiloelectronvolts (keV) have wavelengths comparable to those of typical atomic spacings in solid materials, measured in angstroms (1 Å = 10^{-10} m). Under certain conditions, crystalline arrays of atoms can therefore act as interference gratings (that is, ordered arrays of scattering centres) for x-ray light, which can therefore be diffracted. On the other hand, electronic transitions involving valence electrons have energies that are in the range of ultraviolet (UV) and soft-x-ray photons, which are hence useful as probes in the investigation of the chemical nature and electronic properties of materials.
Figure 1.4  Publications which explicitly mention ‘synchrotron’ or ‘synchrotron radiation’ (blue data), and ‘XFEL’, ‘x-ray free-electron laser’, or ‘X-FEL’ (yellow data, all entries case insensitive) in the field ‘topic’ in the Web of Science database, since the first paper by McMillan in 1945 [7]. Papers relating to astronomy, particle fields, and nuclear physics were excluded. Note also that many publications that contain data recorded at synchrotrons and/or XFELs do not include these keywords and that the actual total number of reports relying at least partly on them is substantially higher.

Synchrotron storage rings are very powerful sources of x-rays. Synchrotron facilities are nowadays designed to generate tuneable beams of electromagnetic radiation from the far infrared to the hard x-ray regime. In terms of their ‘brilliance’, the standard figure of merit for synchrotrons precisely defined in Chapter 3, modern synchrotrons are to laboratory-based x-ray sources what modern computers are to the original Colossus valve-based computer used to crack the Enigma code in 1943! Indeed, in the last six decades, there has been an increase in the brilliance available to researchers by a factor of almost $10^{23}$ (see Figure 1.5), whereby the most recent advance by nine to ten orders of magnitude of peak brilliance has been obtained through the emergence of XFELs in the first decade of the twenty-first century (see Chapter 4).

Synchrotrons consist of an evacuated storage ring in which high-energy electrons circulate at highly relativistic velocities, and so-called ‘beamlines’. These latter utilize the synchrotron light emitted by the electrons tangential to their orbital path, at positions defined by components known as bending magnets and insertion devices (see Figure 1.6).

This text will cover the use of synchrotron radiation for the determination of materials’ structures and properties in physics, chemistry, biology, and related disciplines such as archaeology and environmental science. In general, a biologist has a very different training in science compared to that of a physicist. I have therefore tried to pitch the contents of this text in such a manner that it should be accessible to all newcomers to synchrotron radiation. Certain chapters and sections will undoubtedly leave some readers cold – for example, it is unlikely that an archaeologist will see much relevance to his or her research in the arcane joys of surface x-ray diffraction. Accordingly, the tone of the different subjects and the depth to which they are explained has been adapted as much as possible to the demands and scientific profiles of the probable users.

After the Introduction, fundamentals of the interactions of high-energy x-rays with matter are discussed in Chapter 2. Next, the basic physics and the most important technical aspects of synchrotron and XFEL facilities are covered in Chapters 3 and 4, respectively, while details of the optics and instrumentation found at beamlines
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3rd-generation undulators

Bending magnets and wigglers

FELs

DLSRs

Undulators

Bending magnets and wigglers

Sealed tube

Rotating anode

Figure 1.5 The brilliance of x-ray sources. (a) A historical perspective, showing the enormous increase in brilliance, beginning in the second half of the twentieth century. The gradient of the curve (plotted on a logarithmic ordinate axis) since the 1960s equates to, on average, a doubling of brilliance every fourteen months. This fairly comprehensively outstrips the red line showing the approximate doubling every 24 months in computing power, according to the much-vaunted Moore’s law. (b) Typical spectral-brilliance curves of devices commonly used in fourth-generation (DLSR) synchrotrons. The positions of the K-absorption edges of carbon, oxygen, copper, and selenium are also shown. Conversion to peak brilliance requires a multiplication of the average brilliance shown here by $\Delta T/\Delta \tau$, the ratio of the pulse separation to the pulse width, and is of the order of 100.

are summarized in Chapter 5. Although many users do not need to understand exactly how the x-rays they are using are generated and manipulated, it is hoped that the information provided in Chapters 3 to 5 will help guide them as to what any particular facility or beamline can realistically provide for potential experiments.

The second part of the book covers synchrotron techniques and applications. The methods described in Chapters 6 to 8 are, as far as possible, accompanied by representative and illustrative examples. The reader is also encouraged to refer to the original sources of these selected examples to obtain still deeper insights and become aware of subtleties peculiar to individual experiments – beamtime is expensive, and a user with an understanding of potential pitfalls and experimental obstacles is a valuable member of any team.

