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Introduction to electron crystallography

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Everything in Nature, macroscopic or microscopic, inorganic, organic or biological, has its specific properties. Most properties of matter depend on the atomic structures, and many techniques have been developed over the centuries for structure analysis. The greatest of them all, structure analysis of single crystals by X-ray diffraction, X-ray crystallography, was founded in 1912, and remains the most important technique for studying structures of periodically ordered objects at atomic resolution. Electron diffraction of single crystals was discovered fifteen years later by Thomson, Davisson and Germer. The wave property of electrons was exploited in the invention of the electron microscope by Knoll and Ruska in 1932. Since then, electron microscopes have been used in many fields as a tool for exploring and visualising the microscopic world in all its beauty. Between the first blurred images and today's sharp atomic resolution lies seventy years of untiring engineering. More recently, the unprecedented power of computers has made it possible to analyse quantitatively, and even further improve, these images. The amalgamation of electron diffraction and atomic resolution electron microscopy with crystallographic image processing has created a new powerful tool for structure analysis - electron crystallography.

1   The history of electron crystallography

Electron diffraction analysis started early in Moscow Structure analysis of crystals by electron diffraction (ED) was first pursued in 1937-1938, by a group of crystallographers in the former Soviet Union, led by Pinsker and Vainshtein. At that time, neither theories nor techniques for structure analysis of crystals by electron diffraction were available. These scientists put large efforts into designing electron diffraction cameras and developing electron diffraction into a complete and independent structure analysis method. Ten years later the first Fourier map of a crystal structure based on electron diffraction data was obtained by Vainshtein and Pinsker [1]. It was $BaCl_2 \cdot H_2O$ (Fig. 1).
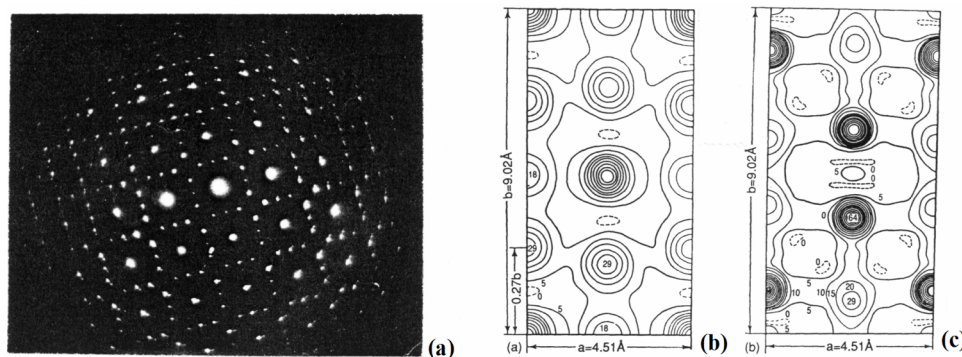

Fig. 1   (a) Electron diffraction of $BaCl_2 \cdot H_2O$ from a twinned crystal. (b) Projection of the Patterson function. The peaks with heights 29 and 18 correspond to the Ba-Ba and Ba-Cl distance vectors, respectively. (c) The Fourier map for the same structure. The strongest peaks with height 64 correspond to the projection of the Ba and Cl ions, while the next strongest peaks, correspond to the projection of the Cl ions and H_2O. From [2].

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For twenty years, the Soviet group used their electron diffraction cameras with relatively low accelerating voltages (<100 kV) to collect electron diffraction data of a large number of structures, such as basic salts, metal nitrides and carbides, semiconducting alloys and clay minerals, as well as some organic crystals. Using this electron diffraction data, they addressed various problems which then could not be solved by X-ray diffraction, such as location of hydrogen atoms in crystals. These studies led to great expectations for the future of electron diffraction. Vainshtein wrote in his book (1956): "*There is no doubt now that electron diffraction may be used for the complete analysis of crystals whose structure is unknown*" [3]. This pioneering work was recently summarised in a review article by Vainshtein, Zvyagin and Avilov [2] (1992).

