BL02U1: The Relocated Macromolecular Crystallography Beamline at the Shanghai Synchrotron Radiation Facility

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Abstract

Macromolecular crystallography beamline BL17U1 at the Shanghai Synchrotron Radiation Facility has been relocated, upgraded, and given a new ID (BL02U1). It now delivers X-rays in the energy range of 6–16 keV, with a focused beam of 11.6 µm × 4.8 µm and photon flux greater than 10^{12} phs/s. The high credibility and stability of the beam and good timing synchronization of the equipment significantly improve the experimental efficiency. Since June 2021, when it officially opened to users, over 4200 h of beamtime have been provided to over 200 research groups to collect data at the beamline. Its good performance and stable operation have led to the resolution of several structures based on data collected at the beamline.

Full Text

Preamble

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Abstract: The macromolecular crystallography beamline BL17U1 at the Shanghai Synchrotron Radiation Facility has been relocated, upgraded, and re-designated as BL02U1. The new beamline delivers X-rays in the energy range of 6–16 keV, with a focused beam size of 11.6 µm × 4.8 µm and photon flux exceeding 10^{12} phs/s. The high reliability and stability of the beam, along with excellent timing synchronization of the equipment, significantly improve experimental efficiency. Since officially opening to users in June 2021, the beamline has provided over 4200 hours of beamtime to more than 200 research groups for data collection. Its excellent performance and stable operation have enabled the determination of numerous protein structures using data collected at the beamline.

Keywords: Macromolecular crystallography beamline Shanghai Synchrotron Radiation Facility BL02U1

1. Introduction

Macromolecular crystallography (MX) employs X-ray diffraction (XRD) to determine three-dimensional structures and elucidate structure-function relationships of biological molecules, representing the most effective method for solving the spatial structures of proteins, nucleic acids, and other biological macromolecules. As of February 2023, the Protein Data Bank (PDB) contained 201,196 protein structures, of which 172,859 were determined by crystallographic methods. The typical workflow for macromolecular structure determination comprises four main steps: (1) expression and purification of the target protein, (2) crystal growth, (3) X-ray diffraction data collection from protein crystals, and (4) computational analysis to obtain the three-dimensional structure. Steps 2 and 3 are the most critical and time-consuming phases, as obtaining suitable crystals and collecting high-quality diffraction data require considerable effort. As a dedicated diffraction data collection platform, a macromolecular crystallography beamline leverages the high brightness, excellent collimation, and tunable wavelength characteristics of synchrotron X-rays to serve as a powerful tool for protein structure analysis.

The macromolecular crystallography beamline BL17U1 at the Shanghai Synchrotron Radiation Facility (SSRF) has been a dedicated undulator beamline for MX since 2009, delivering high photon flux (>10^{12} phs/s) within a 67 µm × 23 µm spot on the sample across an energy range of 5–18 keV [**?**]. Over the past decade, the beamline has provided over 4000 hours of beamtime annually for MX research, contributing to the determination of more than 4100 protein structures [**?**], including several related to COVID-19 pathogenesis [**?**] and others concerning antibodies, specific drugs, and vaccines for COVID-19 [**?**]. Both academic institutions and commercial companies have benefited from the stable and efficient operation of the beamline [**?**].

In recent years, growing demand for microcrystallography has driven the development of smaller beamlines with higher flux densities as a new direction for

MX research [?]. Studies have shown that micrometer-sized X-ray beams can reduce radiation damage to protein crystals because the energy deposition rate per unit mass of irradiated crystal decreases significantly for beam sizes smaller than 15 µm, with optimal sizes as small as 5 µm [?, ?]. Another advantage of highly brilliant micrometer-sized beams is improved diffraction resolution for small crystals, which can accelerate crystal screening in some cases [?]. To address these challenging protein crystal structures, several approaches have been proposed to reduce the beam spot size at beamlines [?, ?]. As part of the SSRF Phase II project, beamline BL17U1 was redesigned for microfocusing in early 2019, decommissioned on February 8, 2021, and rebuilt as BL02U1.

The new beamline utilizes one of two canted undulators sharing a straight section in sector 02 of the SSRF storage ring. The shorter undulator and canted beamline layout result in a more limited energy range for the delivered X-rays. The total beamline length is approximately 45 m, including the front end and experimental hutch. Following rapid installation and alignment, the relocated beamline was completed on May 31, 2021.

2. Beamline

The key optical components comprise an undulator, a monochromator, and a focusing mirror. As a canted-layout beamline, the proximity to the adjacent beamline must be considered, which constrains the placement of optical components and experimental stations. To increase the separation distance, two flat horizontal reflecting mirrors (HRM) are positioned downstream of the double-crystal monochromator (DCM).

