Review

Cite this article: Clegg W. 2019 The development and exploitation of synchrotron single-crystal diffraction for chemistry and materials. *Phil. Trans. R. Soc. A* **377**: 20180239. <http://dx.doi.org/10.1098/rsta.2018.0239>

Accepted: 19 February 2019

One contribution of 14 to a theme issue 'Fifty years of synchrotron science: achievements and opportunities'.

Subject Areas:

crystallography, materials science, inorganic chemistry, organic chemistry, organometallic chemistry, supramolecular chemistry

Keywords:

synchrotron radiation, single-crystal diffraction, remote access, beamline, chemical crystallography

Author for correspondence:

William Clegg

e-mail: bill.clegg@ncl.ac.uk

The development and exploitation of synchrotron single-crystal diffraction for chemistry and materials

William Clegg

Chemistry, School of Natural and Environmental Sciences,
Newcastle University, Newcastle upon Tyne NE1 7RU, UK

WC, 0000-0003-1643-5298

A historical account is given of the 25-year development of dedicated synchrotron beamlines for single-crystal diffraction as applied to the so-called small-molecule fields of chemistry and materials science. Designs have drawn on previous successful models in macromolecular crystallography, with appropriate modifications in view of the different properties and behaviour of the respective sample types. Key factors in making these facilities attractive and productive for users include familiarity of operational procedures and the availability of experimental techniques and features normally found in local chemical crystallography laboratories, especially for the handling of samples and processing of diffraction data. Beamlines dedicated to single-crystal diffraction rather than shared with other techniques can be optimized for effective and efficient use. The experience gained from the original design, development and exploitation of stations 9.8 and 16.2SMX at the Daresbury Laboratory Synchrotron Radiation Source and beamline 11.3.1 at the Advanced Light Source have led to highly productive current facilities at ALS beamline 12.2.1 and Diamond Light Source beamline I19, including the recent introduction of remote-access operation. Such facilities have generated and continue to provide major impact in academic and commercial research that could otherwise not be achieved, including patents and applications in pharmaceuticals, energy and gas storage systems, and government policy.

This article is part of the theme issue 'Fifty years of synchrotron science: achievements and opportunities'.

1. Introduction

The recent conference UKSR50, held in Liverpool in June 2018, celebrated 50 years of synchrotron radiation in the UK and its global impact (<http://www.uksr50.org/>, accessed on 11 January 2019). Early exploratory work led to the NINA Synchrotron Radiation Facility at Daresbury Laboratory in Cheshire in 1970, and subsequently to the establishment of the world's first dedicated multi-GeV storage ring, the Synchrotron Radiation Source (SRS) on the same site. The SRS was operated from 1980 to 2008 and saw numerous developments and enhancements to its performance and capabilities during that period. Many other so-called second-generation synchrotron sources (storage rings dedicated to the production and exploitation of synchrotron radiation) followed around the world, before the main focus shifted to third-generation sources in which the radiation is derived principally from insertion devices rather than bending magnets (figure 1).

The advantages of synchrotron radiation for various forms of spectroscopy were clear from the outset, and powder X-ray diffraction facilities were also developed as extensions of conventional in-house laboratory techniques. For single-crystal diffraction, studies of muscle structure and function in the 1970s benefited from the higher intensity available from synchrotron sources and, before long, led rapidly to major applications in protein crystallography [1], commonly referred to now by the more general term of macromolecular crystallography (MX).

In contrast to life science applications, synchrotron provision for single-crystal diffraction in the physical sciences developed much more slowly. Until about 25 years ago such facilities were either shared with other techniques (MX, powder diffraction, small-angle scattering or forms of spectroscopy) on a single multi-purpose beamline, or developed and used mainly by a specific group of users rather than being generally available. Indeed, it is still the case that most synchrotron beamlines offering 'small-molecule' single-crystal diffraction capabilities do so in a shared part-time mode of operation, and dedicated beamlines remain scarce.