The method of structure analysis developed by the Soviet group was based on the kinematical approximation that ED intensity is directly related (proportional) to the square of structure factor amplitudes. The same method had also been applied by Cowley in Melbourne for solving a few structures [4-7]. In 1957 Cowley and Moodie introduced a theoretical approach [8], based on physical optics, to the scattering of electrons by atoms and crystals. This was the *n*-beam dynamical diffraction theory. This theory provided the basis of multi-slice calculation which enabled the simulation of dynamical intensities of electron diffraction patterns, and later electron microscope images. The theory showed that if dynamical scattering is significant, intensities of electron diffraction are usually not related to structure factors in a simple way. Since that day, the fear of dynamical effects has hampered efforts to analyse structures by electron diffraction.

Experimental electron diffraction amplitudes, just as X-ray diffraction, do not contain the phase information of the structure factor which is needed for solving unknown structures. Various methods, such as the Patterson method and different trial and error techniques, were used for finding phase information in X-ray crystallography. These methods were used by the Soviet group also for phasing electron diffraction data. In 1953, Hauptmann and Karle introduced the so-called direct methods, for solving the phase problem [9]. The direct methods, combined with the development of computers, accelerated very much the development of X-ray crystallography. In 1976, Dorset and Hauptmann in Buffalo for the first time applied the direct methods to electron diffraction data [10]. This pushed structure analysis by electron diffraction a significant step forward. Using the direct phasing methods, Dorset has successfully phased electron diffraction data of various organic and inorganic crystals. These include aromatic molecules, lipids and other linear molecules and polymers, as well as some of the inorganic crystals previously collected by the Soviet group. His work has shown that electron diffraction, just as X-ray diffraction data, can be used for *ab initio* crystal structure determination.

Electron microscopy can be combined with image processing   At the time when the different phasing methods developed for X-ray crystallography were applied for finding the lost phase information in electron diffraction, DeRosier and Klug in 1968 at the MRC laboratory of Molecular Biology in Cambridge introduced a method of reconstruction of three-dimensional objects from a set of electron microscope images [11]. This 3D reconstruction method is based on the fact that both phase and amplitude information are present in electron microscopy (EM) images and can be extracted from the Fourier transform of images by digitised image processing. They compared the 3D reconstruction method with the structure analysis method in X-ray diffraction and wrote: "*The difference is that the 'phase', which together with the amplitudes of the Fourier components allows the reconstruction of a three dimensional map, is lost in recording the X-ray diffraction data. It is preserved, however, by the focusing of the diffracted electron beam into an image*".

The 3D reconstruction method introduced by DeRosier and Klug created a revolution in structural molecular biology. Hundreds of macromolecular structures, including membrane proteins and viruses, were determined by this method. A most significant result was the 3D structure of purple membrane (Fig. 2), solved to a resolution of 7 Å from EM images and electron diffraction data by Henderson and Unwin in 1975 [12]. This was the first study giving information on the internal structure of a membrane protein. It was to take another ten years before the first X-ray crystal structure of a membrane protein, the photosynthetic reaction center, was solved by Michel, Deisenhofer and Huber, a work for which they were awarded the Nobel Prize in Chemistry in 1988.

Later, both images and ED patterns of purple membrane with higher resolution were obtained. Combining data from images and electron diffraction, a 3D structure model of purple membrane at atomic resolution (3.5 Å) was deduced [13]. Since then several other membrane structures, including PhoE porin and light harvesting complex, have also been solved to near atomic resolution (3 - 4 Å) [14,15]. A recent review on membrane proteins solved by EM is [16].

The main problem with structural studies of proteins is radiation damage, which limits the resolution of EM images. Huge efforts have been put into solving this problem, such as finding the best crystal and imaging conditions and developing the image processing method [17]. A major breakthrough was the introduction of

cryo-electron microscopy, which both allowed studies of unstained biological structures and gave some increased survival time in the harsh electron beam of these fragile compounds. With cryo-EM it is even possible to study individual protein molecules and complexes, ribosomes and viruses. In order to get to high resolution, low-dose cryo-EM is applied. Due to the very low contrast and poor signal-to-noise ratio, images of thousands of particles are merged in 3D after advanced methods for aligning their orientations.

