Simulations of kilohertz serial femtosecond crystallography with a compact X-ray light source

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Introduction

X-ray free electron lasers (XFELs) have allowed for the use of very short high intensity x-ray pulses for crystallographic experiments. However, with only 5 XFELs operational in the world, and costs on the order of a billion dollars to construct new ones, access to these resources remains very limited. New x-ray sources are being developed to meet this need for accessibility, with the compact x-ray light source[1] (CXLS) currently under assembly at Arizona State University, and the compact XFEL[2] (CXFEL) offering even further improvements on the x-ray source while remaining small and cheap. These new sources are expected to greatly increase access for structural biologists looking to perform serial femtosecond crystallography (SFX) experiments

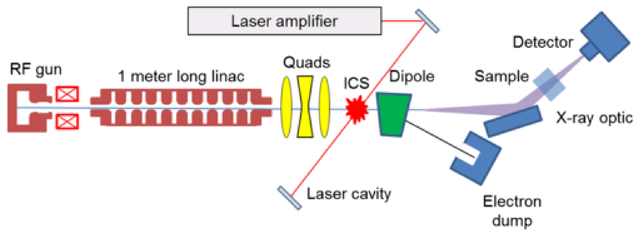

Figure 1: A diagram of the CXLS setup. The size of the light source is small enough to be highly accessible for widespread medical and scientific use. X-ray divergence on the order of several mrad leads to shorter beamlines. This image has been adapted from Graves *et al.* 2014 as per the Creative Commons Attribution 3.0 License.

	LCP-SMX @ ALS 8.3.1	LCP-SFX @ LCLS	CXFEL @ ASU	CXLS @ ASU
flux	1E12 photons / **sec**	6E9 ph / **shot**	1E11 ph/sec	5E9 ph/sec **(1E11)** 1E8 ph/pulse **(1E8)**
beam size	100 µm (hor)	1 µm diameter	0.25 – 0.7 µm	3x3 µm
beam divergence	2 x 0.34 mrad	< 3 µrad	0.1 - 0.6 mrad	4 mrad
energy	11 keV	9 keV	8 keV	1-40 keV
bandwidth	0.014 % (Si 111)	0.1% (SASE)	0.01 – 1 %	0.1% **(5%)**
detector	Pilatus 6 M	CSPAD	EIGER and …?	EIGER …?
frame rate	25 Hz	120 Hz	1000 Hz	1000 Hz
pulse duration	40 **ms** exposure	20-50 fs	0.4 - 40 fs	< 500 fs
LCP jet diameter	100 µm	50 - 75 µm	50 µm (proposed)	50 µm (proposed)
LCP jet flow rate	100 µm / s	2 mm/s	10 µm / 1 ms = 10 cm / s	10 µm / 1 ms = 10 cm / s

Table 1: SFX experimental parameters at various x-ray sources. Numbers in red are for the CXLS operating at 5% bandwidth. The CXFEL has the most tightly focused beam, but a greater divergence compared to LCLS.

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Conventional vs. Serial Crystallography

X-ray macromolecular crystallography (MX) is the dominant technique for protein structure determination. In a typical MX experiment (Fig. 2), the sample is mounted on a goniometer, exposed to an X-ray beam, and a 2D detector records the resulting diffraction pattern. The crystal is rotated to sample various orientations so that 3D structural information can be determined. However, radiation damage to the crystal severely limits the dosage that can be administered before significantly damaging the molecular structure. Cryo-cooling is often used to slow radiation damage, raising questions about structural artifacts caused by cooling, and hindering studies of protein dynamics.

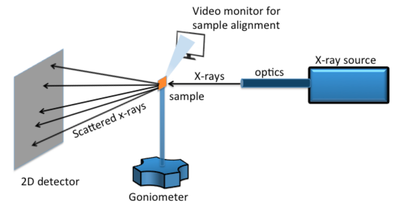

Figure 2: A diagram for a conventional crystallography experiment (Barron, 2018). The crystalline sample is mounted onto a goniometer in a known orientation and exposed to X-ray radiation which diffracts onto a detector. The crystal is rotated to sample various orientations.

