Preface for Special Issue on Biology with X-ray Lasers 2

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In 1970, Breedlove and Tramel and later Solem and Baldwin (1982) suggested that the problem of radiation damage in structural biology might be solved by destroying the sample with a short pulse of intense radiation, because a few photons should be scattered before the onset of radiation damage. Following pioneering work by many, this outlandish idea is now a reality (see, e.g., Neutze *et al.*, 2000; Gaffney and Chapman, 2007; Spence, 2008; Chapman *et al.*, 2011; and Boutet *et al.*, 2012)). This Special Issue, the proceedings of a meeting organized by the NSF Science & Technology Center for Biology with X-ray Lasers, constitutes a timely report on the latest developments, and a tantalizing view of what is yet to come.

There has been progress on all fronts: instrumental, technical, and scientific. These developments have transformed heroic "campaigns" to focused experiments with acceptable requirements in beamtime and materials. Structure determinations, which in 2011 took 18 months from experiment to submitted paper, can now be completed in a few weeks, with a factor of 10 less beamtime, a factor of 4 less time for data analysis, and a factor of 100 less protein. Critical steps, such as de novo structure determination, have been demonstrated (Barends *et al.*, 2014), and a wide variety of alternative approaches are under development (see this issue). The sheer range of systems shown to be amenable to Serial Femtosecond Crystallography has left little doubt about the validity of this approach, and its ability to deliver hitherto inaccessible insights into difficult systems and processes. The experimental and algorithmic methods developed for X-ray laser applications are increasingly migrating to synchrotrons.

Recent experiments reported here also demonstrate the power of X-ray laser methods for time-resolved work, where the use of protein nanocrystals smaller than the optical absorption length of the pump light has produced the largest differences in a density map ever seen (Tenboer *et al.*, 2014). Indeed, the "diffract-before-destroy" approach is now poised to extend serial femtosecond methods to non-cyclic processes, including enzymology, and sub-picosecond timescales inaccessible at synchrotrons. For longer times, mixing jets using nanocrystals smaller than diffusion lengths promise to allow diffusive mixing for the first time. More generally, the elucidation of femtosecond processes linking chemistry to biology is an enticing prospect under active investigation.

The promise of determining structure without crystals has proved difficult to realize, but initial results are now emerging (Ekeberg *et al.*, 2015), with more anticipated from an international collaboration involving many leading groups (Aquila *et al.*, 2015). Recently, electron-based single-particle methods have begun to produce conformational movies and energy landscapes (Dashti *et al.*, 2014) but remain constrained by the number of available snapshots. The X-ray laser has the capability to produce extremely large datasets under physiological conditions. As reported in this issue, it is imperative to develop means for compiling large datasets of useful snapshots obtained under tightly controlled and reproducible imaging conditions, and to correct any remaining imaging artifacts algorithmically.

In a short time, the application of X-ray lasers to biology has moved from a debate on validity to a rapidly growing demonstration of unprecedented access to a treasure trove of new information. The reports in this Special Issue make it clear that the best is yet to come.

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