The resolution of EM images of crystals of biological macromolecules is limited by large unit cells, poor crystal ordering and radiation sensitivity. Structures of biological macromolecules can be obtained to high resolution from single crystal X-ray diffraction. However, it is often difficult to make 3D crystals large enough for X-ray diffraction analysis of biological macromolecules. This is especially true for membrane proteins which, however, often form 2D crystals, ideally suited for EM and ED studies. With its advantages, electron microscopy combined with image processing has become a standard technique for protein structure determination, for those crystals which are not sufficiently large for single crystal X-ray diffraction. A recent book [18] gives a comprehensive overview of the field of structure determination of biological molecules by EM.
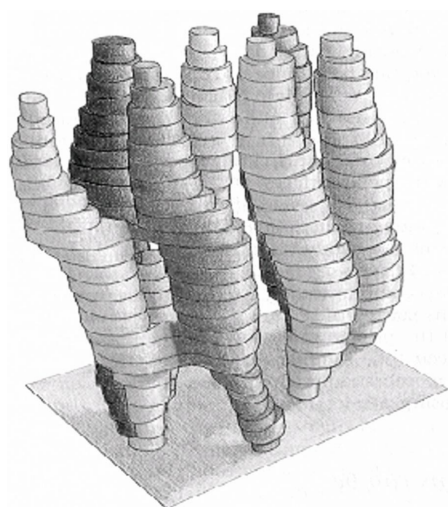

Fig. 2 A balsa-wood model of bacteriorhodopsin, the first membrane protein to be solved. 7 rods are seen – theses are α-helices crossing the lipid bilayer membrane. The resolution is 7 Å in the plane but less in the z-direction. That is why the 7 helices are not connected. From [12].
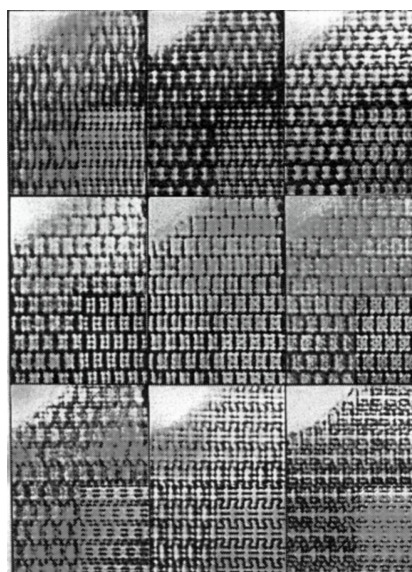

Fig. 3 The first focal series of EM images of $Ti_2Nb_{10}O_{29}$ near atomic resolution (4Å) with simulated images inset. Images were simulated with Cs of 1.8 mm, crystal thickness of 35 Å, beam convergence of 1.4 mrad and defocus values (from left to right and down-wards): 0, -160, -320, -480, -640, -800, -960, -1280, -1600 Å, respectively. (From [21].)

Most inorganic crystals diffract to much higher resolution than biological samples do, due to smaller unit cells, better ordering and less radiation sensitivity. It is relatively easy to get high resolution electron microscopy (HRTEM) images and diffraction patterns from them. The first EM images near atomic resolution (4 Å) showing details within a unit cell were obtained from a thin crystal of $Ti_2Nb_{10}O_{29}$ by Ijima [19], then working at Arizona State University. It was found that the contrast of HRTEM images changed with optical conditions and crystal thickness. In order to interpret the contrast changes, O'Keefe in Melbourne [20] wrote a computer program (later to become the SHRLI simulation program), using the multi-slice calculation method to simulate series of images of $Ti_2Nb_{10}O_{29}$ under different defocus and thickness conditions. The contrast changes in the experimental images could be interpreted successfully by these image simulations (Fig. 3). The success of image simulation led many microscopists to study the effects of the contrast transfer function and specimen thickness on images. Soon a consensus was reached that experimental HRTEM images can never be directly interpreted and used for solving atomic structures, but have to be confirmed by image simulation. Structure determination by image simulation was done in the following way:

- Assume a structure model and simulate a large number of HRTEM images by choosing a series of thicknesses, defocus values and possibly other optical parameters.