The most obvious and best-known advantage of synchrotron radiation over a conventional laboratory X-ray tube, or even over the most advanced widely used current in-house X-ray sources, is the markedly higher intensity, whether this is measured by raw flux, brightness or brilliance, criteria used for comparison of X-ray sources [2]. Comparisons of different X-ray sources are not straightforward, as different characteristics are quoted and the most appropriate intensity-related property is dependent on the particular application, technique and samples. Recent major improvements in 'home laboratory' X-ray sources beyond fixed and rotating anodes have included the development of a range of microfocus targets coupled with a variety of X-ray optics arrangements, and of liquid-anode sources, claimed to be currently the world's brightest (<https://www.excillum.com/products/metaljet-sources/metaljet-d2-70-kv/>, accessed on 11 January 2019). Nevertheless, improvements are also being made in the design and operation of synchrotron sources, so that they generally maintain an advantage of several orders of magnitude over home sources; for example, the maximum 'peak brightness' of current liquid-anode sources is quoted as between 10^{10} and 10^{11} photons/(s mm² mrad²), while current European Synchrotron Radiation Facility (ESRF) beamlines deliver typically around 10^{20} photons/(s mm² mrad² 0.1%bw) with plans to increase this by a factor of 100 in the ESRF-EBS upgrade design [3]. The opportunity to select from a wide range of wavelengths can also be important for the avoidance/reduction or deliberate exploitation of particular physical effects such as absorption and resonant scattering, the latter being valuable for absolute configuration studies of chiral substances. More specialized experiments make use of the pulsed nature of a synchrotron beam in time-resolved studies of excited states (photocrystallography) or exploit the greater penetration of short-wavelength (high-energy) X-rays through sample environment containers such as high-pressure diamond anvil cells or reaction gas cells. Some examples are given later.

2. Station 9.8 at the Synchrotron Radiation Source

The SRS at Daresbury Laboratory was a 2 GeV second-generation storage ring, in which all the original beamlines were based on bending magnets; many of the beamlines divided the generated

Figure 1. A schematic diagram of a third-generation synchrotron storage ring, showing the location of bending magnets at the polygon vertices and insertion devices in the straight sections.

fan of synchrotron radiation into fractions fed to different user experimental end-stations. A later development was the introduction of a three-pole wavelength-shifting wiggler as an insertion device in one of the straight sections between bending magnets. This gave enhanced intensity at higher photon energies (shorter X-ray wavelengths) and supported a total of seven end-stations, most of which were used for powder and macromolecular single-crystal diffraction (stations 9.1 to 9.7). A second wiggler was subsequently added (stations 16.1–16.5). At this stage, the SRS offered a range of powder diffraction beamlines, both angle-dispersive and energy-dispersive, which were widely and effectively used in chemistry and materials science as well as other applications; similar provision could be found at other synchrotron facilities around the world. After a few years, as scientific priorities changed and experimental facilities were developed, the provision for energy-dispersive powder diffraction was found to be in excess of need, and the opportunity arose to convert station 9.7 to 80% usage for single-crystal diffraction, for which there was a substantial demonstrated demand following limited use of some available time on an SRS macromolecular crystallography beamline and elsewhere [4]. A user-led consortium of academic researchers and SRS scientists and engineers was formed for this project, and funding was obtained from the Science and Engineering Research Council (SERC, subsequently EPSRC; Principal Investigator William Clegg of Newcastle University, Co-Investigator Richard Catlow of The Royal Institution of Great Britain) with major personnel and other resource support from Daresbury Laboratory (local team led by Robert Cernik).

Design, construction and commissioning of the new station 9.8 took place in 1994–1997 [5]. With SERC responsive-mode funding, the project was constrained in time and budget. As a new facility initially sharing with, and subsequently taking over completely from, the existing station 9.7 set-up, it also had significant geometrical space constraints. In consequence, the station was designed using known technology and ingredients proven at SRS, together with commercial goniometer and detector systems, the latter being a new charge-coupled device (CCD) diffractometer of a type already installed and successfully in use at Newcastle; some minor changes were required for synchrotron application, particularly in view of the horizontal polarization of the incident X-ray beam and its much higher intensity. Space constraints dictated a single-bounce horizontally focusing monochromator (a bent silicon single crystal) to direct the beam away from the hutch wall, together with one vertically focusing mirror; with this arrangement, changing the wavelength involved moving the entire assembly of mirror, incident beam pipe and diffractometer on a long arm pivoted around the vertical monochromator rotation axis (figure 2). This somewhat cumbersome arrangement is not ideal and would not have been adopted without the geometrical constraints, but in practice, the incident wavelength was not very often changed, with the Zr *K* absorption edge (λ around 0.689 Å, similar to that from a