1.1 A Potted History of X-rays

Electromagnetic radiation, across the spectral range from radio waves to gamma rays, has historically been the most ubiquitous probe in the natural sciences for the investigation and understanding of matter. It continues to be so to this day. Before a century or so ago, however, mankind only had the very narrow band of visible light from
Electron storage ring

Detector

Sample

Focussing optics

Monochromator

Bending magnet or insertion device

Figure 1.6 Schematic of a modern synchrotron. Electrons moving at highly relativistic velocities in an evacuated storage ring emit electromagnetic (synchrotron) radiation as their direction is changed by bending magnets, used to steer them along a closed path, or by so-called ‘insertion devices’ placed in straight sections of the storage ring, which ‘shake’ the electrons to and fro but maintain an average straight trajectory. At the beamlines tangential to the storage ring (of which there are typically 10 to 50, depending on the size of the facility; only one is shown here) the radiation is normally (but not always) monochromatized and focused using x-ray optics onto a sample.

On the evening of the 8 November 1895, Röntgen first detected x-rays. In his darkened room, he found that, when running a high-voltage discharge tube enclosed in thick black cardboard, which excluded all visible light, a paper plate covered on one side with barium platinocyanide would nevertheless fluoresce, even when it was as far as two metres from the discharge tube. Röntgen concluded that the discharge must be emitting a new form of invisible radiation\(^3\) that could escape the confines of the glass discharge tube and the surrounding covering – their unknown nature led him to name them x-rays [8].

Röntgen immediately discovered that these x-rays were also able to stain photographic plates. Using this phenomenon, he demonstrated in subsequent experiments that objects of different thicknesses and density placed in the path of these rays showed differing degrees of transparency. When Röntgen placed the hand of his colleague at Würzburg, the Swiss anatomist Albert von Kölliker, in the path of the rays over a photographic plate, he observed after development of the plate an image showing the shadows thrown by the finger bones and a

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\(^3\) Scientific insight and fame is sometimes a fickle mistress – in the decade immediately preceding Röntgen’s almost immediate and correct interpretation of the cause of the fluorescing plate, the British scientist Sir William Crookes sought unsuccessfully to explain the repeated fogging of photographic plates stored near his cathode-ray tubes.
Figure 1.7  Left: this postage stamp, depicting Wilhelm C. Röntgen, was first issued in April 1939. The message translates as ‘Fight cancer. Cancer is curable.’ – the use of x-rays in oncology was already established soon after their discovery. Reprinted from http://commons.wikimedia.org/wiki/File:DanzigWilhelmKonrad%C3%88ntgen25Pf1939.jpg. Right: one of the first radiographic images, recorded by Röntgen. Reprinted from Lino Piotto, Toger Gent, and Giovanni Bibbo, Myth busting – in the world of x-rays, The Radiographer, 54, Copyright 2007, with permission of Lino Piotto.

ring, surrounded by the penumbra of the flesh, which absorbed fewer of the rays and therefore threw a fainter shadow\(^4\) [Figure 1.7(right)]. In further experiments, Röntgen showed that the x-rays were produced by the impact of high-energy electrons on a material object. For his discovery of x-rays, Röntgen would receive the first ever Nobel Prize in Physics in 1901.

In 1909, characteristic x-radiation was discovered by the British physicists Barkla and Sadler [9] (see Figure 1.8) – Barkla would also receive the Nobel Prize in 1917. The term ‘characteristic’ refers to the narrow, intense x-ray emission lines, or x-ray fluorescence, found when a material is bombarded with energetic particles such as electrons or, indeed, x-rays. Each element has a unique set of lines, which, like a fingerprint, characterizes that element alone, and is a manifestation of the discrete energy levels of electronic states in atoms and their dependence on atomic number.

It was Henry G. J. Moseley, however, who would provide the correct interpretation of characteristic radiation, using an x-ray spectrometer of the type invented by the Braggs, and encapsulated in Moseley’s law [10] (see Figure 1.9). A brilliant and hugely promising young scientist, tragically, Moseley would die at Gallipoli in the First World War the following year\(^5\).

