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EDITORIAL

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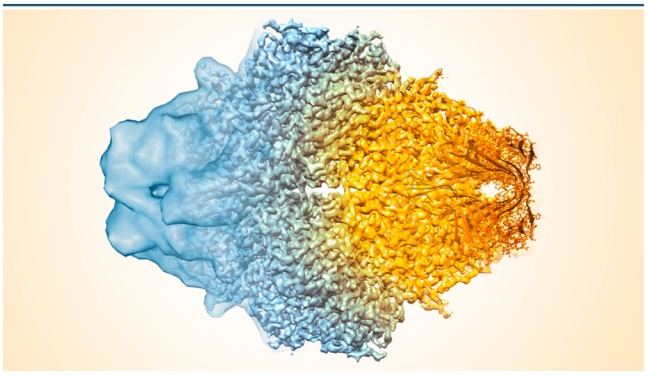
Atoms out of Blobs: CryoEM Takes the Nobel Prize in Chemistry

I am often asked by students and colleagues, what is the definition of "chemical biology"? The discussion often leads to where the boundary lies between the two fields, and, for me, chemistry starts when the conversation focuses on molecules and atoms. So I have come to view "chemical biology" as the study of chemical matter in biological settings. This year's chemistry Nobel Prize, awarded to Jacques Dubochet (University of Lausanne), Joachim Frank (Columbia University), and Richard Henderson (MRC Laboratory of Molecular Biology), recognized the impact that cryo electron microscopy has had on our ability to describe biological assemblies in molecular and, recently, atomic detail. The technique has enabled an unprecedented view of biological structures that have transformed our mechanistic understanding from biology to chemistry.

For over 60 years, microscopes that illuminate samples with short wavelengths of electrons have allowed several varieties of electron microscopy to reveal details of inert materials and fixed samples. But due to the highly destructive nature of those high-energy electrons, scientists thought high-resolution images of sensitive biological samples would be impossible. Rather, X-ray crystallography was the go-to technique for structural data on highly sensitive samples like proteins, and also provided atomic-level resolution that had eluded cryoEM practitioners until quite recently.



Cryo-EM has evolved over the years to now provide atomic resolution shown here with β-galactosidase. Credit: Sriram Subramaniam/NCI.

A major breakthrough in cryoEM occurred in the 1980s when physics experiments in the rapid freezing of water showed a way around the sample destruction process. It was known that frozen samples would fare better in cryoEM, but the ice crystals that typically formed around biological samples resulted in smeary images. Rapid freezing thwarted water crystallization and enabled far better cryoEM images, such as those of the bacteriorhodopsin, the plant light-harvesting complex, and the $\alpha\beta$ tubulin dimer. The door was now open to pursue studies of large multicomponent complexes, membrane proteins, and all kinds of assemblies that defied X-ray crystallography due to size or poor crystallization behaviors.

Landmark cryoEM studies soared in the 1990s, but still the technique was criticized for its lack of atomic resolution. The images showed where individual protein "blobs" were oriented in larger complexes, but the positions of their atoms were impossible to discern. Indeed, cryoEM images of large complexes could only be translated into atomic-resolution structures by modeling in the X-ray structures of their individual component molecules.

Then, in 2013 a breakthrough in detector technology shattered that limitation and cryoEM resolution can now compete with X-ray methods. Indeed, here at *ACS Central Science* we commissioned a 2015 Hub article, "Breaking the Crystal Ceiling", to examine what then were brand new developments. Dozens of high-resolution structures have been solved just in the last year, and we are likely only at the beginning of this cryoEM revolution.

Chemistry as the central science is always going to interface with other disciplines. CryoEM blends aspects of physics, analytical chemistry, and algorithm development in order to advance our understanding of biology, materials, and various dynamic processes. It is a new lens through which to study molecules and atoms, and we proudly embrace this Nobel Prize as an achievement for chemistry.

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Notes

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