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book reviews

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Biology with Free-Electron X-ray Lasers: Papers of a Discussion Meeting Issue, *Philos. Trans. R. Soc. B*, 17 July 2014, Vol. 369, No. 1647, edited by John C. H. Spence and Henry N. Chapman. London: The Royal Society

In October 2013 a two-day Royal Society Discussion Meeting entitled 'X-ray Lasers in Biology' was held in London, organized by Professor Henry Chapman and Professor John Spence, and whose event details were as follows: '*The recent invention of the hard X-ray laser (XFEL) has opened new vistas for structural and dynamic biology. This meeting will review the latest work, outline opportunities for future research, and describe the new techniques (snapshot SAXS, serial nanocrystallography, single-particle imaging) which take advantage of the atomic spatial resolution and femtosecond time resolution of the XFEL*'. This was immediately followed by a meeting at The Royal Society's Chicheley Hall, in rural Buckinghamshire, whose details were: '*[to] bring together leaders in the development of new techniques for the study of molecular structure and interactions in biology using the recently invented hard X-ray laser. Topics will include time-resolved protein nanocrystallography, femtosecond wide-angle X-ray diffraction, sample delivery devices, data analysis and diffraction theory, and detector systems*'. The speakers at the two meetings were invited to submit papers for this special issue of *Philosophical Transactions*, resulting in 26 papers being published in this volume.

In the Forward to the Proceedings volume, John Spence and Henry Chapman recognize the late Dame Professor Louise Johnson FRS in her role as proposal submitter with them to The Royal Society for this event and also pay tribute to 'her support for this field at a time when it had many sceptics'. Indeed the review article by Louise, with Liz Duke (formerly at SRS Daresbury Laboratory and now at Diamond Light Source) (Duke & Johnson, 2010), entitled 'Macromolecular crystallography at synchrotron radiation sources: current status and future developments', includes a detailed, and indeed I would observe sparkling, section reviewing 'Free electron lasers (FELs): ultra-bright sources for the future'.

From the outset the X-ray laser arrival has clearly been very exciting. In general, though, the biological crystallography community reaction to the X-ray laser was as controversial as whether synchrotron radiation would be useful in protein crystallography! [see the first sentence of Phillips *et al.* (1976)].

Synchrotron radiation indeed has had a profound impact on the field of protein crystallography with approximately 90% of X-ray single-crystal structure determinations being from synchrotrons (see http://biosync.sbkb.org/). Will X-ray lasers have as big an impact? Certainly, in terms of hardware on the ground, national and supra-national facilities for X-ray users are appearing apace; X-ray free-electron lasers have been constructed at SLAC (the LCLS) and at SPring-8 (SACLA), with the European facility (EuroXFEL) under construction at DESY in Hamburg, to mention just three. In addition, there will be a growing number of national machines as use of softer X-rays (up to 5 Å wavelength) rather than harder X-rays can still allow very good resolution biological diffraction studies, with stronger scattering than the usual hard X-rays of 12 keV, and yet be cheaper machines to build [Helliwell (2004) and also see the articles in the volume by Spence *et al.* and by Chapman *et al.*]. These machines, based upon long linear accelerators and long undulator sections, have pulse lengths of $\sim$10 fs with some ten orders of magnitude larger peak (*i.e.* instantaneous) spectral brightness than the storage-ring-based sources, with the latter having a higher integrated flux delivery.

Time-resolved Laue protein crystallography at the ESRF opened up the whole new field of sub-nanosecond crystal structure analyses. There are a limited number of such time-resolved studies in the literature. Why is this? Firstly, crystal lattice interactions can block the necessary structural changes for a given biochemical reaction to proceed. Secondly, crystal size determines its scattering strength and thereby the required exposure time, clearly increasing as a sample gets smaller. The latter obviously can be at odds with the intrinsic time resolution required to monitor a given molecular structural change; different measuring protocols try to ease past this challenge, such as the Hadamard measuring sequence (Yorke *et al.*, 2014) or the simpler approach of crystal-to-crystal averaging at equivalent time-slices (Helliwell *et al.*, 1998). Meanwhile the X-ray laser now gives us femtosecond duration pulses, typically 10 fs up to $\sim$50 fs. Their use is attractive for the fastest time-resolved protein crystallography studies as is beautifully and excitingly described in this volume, for example by Keith Moffat, Richard Neutze, Petra Fromme and V. K. Yachandra and their co-authors. It has been proposed that single molecules could even be studied, which would free us from the crystal lattice restrictions referred to above.

Overall this Proceedings volume gives an extensive compilation of X-ray laser science applied to structural biology, including, as mentioned above, various time-resolved structural studies. There are 26 publications in the volume, each one carefully introduced by Spence and Chapman in their Forward. These articles are organized into two parts, firstly covering Biology and secondly covering Technique development.

Unfortunately there are two aspects missing: firstly, some key talks are not in the volume and, secondly, the tradition of The Royal Society to record the discussion is not followed. The missing talks are obviously a pity, but those speakers will no doubt prominently record their latest results soon, but to not record the discussion in this volume is a real loss. At times this discussion was very vigorous, and sparkled. For those that were there like myself the discussions are etched upon my memory. However, for those not present I commend that The Royal Society reintroduce the publication of the discussion after talks. (For those unfamiliar with how this works, those members of the audience who wish to write out their questions or observations do so on a simple form and speakers have chance to put in writing their answers.)

A potential weakness of any conference proceedings is hasty refereeing and incomplete revisions. However, in this case the efforts

of The Royal Society publishing officers and editors appear to have been thorough.

Probably the most challenging aspect of all X-ray laser (anticipated) science is the extraordinary vision to reach 'diffraction from a single molecule' (Neutze *et al.*, 2000). In the article in this volume by Altarelli & Mancuso, of the EuroXFEL, they affirm that: '*It is expected that the EuroXFEL (under construction in Hamburg) with its unique features of the source and the advanced features of the instrumentation will allow operation modes with more efficient use of sample materials, faster acquisition times, and conditions better approaching feasibility of* ***single molecule*** *imaging.*' [The use of bold is mine.]

To sum up, this Proceedings volume, albeit with the core limitation of a missing discussion, is an excellent and broad coverage of this vigorously developing field of X-ray lasers in biology.

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John R. Helliwell
School of Chemistry, University of Manchester, Manchester M13 9PL, UK