In 1912, the year he became Professor of Physics at Zürich University, Max von Laue conjectured that periodic, crystalline, structures might diffract waves if their wavelength were of the same order of magnitude as the crystalline periodicity and that x-rays might just fit the bill. He discussed these ideas with his colleagues Arnold

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\(^4\) There seems to be some dispute as to whether the first x-ray photograph was of von Kölliker’s or Röntgen’s wife’s hand. The image shown in Figure 1.7 was recorded at a demonstration at the Physical Institute on 23 January 1896 and is Kölliker’s hand. Another very similar image is undated and was only later attributed to Röntgen’s wife.

\(^5\) Isaac Asimov would later write ‘In view of what he might still have accomplished (he was only 27 when he died), his death might well have been the most costly single death of a war to mankind generally’. Ironically, this observation is further compounded by the fact that the disastrous Gallipoli Campaign (at least from the perspective of the British) was instigated by arguably one of the other most important characters to influence twentieth century history, Winston Churchill.
Sommerfeld and Wilhelm Wien during a skiing expedition. Despite Sommerfeld’s objection that the supposed amplitude of thermal motion of the atoms within the crystal would be so large (relative to the wavelength of x-rays to be used) that the diffraction pattern would be completely washed out, Laue was able to convince Walter Friedrich, one of Sommerfeld’s assistants, and Paul Knipping, a diploma student of Röntgen’s, to record the first
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Figure 1.10 Max von Laue and the first x-ray diffraction pattern of copper sulfate.

Figure 1.11 W. H. Bragg, his son W. L. Bragg, and the diffraction of x-rays by crystals.

diffraction pattern of a crystal of copper sulfate (Figure 1.10). Von Laue was awarded the Nobel Prize in Physics in 1914 for this discovery.

This was indeed a hectic and exceedingly productive period. In 1913, the year between the recording of the first diffraction pattern and von Laue receiving his Nobel Prize, the father-and-son team of Sir William Henry Bragg and William Lawrence Bragg were working on the theory and experimental techniques required to obtain detailed atomic structural information about crystals from their diffraction spot intensities and positions (Figure 1.11). The importance of their work is reflected by the fact that they would be awarded the Nobel Prize in Physics only two years later in 1915 ‘for their services in the analysis of crystal structure by means of x-rays’. Among other

6 This very first diffraction pattern was of a raw, triclinic, copper sulfate pentahydrate crystal (the ubiquitous bright-blue crystal found in school chemistry laboratories) and should not be confused with the much cleaner, and thus more famous, pattern recorded shortly thereafter of a 0.5 mm thick (001)-platelet of cubic zinc sulfide.
things, they formulated the famous Bragg law, which describes the mechanism by which x-ray diffraction occurs. Crucially, the son, W. L. Bragg, also explained why diffracted spots had the intensities they did, and was able, using these principles, to determine the internal atomic structure of some simple minerals [11, 12]. The foundations of x-ray crystallography had been laid down [13].

This culminated some forty years later in one of the most important scientific discoveries of the twentieth century, namely the determination in 1953 of the structure of deoxyribonucleic acid (DNA) and the mechanism by which it replicates [1], for which James Watson, Francis Crick, and Maurice Wilkins would be awarded the Nobel Prize in Medicine in 1962. Their discovery, which revolutionized biology and provided an atomistic view of the stuff of life, was in no small measure assisted by x-ray diffractograms recorded by Rosalind Franklin at University College, London [14]. The detailed information which was gleaned by these patterns (in particular the central ‘X’ motif, so characteristic of diffraction from double-helical structures) was only made possible by the high quality of both the crystals of salts of DNA prepared by Franklin, and of the diffractometer that was available (see Figure 1.12).

Although the diffraction patterns recorded by Franklin provided one of the last and most important clues for Watson and Crick in their model-building approach to the structural solution of DNA, the molecular details were primarily deduced using chemical and geometrical arguments. In the same year that Watson, Crick, and Wilkins were awarded the Nobel Prize in Medicine, the Prize in Chemistry was won by their Cavendish Laboratory colleagues, John Kendrew⁷ and Max Perutz, for their determination by x-ray diffraction of the atomic structures of myoglobin (Kendrew [16]) and haemoglobin (Perutz [17]) (Figure 1.13). It was Perutz’s invention of the technique of multiple isomorphous replacement in x-ray crystallography that provided the breakthrough in what had until then seemed the insurmountable problem of solving the structure of a crystal containing a molecule of a mass of approximately 17 000 Da⁸.