- Compare simulated images with experimental images and select the thickness and optical parameters giving the best fit of simulated and experimental images.
- Modify the structure model and calculate HRTEM images using the selected thickness and optical parameters.

There are several disadvantages with the image simulation method. A nearly correct structure model is needed beforehand. This is often not available, especially for new, unknown relatively complicated structures. The computation and interpretation are very time-consuming. Images are compared visually and no quantitative figure of merit is used for judging how well images and simulations agree.

The first attempt to interpret images of inorganic crystals without simulation was done by Klug [22]. They applied the crystallographic image processing method to a through-focus series of HRTEM images of a $GeNb_9O_{25}$ crystal and corrected for the contrast changes caused by the contrast transfer function. They showed that the correct structure projection could be retrieved from every single image in the series. The crystallographic image processing method was then used by Hovmöller's group in Stockholm for solving crystal structures of a number of niobium oxides, e.g. $K_{8-x}Nb_{16-x}W_{12+x}O_{80}$ [23], $Cs_xNb_{54}(O,F)_{146}$ [24] and $Na_3Nb_{12}O_{31}F$ [25].
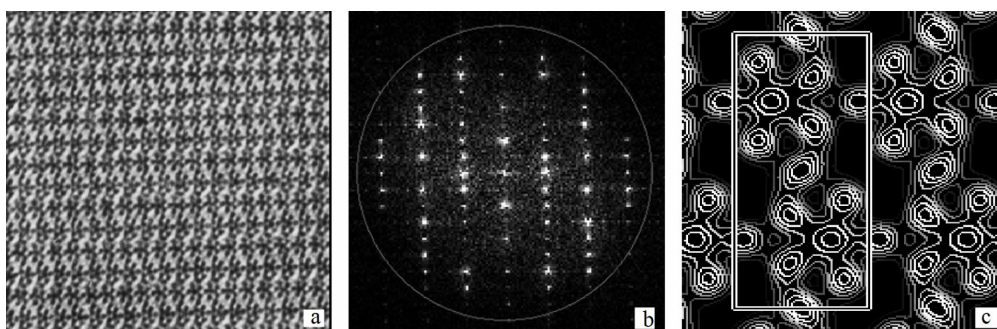

Fig. 4 The first EM image (a) to be scanned into a computer and then processed by Fourier techniques (b) was $K_{8-x}Nb_{16-x}W_{12+x}O_{80}$. The five crystallographically unique Nb/W metal atoms were found in the reconstructed projected potential map (c) within 0.10 Å of their correct positions as determined by X-ray crystallography. Adapted from [23].

In the projected potential maps obtained by crystallographic image processing from experimental HRTEM images at 2.5 Å resolution, all heavy atoms could be resolved. Atomic positions could be determined with an accuracy of about 0.1 Å (see fig. 4). Later Li Fan-hua's and Fan Hai-fu's groups in Beijing applied the image processing method, combined with image deconvolution and phase extension by maximum entropy and direct methods, to solve the crystal structure of $K_2O·7Nb_2O_5$ [26]. They also applied the direct methods for solving unconventional crystal structures such as quasicrystals [27] and incommensurately modulated structures [28], [29].