2.1 Source

BL02U1 and BL02U2 share a straight section in sector 02 of the SSRF, a third-generation light source featuring a 3.5 GeV storage ring with a circumference of 432 m. The upstream undulator (02U1) that delivers photons to BL02U1 is canted inboard by 3 mrad relative to the storage ring, while the downstream undulator (02U2) is canted outboard by 3 mrad, resulting in a total canting angle of 6 mrad between them.

Based on the storage ring's emittance of 4.03 nm-rad, the X-ray source exhibits a size of 386 µm (FWHM) and divergence of 80 µrad (FWHM) horizontally, and 26 µm (FWHM) and 23 µrad (FWHM) vertically.

The beamline source is a 1.52 m long in-vacuum undulator (IVU) comprising 69 periods of NdFeB magnets, each 22 mm in length. Under current operating conditions, the IVU has a minimum gap of 6 mm, a peak magnetic field of 0.902 T, and a maximum K value of 1.81. The fundamental harmonic energy ranges from 2.0 to 5.1 keV when the IVU gap is tuned between 6–30 mm. The undulator phase error is approximately 1.7° (rms) across the entire gap range. The IVU generates a maximum total power of 2.74 kW, of which only 65 W is confined within the central cone accepted by the beamline (100 µrad horizontally

× 50 µrad vertically). At an IVU gap of 7.375 mm, the undulator delivers X-ray photons at 12.6 keV with a flux of 1.94$×10^{14}$ phs/s/0.1%BW in the central cone.

2.2 Beamline Optics

The optical design was optimized to accommodate the canted layout while delivering maximum photon flux in a focused beam smaller than 20 µm, covering a photon energy range of 6–16 keV, achieving an energy resolution of 2$×10^{-4}$, and maximizing the working distance at the experimental station. The main optical components along the beamline include the white-beam slit, white-beam scanning wire, DCM, first diagnostic screen, first HRM, second HRM, second diagnostic screen, beam position monitor (BPM), monochromatic-beam slit, and Kirkpatrick–Baez (K-B) focusing mirror pair, as illustrated in Fig. 1 [Figure 1: see original paper].

The white-beam slit is located 20.5 m from the undulator, defining the beamline acceptance angle as 0.1 mrad × 0.05 mrad (horizontal × vertical). To withstand heat loads up to 1500 W, the absorber is fabricated from tantalum with a sloped incident surface that accepts the beam at a grazing angle of 2° to reduce power density, and is water-cooled to protect against thermal damage.

The monochromator employs a vertical geometry. To cover the 6–16 keV photon energy range, a pair of Si(111) crystals in a (+n, -n) arrangement monochromatizes the beam without dispersion. The Bragg rotation axis carries both crystals, with the first crystal at the rotation center. The exit beam position is fixed by translating the gap between the crystals. The second crystal is sufficiently long to accommodate beam motion during Bragg angle variation, eliminating the need for a second translation stage. Two piezo-positioners mounted on the second crystal enable fine pitch and roll adjustments.

The reflecting mirrors for the two HRMs, located at 28 m and 30 m, were manufactured with identical geometry for simplified maintenance and cost efficiency. Each HRM operates at a grazing angle of 3.5 mrad and is coated with rhodium, providing reflectivity greater than 89% across the 6–16 keV energy range.

The monochromatic beam slit at 35.8 m defines the acceptance angle for the downstream focusing system. The slit blades consist of two L-shaped tantalum blocks facing each other, each driven by two perpendicular motors for horizontal and vertical motion. The blocks can be moved to overlap and completely block the beam.

Two elliptical surface mirrors with fixed curvature, positioned at 40.575 m and 41.845 m, form a K-B mirror pair that focuses the beam at the sample position (43.245 m) with demagnifications of 15.2 (vertical) and 29.89 (horizontal). As a compromise between mirror acceptance angle and experimental station working distance, each mirror operates at a grazing angle of 4 mrad, which limits the reflectivity of the rhodium coating for photon energies above 16 keV but enhances

photon flux at 12.6 keV.

A white-beam scanning wire upstream of the DCM and two diagnostic screens downstream of the DCM are used for beam commissioning. The scanning wire comprises two crossing wires oriented at 45° in a plane perpendicular to the beam, enabling simultaneous photoelectric measurements in both horizontal and vertical directions. Diagnostic screens equipped with YAG:Ce scintillators downstream of the DCM and second HRM facilitate monochromatic beam analysis.