Figure 2. The experimental hut of SRS station 9.8 before closure in 2008. From right to left: monochromator to the left of the door, short vacuum pipe, focusing mirror vessel, long vacuum pipe (covering the former location of station 9.7 equipment), low-temperature device mounted horizontally, goniometer and CCD detector, all of these mounted on the movable alignment arm.

conventional Mo X-ray tube at $0.71073 \text{ \AA}$) widely used. Indeed, the intention throughout the project was to provide a facility with an operation as similar as possible to that normally available in local university laboratories so that scientists without synchrotron experience would find it relatively attractive and easy to use. Routine low-temperature data collection and the availability of familiar equipment for handling air-sensitive and other difficult samples were considered essential from the outset.

The 3-year project was enormously aided by the award to me of a 3-year formal Joint Appointment, allowing me to spend about 50% of my time for this period at Daresbury Laboratory, some 250 km from home. This was particularly valuable in the final year, much of which was devoted to optimizing operation and commissioning the facility with a wide range of samples provided by a large number of invited research collaborators. It was completed on time, within budget, and to better than the design specifications (to quote the Director of Synchrotron Radiation, David Norman, at the official hand-over ceremony) and in late 1997 station 9.8 became a full user facility of the SRS, available for standard research proposals by individual research groups in the same way as other beamlines. With the decommissioning of the station 9.7 operation not long afterwards, station 9.8 became the world's first fully dedicated single-crystal synchrotron X-ray diffraction facility of its kind. Its success and popularity was such that a near-clone, but with lower flux and a fixed X-ray wavelength around $0.84 \text{ \AA}$, was developed as station 16.2SMX a few years later along with replacement of the original 9.8 diffractometer and detector by newer systems, and the two stations were oversubscribed by academic and commercial users until the closure of the SRS in 2008. With the original equipment of station 9.8, a full data collection covering more than a hemisphere of reciprocal space typically took around 5 h, and this was reduced to about 1 h with the upgraded diffractometer and detector.

In 2001, with EPSRC funding and linked to the existing National Crystallography Service based on laboratory equipment at Southampton University, we set up a Newcastle-operated data collection and structure solution service for academic users, which ran until the closure of the SRS in 2008 and was then transferred to beamline I19 at Diamond Light Source (DLS). A

Figure 3. The first three published structures from SRS station 9.8: (a) an interlocking organic catenane $C_{36}H_{44}O_{10} \cdot C_{32}H_{12}N_4O_8$ as a dimethylsulfoxide solvate [6]; (b) an iridium–borane cluster $(Me_3P)_2(CO)Ir(B_{17}H_{20})$ [7]; and (c) a cobalt aluminium phosphate network structure DAF5 templated by an organic amine $C_{10}H_{20}N_2$ [8].

further spin-off benefit from the project, and particularly from the initial 50% and later 20% Joint Appointments, was the development of regular biennial training schools in synchrotron radiation science for postgraduate students and early-career researchers, which I helped to plan and run at Daresbury Laboratory and Chester College (now Chester University); these, in modified form, continue to the present day at Oxford and DLS, organized principally by DLS staff, the most recent one being in September 2018.

The first diffraction data were collected on station 9.8 during the commissioning phase of the original construction project, from late 1996; over the next 12 months, many datasets were measured for a wide range of samples from small organic molecules through organometallic and supramolecular complexes to polymeric inorganic framework structures. The first three structures to be published nicely demonstrate this variety, with one organic catenane [6], one metal complex of a borane ligand [7] and one templated cobalt-containing aluminophosphate [8] (figure 3). These provided a suitable set of results for the 1996–1997 SRS Annual Report [9]. The ePublications Archive of the Science and Technology Facilities Council (STFC, successor to CCLRC as the Research Council responsible for the funding of the SRS in its final years) lists over 440 publications from station 9.8 between 1997 and 2008 (<https://epubs.stfc.ac.uk/search/result?q=orgunitid%3A489>, accessed on 11 January 2019). This is certainly an incomplete record: publications up to 2008 resulting from synchrotron data collected by my own research group number around 140 (120 of them in the ePublications Archive), and about 240 to the present time, a substantial number of the more recent ones also based on data collected at station 9.8.

