

*Imaging protein dynamics with an X-ray laser*

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In the progression of interest from molecular structure to function and new relevant techniques, the free-electron X-ray laser (XFEL) occupies a unique niche with its ability to obtain time-resolved atomic-resolution images of hydrated proteins under conditions of negligible radiation damage. This allows us to image molecular machines at work under physiological conditions, in the correct thermal bath, by using short pulses, instead of cooling, to reduce radiation damage. In its second five years, the NSF-funded BioXFEL 7-campus consortium in the USA aims to build on our preliminary results in this field, which I will review.

Femtosecond X-ray snapshots are recorded at 120 Hz before the onset of damage in both pump-probe and mixing-jet experiments which out-run radiation damage (see [1] for a review). Three time-resolved modes are in development - serial crystallography (SFX), single-particle studies (eg one virus per shot) and fast solution scattering (FSS). For SFX, where atomic resolution is possible using micron-sized crystals, the Schmidt group [2] have led efforts to obtain "movies" of the cis-trans isomerisation reaction in photoactive yellow protein with 200 fs time resolution, the same process which occurs in the first event in human vision. I will also review experimental work aimed at snapshot imaging of enzyme-substrate reactions over much longer time-scales, using the mixing-jet technology we are developing for that purpose, and show preliminary results. I'll also summarize progress on the ambitious single-particle project, a large collaboration at the Linac Coherent Light Source at the US DOE SLAC laboratory, aimed at time-resolved imaging of single particles, and spectacular results from the Chapman group using diffuse scattering to improve resolution in SFX [3].

New XFEL machines are about to come on-line worldwide, in Germany, South Korea and Switzerland, in addition to the two current machines in USA and Japan. I'll also summarize the exciting research opportunities the unique capabilities these machines will soon offer for structural biologists, including applications to GPCR drug targets.

[1] Spence, J.C.H. (2017) in: *Advances in Imaging and Electron Physics*. Ed. P. Hawkes. Elsevier. New York In press.

[2] Pande, K et al. (2016) *Science*. Vol 352, p. 725 - 729 .

[3] Ayyer, K et. al. (2016) *Nature*, 530, p. 202 - 205.

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