Nowadays microscopes can provide images with resolutions beyond 2 Å for inorganic crystals. This resolution is sufficient to resolve interatomic spacing, which means that it should be possible to resolve all atoms. However, images are only projections of the 3D structure and atoms may overlap with each other in the projection. The above mentioned niobium oxides which could be solved from a single projection all have a very short projection axis (4 Å). Heavy atoms are resolved in this projection. Often it is not possible to resolve individual atoms from a single crystal projection because of overlapping, no matter how high the resolution is. Thus HRTEM images from several projections are needed for a complete 3D structure determination. In 1992 Wenk et al. in Berkeley for the first time combined 2D HRTEM images into a 3D reconstruction for solving the structure of an inorganic crystal [30]. They combined, using image processing, HRTEM images (to a resolution of 1.38 Å) taken in five different orientations of the silicate mineral staurolite and constructed a 3D electron potential map. In this map all atoms (Fe, Al, Si and oxygen) were clearly resolved. This work showed that 3D electron crystallography has a great potential also in structure determination of inorganic crystals - perhaps even more promising for inorganic structures than for organic and biological structures, because of the higher resolution.

In HRTEM images of inorganic crystals, phase information of crystallographic structure factors is preserved. However, because of the effects of the contrast transfer function (CTF), the quality of the amplitudes is not very high and the resolution is relatively low. Electron diffraction is not affected by the CTF

and extends to much higher resolution (often better than 1 Å), but on the other hand no phase information is available. Thus, the best way of determining structures by electron crystallography is to combine HRTEM images with electron diffraction data. This was applied by Unwin and Henderson to determine and then compensate for the CTF in the study bacteriorhodopsin [31]. Much later this approach was used also for an inorganic crystal; the structure of $Ti_{11}Se_4$ was first solved by HRTEM images and then refined against accurately quantified electron diffraction data, reaching an accuracy of 0.02 Å for all the atoms [32].

Electron diffraction has also been used for extending the resolution of images, using the direct methods from X-ray crystallography [26,33]. Another method, based on the maximum entropy-likelihood technique was introduced into crystallography by Bricogne in Cambridge in 1991 [34] and programmed by Bricogne and Gilmore in Glasgow [35]. The maximum entropy-likelihood method has been used for phase extension of electron diffraction data. Two successful applications are the extension of HRTEM image resolution of the organic structure perchlorocoronene from 3.2 Å to 1 Å [36] and the 2D projection of the membrane protein bacteriorhodopsin [37].

Since 1990, more and more structures have been solved from HRTEM images and electron diffraction and more and more scientists have become interested in structure analysis by electron crystallography. Several other techniques, such as electron holography [38] and convergent beam electron diffraction (CBED) have also been developed for structure analysis. CBED can provide information not only on the lattice parameters and the symmetry of crystals, but also accurate structure-factor amplitudes and phases [39]. Accurate structure factor determination by CBED can provide information on the location of valence electrons. However, it is more favourable for thick crystals (> 500 Å) with small unit cells (< 10 Å). Structure analysis by CBED has been summarised in two review articles [40,41]. Structure determination of inorganic crystals by HRTEM and selected area electron diffraction has been reviewed recently [42].

2   Electron crystallography has some advantages over X-ray crystallography

X-ray crystallography is still the best technique for complete and accurate determination of crystal structures. Until 2010, over 500 000 organic structures have been solved by single crystal X-ray diffraction and some 100.000 inorganic and 50.000 proteins. However, in certain circumstances electron crystallography has some advantages over X-ray crystallography:

- Electrons interact with matter much stronger than X-rays. Thus much smaller crystals than those needed for single crystal X-ray diffraction can be analysed by electron crystallography. For single crystal X-ray diffraction, crystals should have a size larger than about $50\times50\times50$ μm^3 (or $5\times5\times5$ μm^3 on a synchrotron). For electron diffraction, crystals can be a million times smaller; down to about $0.1\times0.1\times0.01$ μm^3. Even smaller crystals, down to some 10-20 unit cells or indeed single particles, can be studied by HRTEM imaging [43]. Electron crystallography has a promising future for structure analysis of crystals too small for X-ray diffraction analysis, such as grain boundaries, metastable phases etc.
- Electrons can be focused by magnetic lenses to form an image. High resolution electron microscopy images of crystals can be obtained, while X-ray imaging is not possible. The phase information which is lost when registering diffraction patterns is preserved in HRTEM images.
- The mechanism by which electrons interact with crystals is different from that of X-rays. X-rays detect electron density distribution in crystals, while electrons detect electrostatic potential distribution in crystals. Electron crystallography may be used for studying some special problems related to potential distribution such as the oxidation states of atoms in the crystal.
- Almost all crystals suitable for X-ray powder diffraction can be studied by electron diffraction. Several of the most demanding problems with powder diffraction are overcome by electron diffraction. There is no problem of overlapping reflections in electron diffraction and all diffraction spots can be unambiguously indexed. There is no problem of under-determination (less data than unknown parameters) for electron diffraction since 10-100 times more reflections than parameters can be obtained by ED, whereas in X-ray powder diffraction the over-determination is close to one. On the other hand, electron diffraction comes from a single or just a few crystals while X-ray powder diffraction gives the average scattering from a representative sample of thousands or even millions of small crystals. Thus the combination of these two methods is often ideal. For a review see [42].
- HRTEM images can be used for studying defects in crystals.

