Crystal-structure solution through centuries

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The process of crystal-structure determination from diffraction data requires the knowledge of the phases of reflections. This information is essential for locating atoms in the unit cell. However, the phases are usually lost in the process of recording the diffraction data. Therefore then the phases must somehow be recovered, mainly by mathematical calculations. The derivation of the reflection phases is often described as the solution of the *phase problem*. The process of reconstruction of images is a very general one, and its main features equally apply to the perception of the world around in our eyes, in optical and electron microscopes, and in neutron-diffraction experiments.

The phase problem can be solved in various manners. In the 1920th, at the dawn of x-ray diffraction era, structures were solved from the symmetry considerations and by trial-and-error methods. Later, more elaborate methods were developed, like the Patterson method (atomic-pair distribution function), direct methods, multi-wavelength anomalous diffraction (abbreviated MAD), multiple isomorphous replacement (MIR), multi-wavelength anomalous solvent contrast method (MASC), Monte-Carlo random approaches both at the real-space and structure-factors levels, evolutionary methods, combination of structure prediction methods with diffraction techniques, or new recently emerging methods- like the charge-flipping method, a very efficient algorithm very efficient in finding solutions, but without exact theoretical explanation of its successful operation. Today efficient methods are often routinely used not only for solving small-molecule structures, but also those of macromolecules; the data used for solving the structures can be highly incomplete or measured by powder-diffraction methods.

Apart from the computational methods of solving the phase problem, there are also attempts to measure the reflection phases experimentally. The methods allowing the measurements of the phases are based on the basic wave optics, and employ the effect of multiple reflections or crystal-structure holography, and also the pre-phasing of the reflections by using the single-crystal electron diffraction. Many of these new methods can be used owing to the progress in computational hardware and software, and owing to the new designs and development of equipment for measuring the diffraction data.