⁷ In his Nobel lecture, Kendrew speculated that, although ‘this day will not come soon’, a protein’s structure could be predicted based solely on its amino acid sequence, and that ‘x-ray crystallographers can go out of business, perhaps with a certain sense of relief’ [15]. Over sixty years later, we still await this momentous day …
⁸ The Dalton, Da, is a unit of atomic mass equal to a twelfth of the mass of a neutral, unbound atom of carbon. The mass of any element expressed in Da is thus simply equal to their atomic mass.
Two years later, the widely recognized doyenne of macromolecular crystallography, Dorothy Crowfoot-Hodgkin, would receive the Nobel Prize in Chemistry for her seminal work on crystals of complex molecules, in particular for her determination of the structure of penicillin [18] (see Figure 1.14). Of all the facets of crystallography, protein and macromolecular structure determination have surely had the most impact on society. Hodgkin was the first person to record diffraction patterns of crystals of large molecules, beginning with the digestive enzyme pepsin (molecular weight of approximately 35 kDa) in 1934 [19]. In addition, she went on to develop indexing and diffraction-intensity analysis; she was a pioneer in computer-assisted Fourier analysis; and she solved the structures of cholesterol, ferritin, lactoglobulin, the tobacco mosaic virus, penicillin (for which she would receive the Nobel Prize in Chemistry), vitamin B-12, and insulin [20–22]. This last compound defied structural analysis for over 34 years before Hodgkin cracked the problem in 19699.

Most recently, the Nobel Prizes in Chemistry in 2003, 2006, 2009, 2012, and 2018 have all been awarded to biochemistry studies exploiting x-ray crystallography10 – McKinnon and Agre (2003) described the three-dimensional structure of potassium ion channels across cell membranes [24]; Kornberg was awarded the Nobel Prize in 2006 for his studies of the process by which genetic information from DNA is copied to RNA (this process is common to all life forms containing cell nuclei, that is, all life except the prokaryotae) [2]; Ramakrishnan, Steitz, and Yonath (2009) were able to solve the structure of ribosomes and thereby identify their core function in translating DNA code into living matter [25]; while Lefkowitz and Kobilka (2012) determined the structure and mechanistic pathways of so-called G-protein-coupled receptors (GPCRs), chemicals that allow cells to sense their environments and are responsible, among other things, for our bodies being able to sense light, flavour, odour, and many other stimuli [26–28]. Approximately two thirds of all medications operate through GPCRs. Frances Arnold (2018) used synchrotron radiation in her studies of directed evolution of enzymes [29].

It can be argued, judging by the disproportionate number of Nobel Laureates in the field (see Table 1.1), that x-ray science was one of the most influential areas of pure research in the twentieth century, while its impact has touched many other disciplines. It is interesting to note from Table 1.1 that physics garnered the majority of the early Nobel Prizes concerned with x-rays, from which most of the underlying phenomena were explained,

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9 The amino acid sequence of insulin was determined by Frederick Sanger in 1955, but not the detailed arrangement of the atoms in space.
10 Incidentally, such tours de force of structural biology only became possible with other technological advances, not least in x-ray detectors. The 2009 Nobel Prize in Physics was partly awarded to Willard S. Boyle and George E. Smith for their pioneering work on charged-couple device (CCD) imaging technology [23]. CCDs are nowadays ubiquitous as x-ray detectors. The even more-modern photon-counting hybrid pixel detectors, with their generally superior performance (if not at XFELs, for reasons that will become apparent in Section 5.7.9) are nowadays often the first instrument of choice.
while their application in other scientific disciplines would reap Nobel awards in subsequent years. The use of synchrotron radiation has followed a similar path, and indeed the six most recent Nobel Prizes associated with x-rays used synchrotron radiation as a primary tool.

The importance of x-ray science in physics, chemistry, biology, and medicine can thus hardly be overstated. It seems certain that x-rays will continue to play a hugely important rôle in modern science and technology in the twenty-first century, as ever more materials, compounds, and structures in all their varied guises are discovered or, indeed, designed.

1.2 Synchrotron Sources over the Last Seventy Years

The term ‘synchrotron’ was coined by Ed McMillan in his seminal 1945 paper [7]. The concept of the synchrotron, however, was also arrived at independently one year earlier, by Vladimir Veksler. The two men began corresponding and developing the idea of a synchrotron and would, in 1963, share the ‘Atoms for Peace’ Award in recognition of this.

