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Low-resolution phasing

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The collection of papers in this issue form the proceedings of the CCP4 Study Weekend held in York in January 2000. As well as the most recent advances, the meeting covered the basic concepts of low-resolution phasing both by X-ray crystallography and by electron microscopy, and the two techniques were shown to be complementary.

In X-ray crystallography there are still a substantial number of proteins for which phases cannot be obtained experimentally using heavy-atom derivatives or anomalous data and for which no suitable model is available for the molecular-replacement method. The use of direct methods in which no *a priori* phases are needed has become the norm in small-molecule crystallography and some of the ideas are now being applied to macromolecular structures. An overview of such methods and their limitations is given, followed by a number of papers describing *ab initio* methods to determine the molecular envelope. Alternative parameterizations of the problem and the various constraints which can be used to obtain these very low resolution phases as well as the importance of criteria for recognizing correct solutions are discussed. Molecular envelopes for X-ray crystal structures may also be obtained experimentally using contrast variation and a method to generate contrast variation from the anomalous scattering of a single-crystal is described.

The importance of complete data sets, particularly for *ab initio* methods, is now well known and a detailed description of how even the very low resolution reflections can be measured in-house is presented.

Electron-microscopy maps can also be used to provide starting phases for X-ray structures and conversely, low-resolution models obtained by X-ray crystallography can be used to aid the interpretation of electron-microscopy maps. The fundamental processes of electron microscopy are covered and the various stages associated with achieving a three-dimensional image from two-dimensional crystals, one-dimensional helical assemblies or isolated complexes (single particles) are all described. The combination of the two techniques is demonstrated in several papers. In particular, the fitting of X-ray structures into electron-microscopy maps and the difficulties encountered, such as disorder and scaling problems, are described. It is shown that such maps contain enough information to build low-resolution models which can be tested and updated and that, even as low as 30 Å, dramatic changes, such as those occurring on binding of ATP or ADP to GroEL/GroES can be observed.

At very low resolution a binary map provides an adequate description of the electron density, but more detail is required in order to extend the resolution. Use of the Fermi–Dirac distribution to provide a continuous molecular envelope and of wavelet transforms in adding new detail are two-phase extension and improvement methods described here. Phase extension is also achieved by averaging in the case of large virus structures, exploiting the high degree of non-crystallographic symmetry.

Finally, an alternative way to solve the phase problem is described. For non-crystalline particles, this is achieved by over-sampling the diffraction pattern and it is suggested that the same approach may also be used for crystals.