Table 8.1.4.1
Internet addresses of SR facilities with macromolecular crystallography beamlines

Synchrotron-radiation source	Location	Address
ALS, Advanced Light Source	Lawrence Berkeley Lab., Berkeley, California, USA	http://www-als.lbl.gov/als/
ANKA Synchrotron	Karlsruhe, Germany	http://ankaweb.fzk.de/
APS, Advanced Photon Source	Argonne National Lab., Chicago, Illinois, USA	http://epics.aps.anl.gov/
Australian Synchrotron	Clayton, Victoria, Australia	http://www.synchrotron.org.au/
BESSY	Berlin, Germany	http://www.bessy.de/
Brazilian Synchrotron Light Laboratory	Campinas, Brazil	http://www.lnls.br/
BSRF, Beijing Synchrotron Radiation Facility	Beijing, China	http://www.ihep.ac.cn/bsrf/english/main/main.htm
CAMD, Center for Advanced Microstructures and Devices	Baton Rouge, Louisiana, USA	http://www.camd.lsu.edu/
Canadian Light Source	Saskatoon, Canada	http://www.lightsource.ca/
CHESS, Cornell High Energy Synchrotron Source	Ithaca, New York, USA	http://www.chess.cornell.edu/
Diamond Light Source	Harwell Science and Innovation Campus, Didcot, England	http://www.diamond.ac.uk/
Elettra	Trieste, Italy	http://www.elettra.trieste.it
ESRF, European Synchrotron Radiation Facility	Grenoble, France	http://www.esrf.fr/
HASYLAB DESY, Deutsches Elektronen-Synchrotron	Hamburg, Germany	http://www.desy.de/
Kurchatov Center for Synchrotron Radiation and Nanotechnology	Moscow, Russian Federation	http://www.kcsr.kiae.ru/en/
LNLS, National Synchrotron Light Laboratory	Campinas, Brazil	http://www.lnls.br/
MAXLab (see also MAX IV project)	Lund, Sweden	http://www.maxlab.lu.se/, http://www.maxlab.lu.se/maxlab/max4/index.html
NSLS, National Synchrotron Light Source (see also NSLS II; under construction)	Brookhaven National Lab., New York, USA	http://www.nsls.bnl.gov/, http://www.bnl.gov/nsls2/
The Photon Factory, KEK	Tsukuba, Japan	http://pfwww.kek.jp/
PLS, Pohang Light Source	Pohang, Korea	http://pal.postech.ac.kr/
SESAME (Synchrotron-light for Experimental Science and Applications in the Middle East)	Allan, Jordan	http://www.sesame.org.jo/
Shanghai Synchrotron Radiation Facility	Shanghai, China	http://ssrf.sinap.ac.cn/english/1/Introduction.htm
SLS, Swiss Light Source	Paul Scherrer Institut, Villigen, Switzerland	http://sls.web.psi.ch/view.php/about/index.html
Soleil	Gif-sur-Yvette, Paris, France	http://www.synchrotron-soleil.fr/portal/page/portal/Accueil
SPring-8, Super Photon Ring	Riken Go, Japan	http://www.spring8.or.jp/
SRRC, Synchrotron Radiation Research Center	Hsinchu City, Taiwan	http://www.nsrrc.org.tw/
SSRL, Stanford Synchrotron Radiation Laboratory	SLAC, California, USA	http://www-ssrl.slac.stanford.edu/
VEPP-3	Novosibirsk, Russia	http://ssrc.inp.nsk.su/

At the sample position, the intensity of the beam, usually focused, is a useful parameter:

$$\text{Intensity} = \text{photons per s per focal spot area.} \qquad (8.1.4.2)$$

Moreover, the horizontal and vertical convergence angles are ideally kept smaller than the mosaic spread, *e.g.* ~1 mrad, so as to measure reflection intensities with optimal peak-to-background ratio.

Producing a focal spot area that is approximately the size of a typical crystal (~0.1 mm) and with a convergence angle ~1 mrad sets a sample acceptance requirement to be met by the X-ray beam and machine emittance. A machine with an emittance that matches the acceptance of the sample greatly assists the simplicity and performance of the beamline optics (mirror and/or monochromator) design. The common beamline optics schemes are shown in Fig. 8.1.4.1.

In addition to the focal spot area and convergence angles, it is necessary to provide the appropriate spectral characteristics. In monochromatic applications, involving the rotating-crystal diffraction geometry, for example, a particular wavelength, λ, and narrow spectral bandwidth, $\delta\lambda/\lambda$, are used. Fig. 8.1.4.2(*a*) shows an example of a monochromatic oscillation diffraction photograph from a rhinovirus crystal as an example recorded at CHESS, Cornell. Fig. 8.1.4.2(*b*) shows the prediction of a white-beam broad-band Laue diffraction pattern from a protein crystal that was recorded at the SRS wiggler, Daresbury, colour-coded for multiplicity.