Short-wavelength synchrotron radiation generated by relativistic electrons in man-made circular accelerators dates back to shortly after the Second World War. However, the theoretical basis for synchrotron radiation traces back to the time of Thomson’s discovery of the electron in 1897. In the same year, Joseph Larmor derived an expression from classical electrodynamics for the instantaneous total power radiated by an accelerated charged particle (covered in the next chapter), and the following year, the French physicist Alfred Liénard showed the radiated power emitted by electrons moving on a circular path to be proportional to \( (\frac{E}{m_e c^2})^4 / R^2 \), where \( E \) is the electrons’ kinetic energy, \( m_e \) is the electron rest mass, and \( R \) is the radius of the trajectory.

The first observation of synchrotron radiation came on 24 April 1947 at the General Electric Research Laboratory in Schenectady, New York (see Figure 1.15), although it was not being sought and was not immediately recognized for what it was. Here is an excerpt from Herb C. Pollock’s description of this historical event over two decades later in a letter to Dmitri Ivanenko, dated 25 September 1970:
On April 24, Langmuir and I were running the machine and as usual were trying to push the electron gun and its associated pulse transformer to the limit. Some intermittent sparking had occurred and we asked the technician to observe with a mirror around the protective concrete wall. He immediately signaled to turn off the synchrotron as ‘he saw an arc in the tube.’ The vacuum was still excellent, so Langmuir and I came to the end of the wall and observed. At first we thought it might be due to Cerenkov radiation, but it soon became clearer that we were seeing Ivanenko and Pomeranchuk radiation.

A more formal description of their findings can be found in [30]. ‘Ivanenko and Pomeranchuk radiation’ alludes to the two Russian physicists who, in 1944, published their calculations predicting the rate of energy loss due to radiating electrons [31].

Initially, synchrotron radiation was seen as an unwanted but unavoidable loss of energy of charged particles in closed-ring accelerators designed (ironically) to produce intense beams of x-rays by directing accelerated electrons onto a suitable target. Note that this loss is small compared to the particles’ kinetic energy, and this remains true today – even the highest photon energies produced by modern synchrotrons are three to four orders of magnitude smaller than the electrons’ relativistic kinetic energy (see Figure 1.16).

The potential advantages of synchrotron radiation for its own end were detailed by Diran Tomboulian and Paul Hartman from Cornell University in their seminal paper ‘Spectral and Angular Distribution of Ultraviolet Radiation from the 300 MeV Cornell Synchrotron’ in the *Physical Review* [32], describing their findings after being granted two weeks access to investigate the possible applications of synchrotron light. The experimental setup and photographic-plate results reported in this paper, showing the broadband synchrotron radiation emitted by monoenergetic electrons, are reproduced in Figure 1.17.
Figure 1.16  Plot of some representative synchrotron-facility photon-energy ranges as a function of the storage-ring (that is, electron) energy. Note the logarithmic ordinate axis. The yellow bars for the ALS and SLS indicate extensions of the accessible photon energies to higher values through the use of so-called ‘superbends’, described in Section 3.8.1.

Five years later, in 1961, a pilot experimental program exploiting synchrotron radiation began when the National Bureau of Standards modified its 180 MeV electron synchrotron in Washington, D. C., to allow access to the radiation via a tangent section into the machine’s vacuum system. Thus was born the Synchrotron Ultraviolet Radiation Facility (SURF I), the first to cater for regular users of synchrotron radiation.

The first generation of synchrotrons was sometimes referred to as parasitic facilities (reflecting, perhaps, the perception of the primary users of these facilities towards these interlopers), as the synchrotrons were primarily
designed for high-energy or nuclear-physics experiments. In addition to SURF I, facilities in Frascati and in Japan soon after began to attract a regular stream of physicists keen to explore the possibilities of synchrotron radiation. More would soon follow suit. Because most of these early facilities had storage-ring energies around or below 1 GeV, experiments were concentrated in the ultraviolet and soft x-ray regimes. 1964 saw the first users of synchrotron radiation from the 6 GeV Deutsches Elektronen-Synchrotron (DESY) in Hamburg – suddenly the range of synchrotron radiation was extended to the hard x-ray region down to 0.1 Å (about 125 keV). Many further facilities began to accommodate synchrotron-radiation users. One of the first of these was the 240 MeV machine ‘Tantalus’ in Wisconsin. Although not originally designed to provide synchrotron radiation, it became the first facility to be exclusively used for synchrotron experiments, providing radiation in the ultraviolet up to a few tens of eV.

