962-92-1229 **Joachim Frank*** (joachim@wadsworth.org). *Three-dimensional Cryo-electron Microscopy of Biological Macromolecules: the Challenge Posed by Structural Heterogeneity.*

Many of the essential life processes in the cell involve complex localized macromolecular interactions ("macromolecular machines"). Their size, dynamic character, and fragility make it difficult to probe their structure with X-ray crystallography. Cryo-electron microscopy, combined with 3D reconstruction [1], proves to be a superior technique. Given a cryo-specimen (a thin sheet of amorphous ice) containing a large number of macromolecules in unknown, random orientations. The electron microscope is used to produce a single, noisy projection of this specimen. Consider the case first where all macromolecules in the field have identical structure – the different "copies" are related by rigid-body movements. The objective is then to determine, from the image only, the relative orientations of all molecules, and then compute a 3D reconstruction. This problem has found various solutions. A very challenging problem is conformational heterogeneity, resulting from insufficient sample purity or spread of a dynamically changing system. This can be, in the order of increasing difficulty, (i) the coexistence of molecules of different species; (ii) the presence or absence of a functional ligand; and (iii) changes in conformation. The specimen now has to be modeled as containing a number of classes of different objects. The reasons why no solution has yet been found to this problem are the two-fold degeneracy and the small signal-to-noise ratio.

[1] Joachim Frank, Three-Dimensional Electron Microscopy of Macromolecular Assemblies. Academic Press, San Diego 1996. (Received October 02, 2000)