The invention of the 'diffraction-before-destruction' method[3] allowed significantly higher incident intensities by using pulses on the order of 40 femtoseconds (see Table 1) to outrun most of the radiation damage. This provides higher resolution data, even at room temperature, from extremely small crystals. However, since the X-ray pulse at these intensities annihilates the crystals, several thousands of patterns, from different crystals in random orientations, must be taken to acquire a full 3D data set required for structure determination. The CXLS and CXFEL will enable such experiments, and much more, at ASU.

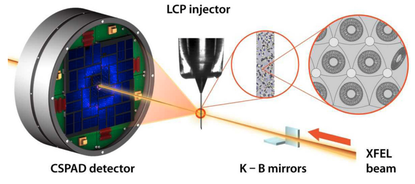

Figure 3: A diagram of a standard SFX experiment (Liu 2013). The incoming X-ray radiation intersects a liquid jet carrying many small crystals in random orientations. The X-rays diffract onto a detector, which represents a slice of reciprocal space. The inset shows an example of a high viscosity medium for SFX sample delivery.

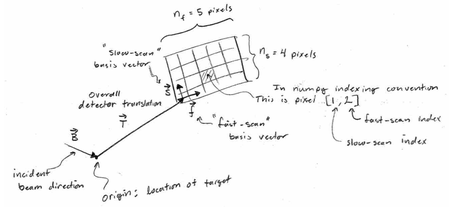

Figure 4: A diagram of the geometry setup in *bornagain*. Each detector pixel's position is specified by the T, S, and F vectors, and each pixel has a q vector associated with it. In *mcsim*, these q vectors are jittered by varying the X-ray wavelength, incident beam vector B, and small rotations of crystallites to simulate mosaic spread.

X-Ray Diffraction Simulation

To evaluate the feasibility of the CXLS and CXFEL for crystallography experiments, we developed diffraction software, called *bornagain*, to simulate crystallography experiments for the two sources. Although other software like CrystFEL's *pattern_sim*, *MLFSOM* and *nanoBragg* exist, *bornagain* is a Python package containing many useful classes for describing X-ray beams, detector geometries, target samples and GPU-based scattering calculations. The simulated X-ray diffraction is based on the Born approximation. A program within *bornagain* called *mcsim* simulates SFX experiments using a large set of parameters. It uses Monte Carlo style simulation of three parameters which affect the spot size: beam divergence, spectral dispersion, and mosaic spread of the crystal. The geometry used by *mcsim* is depicted in Figure 4, and the GUI for *mcsim* is shown in Figure 5.. Characteristic diffraction patterns output by *mcsim* are shown in Figure 6.

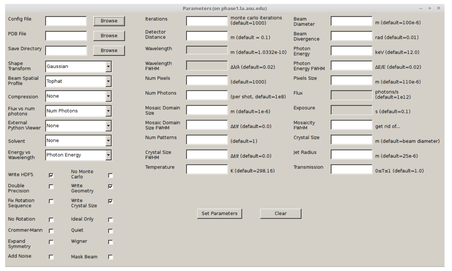

Figure 5: A screenshot of the *mcsim* GUI, which lists many of the parameters implemented in *mcsim*.

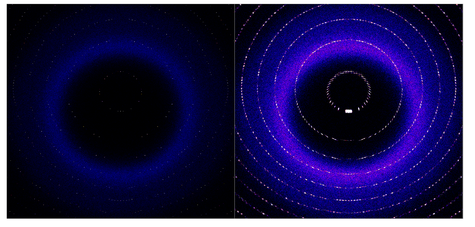

Figure 6a and 6b: Simulated diffraction patterns with a 20 micron lysozyme crystal in a 60 micron diameter water jet. Beam parameters used are for CXLS, with the left hand side showing 3 µrad divergence FWHM and the right hand side showing 8 mrad divergence FWHM.

References

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2. Graves, W. S. *et al.,* ASU Compact XFEL. Paper presented at: FEL 2017. Proceedings of the 38th Intl. FEL Conference; 2017 Aug. 20-25; Santa Fe, NM, USA.
3. Chapman, H. N. *et al.,* Phil. Trans. R. Soc. B 2014 369 20130313. (2014)
Figure 2: Image reprinted from P. M. V. Raja, A. R. Barron (2018) Physical Methods in Chemistry and Nano Science as per the Creative Commons Attribution License.
Figure 3: Image reprinted with permission from AAAS.

Acknowledgements

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