In conclusion, electron crystallography can be used to extend the range of samples amenable to structure

analysis beyond those which can be studied by single crystal X-ray diffraction. Moreover, HRTEM images can supply some initial low resolution phases for X-ray diffraction which may aid in phase determination in X-ray crystallography.

3   The fear of multiple scattering hampered the development of electron crystallography

Although electron crystallography started more than sixty years ago and has many unique advantages, it has not been widely used as a standard technique for crystal structure determination of inorganic crystals. Why is that so? The main reasons are:
- There is a great fear for multiple scattering and non-linear effects.
- The fact that crystallographic structure factor phase information is present in HRTEM images and can be utilised for structure analysis was not generally accepted by microscopists trained in physics.
- HRTEM images are usually not directly interpretable without image processing because of optical distortions, crystal tilt and multiple scattering.
- Until recently, image processing required heavy investments in equipment and programming. This limited the possibility for most laboratories of performing quantitative image analysis.

4   Many questions about electron crystallography still need to be answered

Furthermore, until now there has not existed any textbook on electron crystallography, describing both theory and practice of structure determination of inorganic crystals by electrons. This causes additional difficulties for anyone who wants to establish electron crystallography in a new laboratory. It is important to describe, both in theory and practice, when and how electron crystallography can be used for structure analysis. The following questions need to be answered:
- What information about crystal structures is present in HRTEM images and electron diffraction?
- Which parameters affect HRTEM images and make them difficult to interpret in terms of structure projections?
- Is it possible to obtain accurate structure factors from HRTEM images combined with image processing and electron diffraction?
- How should the information present in HRTEM images and electron diffraction be extracted and used for structure analysis? How can the distortions in HRTEM images be determined and compensated for?
- Is it possible to use relatively simple and cheap devices for structure analysis by HRTEM, electron diffraction and image processing? Is the extracted electron diffraction data accurate enough for structure analysis?
- Is it possible to solve unknown structures in general, not only metal oxides with a short projection axis, from HRTEM images and electron diffraction?

Finally some principal problems in electron crystallography need to be discussed and investigated. These include:
- Are the principles of structure determination by electron crystallography and by X-ray crystallography the same?
- How are the phases and amplitudes obtained from HRTEM images related to those of X-ray structure factors?
- Will multiple scattering and non-linear effects make structure determination by electron crystallography impossible?
- Is there a phase problem in electron crystallography?
- How can images taken with different defocus be combined?

During the last decade a number of very important technical developments have made electron crystallography even more powerful. These include hardware developments such as field emission gun (FEG) electron microscopes for higher resolution, Cs correctors for directly interpretable HRTEM images and precession instruments [44] for higher resolution and more kinematical electron diffraction patterns. With the advent of computer-controlled electron microscopes, software for automatic diffraction tomography [45-47] and rotation methods [48] for collecting complete high quality electron diffraction data in 3D in a matter of hours has become available. At last, it has become possible to collect complete 3D ED data in an automatic way, replacing the previous very time-consuming and highly demanding methods of manually finding exact crystal

orientations (zone axes). It is hoped that soon electron crystallography will become a routine technique, as X-ray crystallography is, for crystal structure determination.

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