Table 8.1.4.1 lists the internet addresses of the SR facilities worldwide that currently have macromolecular beamlines. A considerable suite of information on SR and free electron laser (FEL) sources can also be found at http://www.lightsources.org/cms/. Comprehensive statistics for the macromolecular crystal structures from all the various beamlines over the years can be obtained at http://biosync.rcsb.org/.

8.1.5. Evolution of SR machines and experiments

8.1.5.1. First-generation SR machines

The so-called first generation of SR machines were those which were parasitic on high-energy physics operations, such as DESY in Hamburg, SPEAR in Stanford, NINA in Daresbury and VEPP in Novosibirsk. These machines had high fluxes into the X-ray range and enabled pioneering experiments. Parratt (1959) discussed the use of the CESR (Cornell Electron Storage Ring) for X-ray diffraction and spectroscopy in a very perceptive paper. Cauchois *et al.* (1963) conducted *L*-edge absorption spectroscopy at Frascati and were the first to diffract SR with a crystal (quartz). The opening experimental work in the area of biological diffraction was by Rosenbaum *et al.* (1971). In protein crystallography, multiple-wavelength anomalous-dispersion effects (Fig.

8.1.5.1) were used from the onset (Phillips *et al.*, 1976, 1977; Phillips & Hodgson, 1980; Webb *et al.*, 1977; Harmsen *et al.*, 1976; Helliwell, 1977, 1979), and a reduction in radiation damage was seen for high-resolution data collection (Wilson *et al.*, 1983). Historical insights into the performances of those machines, from the current-day perspective, are described in detail, for example, by Huxley & Holmes (1997) at DESY, Munro (1997) at Daresbury, and Doniach *et al.* (1997) at Stanford. A principal limitation was the problem of source movements, which degraded the focusing of the source onto a small crystal or single fibre and thus degraded the intrinsic spectral brightness of the beam; see, for example, Haslegrove *et al.* (1977), who advocated machine shifts dedicated to SR as a working compromise with the high-energy physicists. Some possible applications that were discussed were unfulfilled until brighter sources became available. The two-wavelength crystallography phasing method of Okaya & Pepinsky (1956) (see also Hoppe & Jakubowski, 1975) and the three-wavelength method of Herzenberg & Lau (1967), as well as the implementation of the algebraic method of Karle (1967, 1980, 1989, 1994), awaited more stable beams, which had to be rapidly and easily tunable over a fine bandpass (ideally 10^{-4}). Experiments to define the anomalous-dispersion coefficients, including dichroism effects, at a large number of wavelengths at several example absorption edges in a variety of crystal structures were conducted at SPEAR (Phillips *et al.*, 1978; Templeton *et al.*, 1980, 1982; Templeton & Templeton, 1985). Large values of f'' were identified at 'white lines', *i.e.* regions of the elemental absorption with pronounced effects (*e.g.* see Fig 8.1.5.1*a*). Values of f' over a continuum of wavelengths in a real compound (*i.e.*, not a metal in the gas phase) (Fig. 8.1.5.1*b*) were explored in a profile approach (now called DAFS, diffraction anomalous fine structure) by Arndt *et al.* (1982) at the newly commissioned SRS, the first dedicated second-generation SR source (see Section 8.1.5.2).