Two BPMs at 32.9 m and 39.9 m monitor monochromatic beam position and direction. These backscattered photodiode QBPMs from FMB Oxford each contain four diodes detecting scattered radiation from two switchable metal foils (0.5 µm nickel and 0.5 µm titanium) for photon detection across different energy ranges.

2.3 Beamline Specification Measurement

Through precise alignment, the beamline efficiently delivers photons from the undulator to the sample. With the undulator gap set to 7.375 mm, the photon flux spectrum spans 11–13 keV, corresponding to the 5th order harmonic of the undulator, as shown in Fig. 2(a) [Figure 2: see original paper].

Energy resolution was evaluated by measuring the absorption spectrum at the Cu K-edge, shown in Fig. 2(b) [Figure 2: see original paper]. The absorption edge characteristics indicate an energy resolution better than 2$×10^{-4}$.

Beam profiles were measured using knife-edge scans. At the sample position, the beam exhibited horizontal and vertical profiles with FWHM values of 11.6 µm and 4.8 µm, respectively, as shown in Fig. 2(c) [Figure 2: see original paper].

Accounting for the undulator tuning curve, absorption in the Be window, and residual air path to the sample, the photon flux at the sample position exceeds 10^{12} phs/s across the 6–16 keV energy range. Flux measurements were performed at 200 mA storage ring current and normalized to 300 mA, as shown in Fig. 2(d) [Figure 2: see original paper].

With its single-stage focusing geometry, beam instability arises from vibrations of the source, DCM crystals, and mirrors, manifesting as beam spot jitter and flux fluctuations. A fluorescence-based beam position monitoring device [**?**] measured beam spot vibrations at 100 Hz sampling rate over 10 s. An ionization chamber with high-frequency readout electronics positioned downstream of the sample measured flux fluctuations at 100 Hz over 10 s. The results show maximum vibrations occurring at 8–9 Hz, as depicted in Fig. 3 [Figure 3: see original paper]. The liquid-nitrogen supply pump for the DCM, operating at 28 Hz, contributed minimally to vertical vibrations. Beam position stability (rms) was 0.6 µm horizontally and 0.5 µm vertically, while flux stability (rms) was 0.34%.

All beamline specifications are summarized in Table 1 . At the sample position, the photon flux at 12.6 keV reaches 4.5$×10^{12}$ phs/s for a spot size of 11.6 µm × 4.8 µm, with beam divergence of approximately 1.3 mrad × 0.25 mrad.

3. Experimental Station

Equipment in the experimental station was rebuilt to accommodate the canted beamline layout, as shown in Fig. 4 [Figure 4: see original paper]. Compact and opposing designs were implemented for the diffractometer and sample changer to prevent interference from the adjacent canted beamline piping. The experimental station provides a working distance of 744 mm between the HRM exit Be window and sample position, accommodating a beam conditioning box on the diffractometer. This box contains a KEI-AT20R attenuator from Kohzu for photon flux control, a 3.3 cm ionization chamber for incident flux monitoring, and a shutter for exposure timing.

3.1 Detector

The detector is a Dectris Eiger2 S 9M capable of frame rates up to 40 Hz. It features 3108 × 3262 pixels, each 75 µm × 75 µm, providing a total detection area of 233 mm × 245 mm. The experimental station layout supports detector-to-sample distances of 150–750 mm, enabling a maximum detectable 2 angle of 39.2° when the detector center aligns with the beam.

3.2 Diffractometer

The rebuilt experimental station employs a custom-built diffractometer named Sealion, shown in Fig. 4 [Figure 4: see original paper]. It consists of a one-axis air-bearing rotation motor, on-axis microscope, collimator, beamstop, and mounting ports for cryostream and fluorescence detectors.

The on-axis microscope comprises a 10× objective lens, 90° reflecting mirror, 12.5:1 zoom lens, and 1× camera tube with a 1/2 CCD camera. Two 2 mm diameter holes drilled through the objective lens and reflecting mirror are precisely aligned to allow beam passage. The microscope achieves resolutions up to 900 lp/mm within a 0.14 mm × 0.19 mm field of view at maximum magnification, and 270 lp/mm within a 1.7 mm × 2.3 mm field of view at minimum magnification, with a 34 mm working distance for sample mounting.

The collimator consists of two tantalum blocks with 50 µm and 300 µm apertures to reduce stray radiation.

3.3 Automation

A custom automatic sample changer called Swordfish handles sample mounting. It features a 6-axis robot arm, gripper, dewar accommodating 21 uni-pucks, and a gas-liquid phase separator for liquid nitrogen supply. The data analysis

pipeline Aquarium [**?**] enables automatic processing of raw data images immediately after collection.