After the development of efficient electron-storage rings for long-term operation, the time was ripe to develop the first dedicated greenfield facilities designed specifically for synchrotron radiation. The 2 GeV Synchrotron Radiation Source (SRS) at Daresbury, England, was the first of these so-called ‘second-generation’ synchrotron sources. Experiments began in 1981. Several more new facilities were soon built and commissioned, while some first-generation sources were upgraded to second-generation status.

At approximately the same time, it was becoming clear that increased x-ray beam brilliance could be achieved by optimizing the property of the electron beam in the storage ring called the ‘emittance’, described in detail in Chapter 3, through careful design of the array of magnets (the ‘magnet lattice’) used to manipulate the electrons, and by employing so-called ‘insertion devices’. These include ‘wigglers’ and ‘undulators’, placed in straight sections in between the curved arcs of large storage rings. They operate by perturbing the path of the electrons in an oscillatory manner, so that, although their average direction remains unchanged, synchrotron radiation is produced. Details of undulators and wigglers are also covered in Chapter 3.

The inclusion of insertion devices in storage rings defined the third generation of synchrotron sources, which were, at the time, designed for optimal brilliance, that is, the amount of power per unit frequency, surface area, and solid angle. The first third-generation facility to be completed was the European Synchrotron Radiation Facility (ESRF, 6 GeV storage ring) in Grenoble, France, which began user experiments in 1994.

At the time of writing, a fourth generation of storage-ring technology is coming of age, in which the electron beams are significantly narrower and more parallel in the orbital plane than was attainable in third-generation facilities. The first of these so-called diffraction-limited storage rings (DLSRs), MAX IV in Lund, Sweden, was officially inaugurated on the Summer solstice of 2016. Many third-generation facilities are undergoing or planning upgrades to DLSR status, which is therefore fast becoming the new standard.

The projected specifications for these storage rings will redefine the benchmark for synchrotrons – it is planned to provide spatial and energy resolutions of the order of 5 nm and 0.1 meV, respectively, while the brilliance and horizontal emittance, at $10^{22}$ to $10^{23}$ photons/mm$^2$/mrad$^2$/0.1% bandwidth and approximately 100 pm-rad, respectively, improve on previous performances by one to two orders of magnitude. These significant improvements have been made possible by recent advances in the design and manufacture of storage-ring magnets, and by the fact that, although the preferred storage-ring energies are in general maintained at fairly moderate values (typically 3 GeV), their circumferences are more typical of those previously used in high-energy storage rings. This is discussed in more detail in Section 3.8.5.

Parallel to these developments in synchrotron technology, x-ray free-electron lasers operating in the angstrom regime have emerged in the last decade. The first of these to come online was the LCLS in 2009. It uses one third of the two-mile-long Stanford Linear Accelerator (SLAC), and has pioneered modern femtosecond x-ray science.

The SPring-8 Angstrom Compact Free Electron Laser (SACLA), located at the SPring-8 complex in the Hyōgo Prefecture, Japan, began operation in 2011, offering XFEL radiation up to approximately 20 keV. The European XFEL in Hamburg, Germany, came online in 2017, while the Pohang Accelerator Laboratory XFEL (PAL-XFEL) in South Korea also began pilot experiments in 2017 [33]. The soft x-ray FEL at FLASH (Hamburg) has served external users since 2005; an upgrade, known as FLASH2020, will feature a new flexible undulator scheme, providing coherent radiation for multicolour experiments over a broad energy range [34]. FERMI@Elettra (Trieste,
Italy) provides radiation between approximately 10 and 60 eV at its first source FEL-1, and extends up to 300 eV using its second source, FEL-2. The SwissFEL at the Paul Scherrer Institute saw first lasing at 24 nm (52 eV) in December 2016; 1 Å hard x-rays were produced in late 2018.

Another third of the SLAC LINAC is now being developed to house LCLS-II, the latest example of x-ray light sources. The major upgrade in design is the use of superconducting niobium (also used at the European XFEL), instead of the copper cavities used for the original LCLS, for the accelerating cavities. This will increase the delivery rate of the femtosecond pulses from 120 Hz to 1 MHz, while the accessible photon energy range will be effectively tripled to 25 keV.

Synchrotrons and XFELs are largely complementary, rather than being competing technologies. On the contrary, it appears that both XFELs and cryo-electron-microscopy (see Appendix A) are driving an increasing demand for synchrotron beamtime, not least in the life sciences. As more DLSRs come online, this trend looks to continue unabated – the future of x-ray science looks bright indeed!

References

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