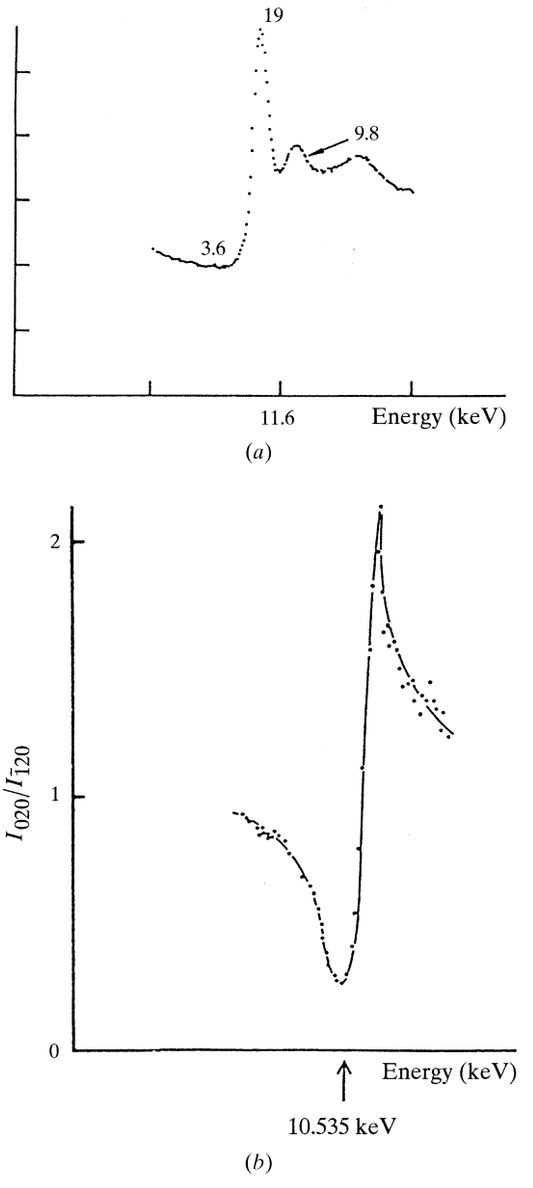

Figure 8.1.5.1
Anomalous dispersion. (*a*) f'' as represented by an absorption spectrum [Pt L_{III} edge for $K_2Pt(CN)_4$ as the example with 19 electrons for f'' at the peak of that 'white line', with pre-edge and post-edge f'' electron values also indicated] (Helliwell, 1984). Reproduced with the permission of the Institute of Physics. (*b*) f' as estimated by a continuous polychromatic profile method. Reproduced with permission from *Nature* (Arndt *et al.*, 1982). Copyright (1982) MacMillan Magazines Limited.

8.1.5.2. Second-generation dedicated machines

The building of dedicated X-ray sources began with the SRS at Daresbury, which came online in 1980, having followed the NINA synchrotron (closed in 1976) and the associated Synchrotron Radiation Facility at Daresbury. Elsewhere in the world, LURE (Lemonnier *et al.*, 1978) and CHESS at Cornell were building up their SR macromolecular crystallography operations in the late 1970s and early 1980s, and the NSLS in Brookhaven and the Photon Factory (PF) in Japan were both under construction. The NSLS and the PF came online in 1983 and 1984, respectively. Thus, there was a rapid increase in the number of operating machines and beamlines worldwide in the X-ray region for protein crystallography. There were teething problems with the SRS with the radio-frequency cavity window problem, interrupting operation for many months in 1983, and at the NSLS in its early period due to vacuum-chamber problems. Pioneering experiments continued and blossomed. Seminal work ensued in virus crystallography [Rossmann & Erickson (1983) at Hamburg and Daresbury; and Usha *et al.* (1984) at LURE], Laue diffraction for time-resolved protein crystallography [Moffat *et al.* (1984) at CHESS; Helliwell (1984, 1985) at the SRS; Cruickshank *et al.* (1987, 1991); Hajdu, Machin *et al.* (1987); Helliwell *et al.* (1989); Bourenkov *et al.* (1996); Neutze & Hajdu (1997)], enzyme catalysis in the crystal [Hajdu, Acharya *et al.* (1987) at the SRS], MAD [Phillips *et al.* (1977); Einspahr *et al.* (1985); Hendrickson (1985); Hendrickson *et al.* (1989) at SPEAR, the SRS and the PF; Guss *et al.* (1988) at SPEAR; Kahn *et al.* (1985) at LURE; Korszun (1987) at CHESS; Mukherjee *et al.* (1989) and Peterson *et al.* (1996) at the SRS; Hädener *et al.* (1999) at the SRS and the ESRF, to cite a few experiments], protein crystallography involving isomorphous replacement with optimized anomalous scattering [Baker *et al.* (1990) at the SRS; Dumas *et al.* (1995) at LURE], small crystals [Hedman *et al.* (1985) at the SRS] and diffuse scattering with SR [Doucet & Benoit (1987); Caspar *et al.* (1988); Glover *et al.* (1991)]. Table 8.1.5.1 shows the impact of the SRS in protein (*i.e.* macromolecular) crystallography integrated over its whole lifetime.

8.1.5.3. Third-generation high spectral brightness machines

As early as 1979, there were discussions on planning a proposal for a high spectral brightness, insertion-device-driven European synchrotron-radiation (ESR) source. A wide variety of discussion

Table 8.1.5.1
Structures in the Protein Data Bank (PDB) for which data were collected at the SRS

The data presented here were compiled in December 2009 (see http://biosync.rcsb.org/biosync_regions/SyncEurope.html#SRS) and are likely to be reasonably complete since the SRS closed operations in August 2008. The SRS has delivered 3.6% of the total of 38 650 macromolecular crystal structures determined using radiation from synchrotrons around the world as of December 2009. The ESRF third-generation source, in comparison, integrated over about half as many years, but about two to three times more beamlines, has delivered 15.6% of the structures, *i.e.* at a rate therefore about three to four times greater than the second-generation SRS.