3. Beamlines at the Advanced Light Source

The success of SRS station 9.8 (and 16.2SMX) demonstrated what could be achieved for chemistry and materials science through synchrotron single-crystal diffraction and attracted large numbers of academic and commercial users. As the first facility of its kind, it served as a model and inspiration for other beamlines around the world. Of these, the two well-established fully dedicated beamlines so far have been at the Advanced Light Source (ALS) in Berkeley, California, and at the DLS in Oxfordshire, UK. A major redesign of beamline 11.3.1 at ALS was undertaken in 2006 by Simon Teat after his considerable contributions to the construction, commissioning and subsequent operation of station 9.8 at SRS followed by a brief spell as Principal Beamline Scientist leading the design of DLS beamline I19. The new ALS beamline, positioned on a bending magnet, closely followed the principles and practice of station 9.8 with a commercial CCD-based goniometer and detector system and it has been enormously productive with a large international community of users [10]; the beamline website lists around 80 publications annually in recent years (<http://chemcryst.lbl.gov/publications-1>, accessed on 13 November 2018).

This beamline has recently been closed and replaced by a more powerful one, 12.2.1, with a complementary metal oxide semiconductor (CMOS) detector and based on a superconducting

bending magnet source, which significantly extends its capabilities. It has also spawned a non-ambient conditions beamline, 12.2.2, principally for high-pressure single-crystal diffraction and powder diffraction over a range of temperatures, also located on a superbend source.

4. Beamline I19 at Diamond Light Source

With the impending closure of the SRS in 2008, a replacement beamline was needed at DLS, the third-generation successor to SRS, the construction of which began a few years earlier. Such a replacement was not included in either of the first two batches of approved beamlines, but a strong case was presented for the third round with such a long list of internationally recognized supporters that a member of the Diamond Science Advisory Committee responsible for the approvals described it as ‘a Who’s Who of UK chemistry’. The case was accepted and an accelerated timetable agreed for the beamline construction, such that it was able to begin operation only a few months after SRS station 9.8 was lost, thus avoiding an extended ‘dark period’; the principal powder diffraction beamline I11 at DLS began operation at about the same time. I was pleased to serve as a member of the working party that wrote the I19 beamline proposal and then went on to monitor the design and construction. As with ALS beamline 11.3.1, the basic principles were much the same as for station 9.8 but with the advantage that the beamline was designed from scratch with only the same space and budget constraints as other new DLS beamlines [11].

DLS beamline I19 is fed by an undulator source and is equipped with a double-crystal monochromator and a pair of focusing mirrors in addition to various other beam conditioning and monitoring devices. It provides two in-line experimental hutches, one for relatively straightforward ambient and low-temperature data collection and the other for work with high-pressure diamond anvil cells, gas cells, lasers and other special sample environments. The standard Hutch 1 was originally set up with a commercial CCD detector attached to a custom-built kappa-geometry four-circle diffractometer driven by commercial software provided by the detector manufacturer; a sample-changing robot was added later (figure 4). In this configuration, a typical data collection took up to about 1 h, a significant proportion of the time being taken up by detector readout and by the need to repeat many of the individual images at higher speed to deal with detector overloads. Our own main use of beamline I19 for the first 2 years was in operation of the EPSRC-funded National Crystallography Service; in 2010, we changed focus to set up a regional consortium for chemistry research groups in UK north-eastern universities, which has been operating continuously since then with recent expansion geographically and in research topics, as well as providing opportunities to contribute significantly to facilities development as described below.

