

Electron crystallography – from slow 2D of simple structures to rapid crystal structure determinations in 3D of very complex structures

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Modern electron crystallography started off in the 1960-ies by the work of Aaron Klug and collaborators in Cambridge, UK. At that time the resolution was around 25 Ångström - enough for showing the icosahedral envelopes of spherical viruses. In 1975 Nigel Unwin and Richard Henderson solved the first structure of a membrane protein, bacteriorhodopsin, using Fourier analysis of EM images of 2D crystals of the protein. The resolution was 7 Å.

In parallel, but essentially without contact with the molecular biologists, inorganic structures were also studied by electron microscopy. The resolution of 3.5-4 Å in the 1970-ies was just enough to see metal atoms in oxides. In 1984 we determined the atomic positions of metal atoms in an Nb/W-oxide by EM to an accuracy of about 0.1 Å.

Because of a confused nomenclature regarding the word "phase", the two communities biological and physical, hardly spoke to each other for decades. Crystallographers consider "phase" as crystal structure factor phases, which describe standing waves of electron density in crystals. These waves have wavelengths that correspond to the d-spacings of reflections. In contrast, the physicists studying inorganic compounds by EM, talked about the phases of the electron waves propagating through the crystals. The wavelengths of these waves are determined by the acceleration voltage of the electron microscope used. For 100 kV to 300 kV, these wavelengths are about 0.037 to 0.025 Å. Already by comparing the wavelengths, it is obvious that the two types of phases are different.

Furthermore, the "structure factor phases" are relative to the fixed position of an origin in the unit cell; a position specific for each of the 230 space groups and listed in the International Tables for Crystallography. The "electron wave phases" are relative to the electron wave as it propagates through the crystal at about half the speed of light. Most importantly, the "structure factor phases" are present in the EM images, as Aaron Klug had already explained in the 1960-ies. These phases can be read out from the Fourier transform of an EM image. In contrast, the "electron wave phases" are lost in the EM images. The phases are always lost in diffraction patterns, whether X-ray or electron diffraction.

The confusion as to the presence or not of the phases in EM images was so large that I wasn't invited as a speaker at the first Electron Crystallography Schools organized by IUCr in Beijing 1993 and Bristol 1994, because "Hovmöller confuses the students". As a reaction to this, Xiaodong Zou and I started our own schools of electron crystallography in Stockholm. From a very modest scale with just a dozen participants, these schools grew and became annual. The greatest honour was when we were invited by Lodovico Riva de Sanseverino to arrange one of the IUCr schools in Erice. This has since become a tradition every seven years.

X-ray crystallography has been done in 3D right from the start, when the structure of NaCl was solved by Bragg & Bragg in 1912. But electron crystallography for minerals and other inorganic crystals remained in 2D, limiting the structures that could be investigated. In the 1980-ies, we developed the software program CRISP, based on the methods developed in Cambridge for Fourier analysis of EM images. At that time, the great concern about distorted intensities in electron diffraction patterns due to multiple scattering, hampered the development.

A major breakthrough was the invention of the precession electron diffraction technique by Roger Vincent and Paul Midgley in Bristol 1994. It was obvious already by just looking at the electron diffraction patterns that the intensities now were much closer to kinematical. However, it was still only in 2D. The step into 3D came as a result of improved instrumentation combined with software developments. The electron microscopes could be programmed to take series of hundreds of diffraction patterns in just minutes. The diffraction patterns were recorded on very fast detectors (cameras). Systems with different geometries, but fundamentally similar, were then developed independently by Ute Kolb and her group in Mainz (ADT) and by our group in Stockholm (RED). Data collection that previously required days or weeks, was speeded up first to hours and now to minutes or even seconds.

With the new techniques RED (rotation electron diffraction) and ADT (automatic diffraction tomography), the data quality was also substantially improved. The intensities obtained by electron diffraction are now approaching those by X-ray diffraction. Perhaps even more important than reliable intensities, is the fact that these modern ways of electron diffraction give us (nearly) complete 3D data.

Today, 3D electron diffraction has become a fast and highly reliable method for crystal structure determination. Data is collected as fast as with synchrotrons. Because of the very strong interaction of electrons with matter, even the finest powder diffracts like single crystals. Hundreds of structures have now been solved by electron diffraction. From zeolites and metal-organic frameworks (MOF) to quasicrystal approximants, pharmaceuticals and proteins are solved from sub-micrometer sized crystals, too small even for synchrotrons.

Finally, after half a century of efforts, electron crystallography is no longer a peculiar young brother from the countryside (compared to X-ray crystallography) but a mature science in its own right.

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