	Station						
Year	10.1	14.1	14.2	7.2	9.5	9.6	Not known
1995	0	0	0	5	6	19	3
1996	0	0	0	6	11	33	0
1997	0	0	0	11	29	43	0
1998	0	0	0	26	32	35	0
1999	0	0	0	28	13	45	4
2000	0	1	0	28	17	60	3
2001	0	13	9	9	16	47	2
2002	0	13	21	7	7	59	2
2003	0	27	38	3	8	41	3
2004	3	40	42	5	2	36	2
2005	18	34	36	1	4	47	1
2006	22	32	22	1	1	23	0
2007	21	37	21	0	0	11	1
2008	51	15	15	2	0	20	1
2009	14	12	5	1	0	3	0
Total	129	224	209	133	146	522	22

documents and workshops, and the ESR Project (ESRP) led by B. Buras and based in Geneva at CERN, culminated in the so-called 'Red Book' in 1987, the *ESRF Foundation Phase Report* (1987), totalling some 1000 pages of machine, beamline and experimental specifications and costs. This, then, was the progenitor of the third-generation sources, characterized by their high energy and high spectral brightness, tailored to optimized undulator emission in the 1 Å range. Actually, the ESRF machine energy was initially set at 5 GeV, but increased to 6 GeV to optimize the production of 14.4 keV photons to better match the nuclear scattering experiments proposed initially by Mossbauer in 1975. Proposals for the US machine, the Advanced Photon Source at 7 GeV, and the Japanese 8 GeV SPring-8 machine followed, with the higher machine energy enhancing the X-ray tuning range of undulators. Thus, MAD tuning-based techniques were facilitated with these machines and studies involving yet-smaller samples (crystals, single fibres or tiny liquid aliquots) or very large unit cells were enabled. As a result, micron-sized protein crystals as well as huge multi-macromolecular biological structures (of large viruses, for example) also became routinely accessible.

8.1.5.4. New national SR machines

Today a variety of enhanced national SR machines have been built. In Switzerland there is the SLS, in the UK there is DIAMOND and in France there is SOLEIL. These machines are more tailored to the bulk of a country's user needs, distinct from the special provisions at the ESRF. The different countries' SR needs, of course, have many aspects in common, with some historical biases. The new sources are, in essence, characterized by high spectral brightness, *i.e.*, low emittance. The 2 GeV SR source ELETTRA in Trieste, the MAXII machine in LUND and the Brazilian Light Source are already operational. In many ways, national sources like the SRS, LURE, DORIS and so on fuelled the case and specification for the ESRF. Now the developments at the ESRF, including high harmonic emission of undulators *via* magnet shimming (Elleaume, 1989) and narrow-gap undulator operation (Elleaume, 1998), are fuelling ideas and the specification of what is possible in the new national SR sources.

8.1.5.5. X-ray free-electron lasers (XFELs)

In terms of the evolution of X-ray sources, X-ray FELs are being constructed at DESY in Hamburg (Brinkmann *et al.*, 1997), at SLAC (Winick, 1995) and at Spring8. Compared to SR, one will have a transversely fully coherent beam, a larger average spectral brightness and, in particular, pulse lengths of ~10 fs full width at half-maximum with eight to ten orders of magnitude larger peak spectral brightness. Such a machine is based on a linear accelerator (linac)-driven XFEL utilizing a linear collider installation (*e.g.*, for a high-energy physics centre-of-mass energy capability of 500 GeV). For this machine there is a 'switchyard' distributing the electrons in a beam to different undulators from which the X-rays are generated in the range 0.1 to ~12 keV. The anticipated r.m.s. opening angle would be 1 mrad and the source diameter would be 20 μm. This source of X-rays would then compete in time resolution with laser-pulse-generated X-ray beams [see Helliwell & Rentzepis (1997) for a survey of that work and a comparison with synchrotron radiation] and would also have higher pulse flux. Coherent methods in the X-ray sciences have been extensively reviewed by Nugent (2009).

8.1.6. SR instrumentation

The divergent continuum of X-rays from the source must be intercepted by the sample cross-sectional area. The crystal sample acceptance, as seen above, is a good way to illustrate to the machine designer the sort of machine emittances required. Likewise, the beamline optics, mirrors and monochromators should not degrade the X-ray beam quality. Mirror surface and shape finish have improved a great deal in the last few decades; slope errors of mirrors, even for difficult shapes like polished cylinders, which on bending give a toroidal reflecting surface, are now around 1 arc second (5.5 μrad) for a length of 1 m. Thus, over focusing distances of 10–20 m, say, the focal-spot smearing contribution from this is 55–110 μm, important for focusing onto small crystals. Further optics developments (*e.g.* Fresnel optics) have yielded micron focus beams and smaller, and are being applied to studying ever-smaller crystals in macromolecular crystallography and obviously have a variety of other diffraction