The number of publications resulting from the use of beamline I19 and recorded in the Diamond Publications Database is approaching 600 (<http://publications.diamond.ac.uk>, accessed on 11 January 2019). The need to expand the capacity of Hutch 1 on beamline I19, while simultaneously making more time available for special experiments in Hutch 2, led a few years ago to a project to upgrade the beamline with more powerful and more efficient data collection systems. At the same time, it was considered important to move away from commercial control software and integrate any new equipment into the complete suite of control and processing software developed by DLS. Thus a large new three-circle diffractometer was custom designed and built, with dual air bearings on all the circles to cope with fast motors, and a Dectris Pilatus 2M pixel detector was installed. This allows continuous data collection at high speed, with no time lost to detector readout [12]. Low-temperature data collection can make use of both nitrogen and helium gas flow systems. The sample-handling robot has been enhanced to give faster sample exchange and with a capacity for up to 112 pre-mounted crystals in seven Unipucks (<https://www.mitegen.com/product/universal-pucks-and-tools/>, accessed on 11 January 2019) of 16 crystals each, kept submerged in liquid nitrogen. Further improvement is planned for 2019 with the installation of a new, mechanically more stable, monochromator, allowing tighter focusing

Figure 4. The original equipment of DLS beamline I19, showing the CCD detector (left), goniometer, low-temperature device and the robot on the right.

of the incident X-ray beam for the smallest sample crystals. A typical data collection now takes 10 min or less once a crystal is mounted and screened for suitability (figure 5).

5. Remote access operation

With the reduction in time required for a full data collection resulting from the I19 beamline upgrade, to 10 min or less plus crystal mounting and screening, the time overheads involved in manually exchanging samples, previously not hugely significant, become very wasteful of allocated experimental time. These overheads include interrupting the interlocked personnel safety of the hutch, dismounting one sample and replacing it by another, searching and locking the hutch and waiting for the imposed safety period before the main X-ray shutter can be reopened. Almost all of this overhead is saved by having many samples pre-mounted and stored in the robot-accessible liquid nitrogen dewar inside the hutch and using the robot to exchange the samples. With the support and assistance of beamline staff, we developed the appropriate techniques and procedures even before the upgrade in 2016, as cryogenic crystal mounting, in-hutch storage and robotic exchange under cryogenic conditions were already possible on site at that time. The advantage of cryogenic mounting and storage over ambient conditions is that crystals sensitive to air, moisture or solvent loss can be handled just as successfully and almost as easily as fully stable crystals; in addition, the cryogenic conditions keep crystals securely fixed in place even when the mounting medium is a viscous oil, widely used for examining and handling sensitive samples, rather than a firm adhesive. The pre-mounting of samples also significantly reduces the real-time pressure on users during the allocated beamtime and makes the experiment less stressful and more conducive to success.

Figure 5. DLS beamline I19 following the 2016 upgrade: left, the large goniometer; top, the detector; bottom centre, the sample position and low-temperature device; right, the robot and samples dewar.

Once the robotic sample exchange is available, further major time savings can be made for users located at a distance from the central facility. The 450–500 km journey from Newcastle upon Tyne to DLS involves several hours by road or rail transport, and a 24 h allocation of experimental time means two nights on site and hence much of 3 days spent on the experiment. This travel and accommodation overhead will become proportionately greater with the expected move to shorter (6 or 8 h) shift allocations appropriate to the much faster data collections now possible. To eliminate this overhead, samples are pre-mounted under cryogenic conditions in the home laboratory, stored under liquid nitrogen, and shipped by courier to DLS in specially designed ‘dry-shipping dewars’ that maintain the low-temperature conditions through adsorption of liquid nitrogen into the dewar lining without requiring the presence of cryogen in liquid form. This procedure also serves to protect the mounted crystals from atmospheric contact and from thermal instability; with practice, it is possible to preserve even the most sensitive crystals for many weeks in a mounted state ready for shipping, without any trace of ice formation during the procedures. These techniques, of course, have been used routinely for many years by MX researchers, and we are simply taking advantage of their developed experience, while recognizing that there are some significant differences in the way that small-molecule and macromolecular crystals respond to such treatment and in how they need to be handled during mounting and in the data collection experiment (<https://www.diamond.ac.uk/Instruments/Mx/Common/Common-Manual/Remote-Access.html>, accessed on 11 January 2019).

