Electron Crystallography Methods for Protein Structure Determination

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X-ray diffraction (XRD) has long been a fundamental tool in materials science, structural chemistry, and structural biology. However, despite significant advancements in laboratory X-ray sources and synchrotron technology, a major obstacle in molecular structure determination remains the growth of crystals of sufficient size and quality. The process of crystal optimization is often time-consuming, complex, and requires large quantities of purified material. In many cases, especially with biological macromolecules and pharmaceutical compounds, it is either impractical or impossible.

Electron crystallography methods, such as 3D ED/MicroED and SerialED, offer promising solutions to these challenges. These techniques enable structure determination from crystals with volumes a billion times smaller than those typically used in single-crystal X-ray diffraction (SCXRD). Since 2007, 3D ED has been successfully used to solve the structures of challenging samples—primarily inorganic materials—deemed impractical for traditional X-ray methods. Researchers across several institutions have developed different approaches for data acquisition, such as automated diffraction tomography (ADT, University of Mainz) and rotation electron diffraction (RED, Stockholm University). In 2013, Gonen's lab made a breakthrough by adapting the MicroED technique for determining the structures of macromolecular crystals.

More recently, a new electron crystallography technique called Serial Electron Diffraction (SerialED) has emerged. This method allows high-resolution, low-damage determination of macromolecular crystal structures, without the need for specialized instrumentation.

At the upcoming CeMMP research symposium, I will present our latest findings and offer future perspectives on the field of electron crystallography.