3.4 User Interface

The custom web-based user interface Finback is shown in Fig. 5 [Figure 5: see original paper]. It displays key experimental information at the top, including electron beam current, photon energy, photon flux, sample temperature, hutch humidity and temperature, sample orientation angle, and detector distance. The robot control command module on the left side also shows sample information, with a goniometer sensor indicating sample mounting status. The central window provides an interactive interface for sample centering, moving the sample to cross-hairs when clicked in the microscope view. The data collection control module on the right lists all key experimental parameters for single-image tests or complete dataset collection.

3.5 Data Collection

The beamline delivers a brilliant beam with flux density exceeding 10^{10} phs/s/μm^2 to the sample, which can cause significant radiation damage and destroy crystals within seconds even at 100 K. Therefore, appropriate data collection strategies using either beam attenuation or short exposure times are essential. Short exposure times require precise timing synchronization among the goniometer, shutter, and detector. The experimental station supports sampling rates up to 40 Hz, enabling a minimum exposure time of 0.025 s per image (40 images per second). To verify reliability, comparative experiments were designed using six thaumatin crystals, with each crystal exposed three times at different locations using varying exposure times and transmittances (Table 2). Transmittance was inversely proportional to exposure time to maintain constant dose rate, with exposure sequences reversed for each crystal to prevent radiation damage from affecting data consistency. Analysis showed Rmerge values of approximately 0.04 for the inner shell of each dataset, with no significant quality differences between long and short exposures. However, short exposure times with high-transmittance beams substantially improved experimental efficiency.

4. Productivity

BL02U1 has been operational for users since June 2021, providing 4200 hours of beamtime as of February 2023. A total of 84 structures determined using this beamline have been deposited in the PDB (http://www.pdb.org), including protein, DNA, and RNA structures.

4.1 Complex Structure: RBD-hACE2

The Omicron and Delta variants represent two of the five “variants of concern (VOC)” defined by the World Health Organization (WHO). Omicron has spread

to 128 countries and regions worldwide, while Delta remains the most contagious variant to date. Understanding how these mutants recognize receptors and invade cells is critical for vaccine and drug development. Gao et al. determined the crystal structures of hACE2 in complex with RBDs from Omicron and Delta variants at 3.0 Å resolution, revealing rearrangements in the interaction interface and altered binding capacity resulting from the mutations [**?**].

4.2 Anti-Infective Therapy

The clpP gene is highly conserved across species. Abnormal activation of bacterial ClpP represents a promising strategy for discovering new antibiotics, though developing selective Staphylococcus aureus ClpP activators that do not interfere with human ClpP function remains challenging. By determining crystal structures, Yang's group identified (R)- and (S)-ZG197 as highly selective S. aureus ClpP activators [**?**]. Key structural elements in human ClpP, particularly W146, and their interaction with a C-terminal motif play crucial roles in activator recognition. These findings demonstrate that species-specific S. aureus ClpP activators are promising therapeutic agents for staphylococcal infections.

4.3 Methyltransferase Ribozyme

Ribozymes catalyze a limited range of chemical reactions, including site-specific methyl transfer. Huang's group determined the crystal structure of a methyltransferase ribozyme at 2.3 Å resolution, revealing a three-channel architecture and RNA folding that creates a specific binding site for the methyl donor substrate [**?**]. The crystal belonged to space group P2$*{2}*2{1}$ with unit cell dimensions a = 50.38 Å, b = 52.5 Å, c = 99.9 Å (PDB entry: 7V9E). Diffraction data were collected at 0.97918 Å wavelength and phased using single-wavelength anomalous dispersion with eleven barium atoms.

5. Discussion and Conclusion

As the first macromolecular crystallography beamline at a third-generation synchrotron facility in mainland China, BL17U1 operated for over a decade as the most important data collection platform for Chinese structural biologists. To enhance performance, the beamline was upgraded and reconstructed within a remarkably short timeframe.

BL02U1 was designed to overcome the constraints of the shortened straight section and canted beamline layout while maintaining high photon flux and an appropriate energy range for macromolecular crystallography. By focusing the beam to ~10 µm, it provides substantially improved photon flux density. The experimental station's use of in-house developed key equipment and control/data acquisition software greatly facilitates operation and maintenance.

Benefiting from high photon flux density and beam stability, experimental efficiency has improved dramatically, reducing data collection times from minutes

to seconds. The high-performance, reliable operation of BL02U1 has enabled determination of numerous protein structures using data collected at this beamline.

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Note: Figure translations are in progress. See original paper for figures.