A remote access experiment has three stages [13]. In the first, before the allocated experimental time, samples are examined and screened in the home laboratory. This has the advantage of using familiar equipment, including the possibility of checking in-house diffraction performance to see if synchrotron investigation is appropriate; the sample, whether the individual crystal screened by local X-ray facilities or others, can be immediately mounted and stored ready for shipping, with others added later as they become available. This can all be done at leisure without the time pressure inevitably generated by mounting samples on site during the synchrotron experiment.

Figure 6. (a) A Unipuck without lid, containing 16 mounted crystals (following removal from the dewar after the experiment); (b) a rack for seven Unipucks, one of which is shown with its lid removed; and (c) a shipping dewar and rack of Unipucks.

We generally mount two or three individual crystals of each sample to allow a choice to be made on the beamline and to allow for variation of quality and for mishaps in the handling. A standard Unipuck holds up to 16 mounted crystals, and a shipping dewar takes seven Unipucks, providing space for 112 individual crystals, approximately 50–60 samples with duplication (figure 6). Of course, more than one dewar can be shipped together, but the robot dewar on DLS I19 can take only seven pucks at a time, so this would involve manual intervention by DLS staff at some stage during the experiment. Shipping protocols have been established by DLS with a preferred courier, so these procedures are completely routine and are handled by standard software as part of the integrated DLS operations software.

It should be noted that this mode of operation also drastically reduces the amount of material transported to the synchrotron for examination; no bulk samples are carried by courier, postal services, or the user in private or public transport, all of which have health and safety implications especially when samples are kept in mother liquor from their synthesis or crystallization, and the minuscule quantities of samples actually shipped are under cryogenic conditions in closed containers. Given that samples for structure determination are usually new synthetic materials with at least partly unknown properties and hazards, this represents a significant advantage. The one particular type of material for which it is a disadvantage is a substance undergoing a major phase transition between ambient and liquid-nitrogen temperatures, resulting in degradation or complete loss of crystallinity. Such materials continue to require manual handling without cryogenic storage, but we do not encounter them at all often in our own research.

The second stage is the data collection experiment itself. Once the shipped samples are loaded into the robot dewar inside the experimental hutch by DLS staff and the standard safety procedures have been followed for securing the hutch and opening the X-ray shutter, formal control of the equipment is passed to the remote users. The techniques and software are essentially identical to those used on site at the beamline, with sample exchanges being handled by the robot, monitored visually by webcams in the hutch. For a user consortium with members in different geographical locations sharing the allocated beamtime, the software operating baton is simply passed from one group to another, with control clearly in one site at a time. This remote access operation requires only a suitable network connection (even a typical fast home broadband connection can be adequate) and a computer running an appropriate remote desktop application (the DLS recommendation is a NoMachine or NX connection (<https://www.nomachine.com/>, accessed on 11 January 2019)), in which it is a distinct advantage to have two or more large

monitors providing an extended desktop display. In this way, users can simultaneously monitor the equipment, the mounted crystal, the diffraction pattern being collected, and the output of data processing software. The data traffic between DLS and the remote user site is relatively light, the extensive raw image data being retained locally at DLS during the data collection. The DLS software includes an automatic pipeline for the determination of a unit cell and orientation matrix, followed by extraction of integrated intensities from the raw images, scaling and an initial attempt at structure solution. This provides a useful initial indication of the data quality and resolution, so that decisions can be made whether to examine further mounted crystals of the same sample or move on to other samples.

The third and final stage is the post-collection processing of the diffraction data with the aim of solving and refining crystal structures. In some cases, the automatic data-processing pipeline provided by DLS leads to an integrated dataset of good quality and a recognizable structure solution, which can subsequently be taken into refinement for a final result. In other cases, particularly when the crystal is of poorer quality and/or is twinned, a more hands-on approach is needed. The user can apply a range of data processing software to the measured and stored images and can convert these to other familiar image formats including those of commercial software packages; the most commonly used conversions are available in the suite of DLS user software. Complete sets of images can be transferred by standard protocols to computers in the local research institution; they are also retained in a DLS archive and can be accessed at any time in the future.

