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Macromolecular structure determination using X-ray FELs

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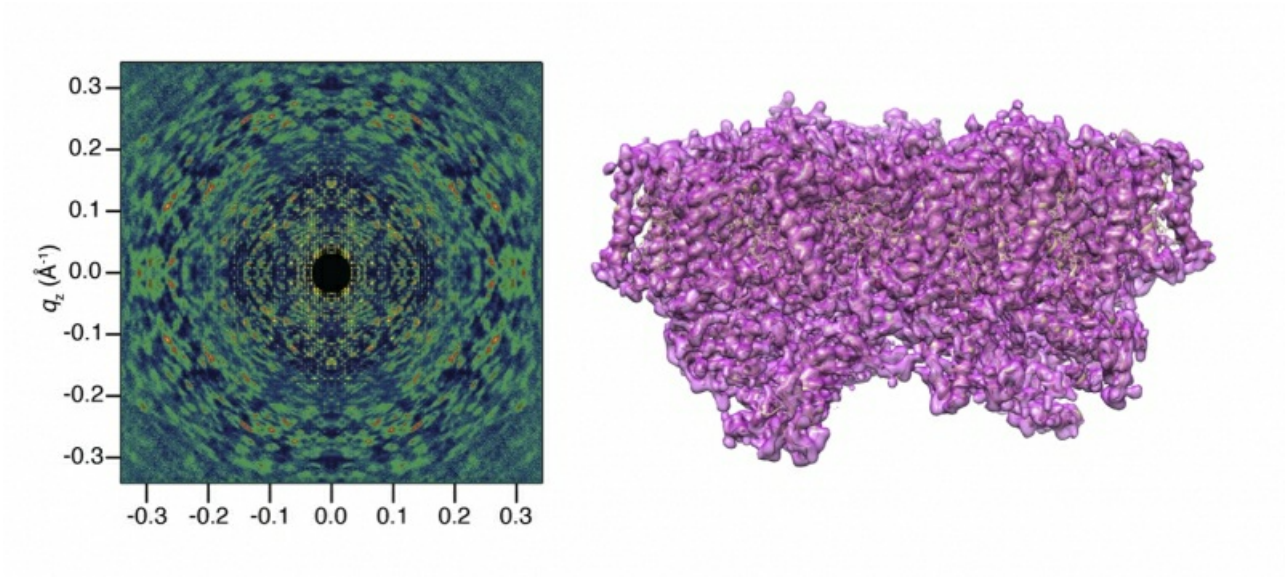
The pulses from X-ray free-electron lasers are a billion times brighter than the brightest synchrotron beams available today. When focused to micron dimensions, such a pulse destroys any material, but if the pulse is short enough then the effect on the scattering pattern due to this interaction can be avoided. This mode of "diffraction before destruction" yields high-resolution structural information from proteins that cannot be grown into large enough crystals or are too radiation sensitive for high-resolution crystallography [1]. This has opened up a new methodology of serial femtosecond crystallography for radiation damage-free structures without the need for cryogenic cooling of the sample. The ability to record diffraction of biological materials using extremely intense and spatially coherent X-ray pulses has also been of interest for imaging non-crystalline samples, such as virus particles and single molecules [2]. Such single- particle imaging is being developed but is challenging due to the very low signal levels (compared to background sources) of tiny non-crystalline particles. There is a very significant advantage of measuring continuous diffraction from non-crystalline objects since it contains vastly more information than is encoded by the Bragg peaks in diffraction patterns of crystals. The increase in information makes it possible to directly determine the diffraction phases, overcoming the well-known phase problem in crystallography.

One way to address the low diffracted signals of single molecules is to place many oriented particles into the beam so that their diffraction signals sum to give a measurable pattern. Laser fields can be used to orient molecules, for example. Disordered crystals also provide a way to obtain a large number of oriented molecules at high density. Translational disorder of molecules in a crystal gives rise to random phases in the scattering from those molecules that destroy the formation of Bragg peaks, and instead gives access to their continuous diffraction patterns. We have found that crystals of large macromolecules such as membrane proteins possess such translational disorder. This has previously limited the achievable crystallographic resolution (largest scattering angles of Bragg peaks) in many cases, but we have managed to measure the much weaker continuous diffraction from crystals of photosystem II, shown in in the figure, that extends far beyond visible Bragg peaks. We have reconstructed an image of this macromolecular complex using the phasing approach of single-molecule diffraction [3].

[1] Chapman, H.N. et al. (2011). Nature 470, 73–77.
[2] Siebert, M. M. et al. (2011). Nature 470, 78–81.
[3] Ayyer, K. et al. (2016). Nature 530, 202–206.



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