6. Shared-usage beamlines

While this account focuses on synchrotron beamlines dedicated to non-macromolecular single-crystal diffraction, there are numerous national and international facilities that provide access to this technique alongside others on shared-usage beamlines. The proportion of time available for single-crystal diffraction varies considerably; other techniques available on the same beamline often include macromolecular crystallography, powder diffraction, small-angle scattering, X-ray absorption spectroscopy and/or imaging. Notable shared-usage beamlines include ID-11 at ESRF, ChemMatCARS at the Advanced Photon Source (APS) at Argonne National Laboratory, Cristal at SOLEIL, Gif-sur-Yvette, France, Belok at the Kurchatov facility in Moscow, MX1 at the Australian Synchrotron, BL2D-SMC at the Pohang Light Source in Korea and BL02B1 at SPring-8, Hyogo, Japan.

7. Specialized applications

The main focus here has been on the determination of static crystal structures using standard crystallographic methods exploiting mainly the high intensity of synchrotron single-crystal diffraction beamlines. For completeness, some wider applications, making use of other synchrotron radiation properties, are indicated with particular examples.

The measurement of diffraction data at low temperatures achievable by devices based on nitrogen gas streams (down to about 80 K) has long been considered routine and such facilities are provided as standard on single-crystal beamlines as well as in many home laboratories. Lower temperatures require helium-based cryogenics, either in closed-loop systems or with a helium gas flow. Until recently, these have been much less widely available, but their use is increasing, with applications such as spin-crossover systems and other structural, electronic and magnetic transitions occurring only at very low temperatures. A recent example is an investigation of diffuse superstructure reflections in a nickel-doped ZrTe_3 alloy at 20 K [14]. Such weak diffuse scattering, important in the characterization of order-disorder phenomena, requires the high intensity of synchrotron radiation and access by use of modern sensitive area detectors to the whole scattering pattern rather than just Bragg reflections [15].

High-pressure studies benefit from the availability of high-intensity synchrotron X-rays at short wavelength, compressing the diffraction pattern to lower Bragg angles so that more data

can be measured with the restricted angular access of diamond anvil cells and other high-pressure containers. Some beamlines, such as ALS 12.2.2, ESRF ID09 and ID27, and the second experimental hutch of DLS I19, are specifically designed for such non-ambient investigations [16]. Short wavelengths (along with low temperatures) are also beneficial for charge-density studies, giving access to high-resolution data and reducing systematic errors such as absorption and extinction [17,18]. A finer selection of X-ray wavelength relative to absorption edges of particular elements present in a sample provides a means of either avoiding or exploiting resonant scattering effects. This can be used for the determination of absolute configuration of chiral molecules, and in order to distinguish more clearly between atoms of elements with similar numbers of electrons, particularly those that are adjacent in the periodic table; an example using several different wavelengths provided reliable discrimination of zinc and gallium and estimates of their occupancies in disordered sites [19].

Dynamic or time-resolved crystallography, investigating the structures of short-lived species, takes advantage of the pulsed nature of synchrotron radiation, particularly for ‘pump–prime’ experiments in which excitation of a sample alternates with recording of the resulting diffraction pattern. Again, this research is facilitated by specialist features of some beamlines [20].

8. Impact

The availability of synchrotron beamlines for chemical and materials research with single-crystal diffraction over the last 20 years or so has considerably extended the scope of the technique to samples that could not be studied with conventional laboratory equipment [21]. This has particularly been the case with pharmaceutical compounds and with the rapid growth of interest in metal–organic frameworks in recent years, including applications for energy and gas storage. This impact runs across both academic and commercial research, and significant use of beamlines has been made by commercial companies [22]. The initial project to construct SRS station 9.8 has led directly to the development of the current dedicated beamlines I19 at DLS and 12.2.1 at ALS, as well as indirectly influencing shared-usage beamlines such as Cristal at SOLEIL and ChemMatCARS at APS, and these facilities have played their part in the training of many researchers, some of whom have continued as major users and beamline scientists. These impacts have been described in a formal Impact Case Study for the 2014 UK Research Excellence Framework, including documentary evidence provided by central facilities and industrial users ([https://results.ref.ac.uk/\(S\(fqds4e323ekbsumi3zj20obs\)\)/DownloadFile/ImpactCaseStudy/pdf?caseStudyId=21355](https://results.ref.ac.uk/(S(fqds4e323ekbsumi3zj20obs))/DownloadFile/ImpactCaseStudy/pdf?caseStudyId=21355), accessed on 11 January 2019) [23]. While much of the commercial exploitation remains confidential, some reports have entered the public domain. Examples of pharmaceutical applications with commercial impact include polymorphism and hydrate studies of the common painkiller sodium diclofenac (<https://www.diamond.ac.uk/industry/Case-Studies/Case-Study-SAFC-Pharmorphix-polymorphism.html>, accessed on 11 January 2019), Sugammadex (marketed as Bridion) as a neuromuscular blocker [24], the influenza neuraminidase inhibitor Tamiflu and the first-generation HIV protease inhibitor Invirase. Patents and spin-out companies arising from synchrotron work include oil refinery usage and nitric oxide storage for microporous materials [23,25], and a recent patent application for a natural product antibiotic with activity against tuberculosis [26]. Recent examples of both academic and commercial research of particular importance and impact are given in science highlights and case studies from DLS [22] (<https://www.diamond.ac.uk/Instruments/Crystallography/I19/highlights.html>, accessed on 11 January 2019) and on the websites of synchrotron facilities generally.

9. Conclusion

Single-crystal X-ray diffraction for chemical and materials applications has seen enormous developments over the years, with particular advances in X-ray sources, detectors and software. While significant enhancements have occurred in laboratory-based X-ray sources, the availability

of synchrotron facilities provides even greater opportunities for studying difficult samples, including extremely small and weakly diffracting crystals as well as samples held in special environmental cells. The most successful and productive beamlines are those that are dedicated to the technique of single-crystal diffraction and are optimized for so-called small-molecule samples. Other important factors are the availability of sample-handling techniques similar to those in home laboratories, routine use of reliable low-temperature devices, a range of available X-ray wavelengths, efficient detectors well matched to the bright X-ray source, and the familiarity of operating procedures and data processing software. Recent hardware and software developments make remote-access operation feasible, straightforward and attractive, and will significantly improve the efficient use of oversubscribed single-crystal diffraction beamlines. The availability of both single-crystal and powder diffraction synchrotron beamlines around the world, with their complementary abilities and applications, provides a vital service for chemistry and materials science.

Data accessibility. This article has no additional data.

Competing interests. I have no competing interests.

Funding. The development and use of the synchrotron facilities described in this article have been generously funded by SERC/EP SRC, CCLRC/STFC, the Synchrotron Radiation Department of Daresbury Laboratory, Diamond Light Source and Newcastle University.

Acknowledgements. Many individuals, groups and organizations have provided support, advice, expertise and samples for the work described here. These include the managements of the various synchrotron facilities; facility user offices; synchrotron facility scientists and engineers; beamline staff; software developers; beamline management and advisory committees and panels; leaders and members of collaborating chemistry research groups; and members of my own research group. For the most part, they are far too numerous to be individually named and thanked. However, particular thanks are due to the following: Dr Marjorie Harding, for introducing me to the capabilities of synchrotron facilities at SRS; Prof. Richard Catlow, as co-applicant on the major grant leading to the design and construction of SRS station 9.8; Prof. Robert Cernik, who led the Daresbury science and engineering team for the station 9.8 project; Prof. Ian Munro, Head of the SR Department of Daresbury Laboratory, for offering me the all-important Joint Appointment; Dr Simon Teat, for his major contributions to the development and use of station 9.8 as a Postdoctoral Researcher and then beamline scientist; Dr David Allan, as Principal Beamline Scientist at DLS I19 and a keen supporter of the remote-access developments; Dr Ross Harrington, as Postdoctoral Researcher and service crystallographer at Newcastle University involved in much of our use of both 9.8 and the initial configuration of I19; and Dr Michael Probert, as current Principal Investigator of the North-east Block Allocation Group of University users of I19 and main driver of the remote-access project.

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