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Electron Densities from Diffraction Patterns of Randomly Oriented Molecules[1]

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A diffraction pattern from a single biological molecule would consist of a more or less continuous intensity distribution rather than Bragg spots. Successive diffraction patterns from molecules of the same protein in a molecular beam would each represent the intensity diffracted by a single molecule in a random orientation. Each diffraction pattern may in fact be regarded as an Ewald sphere passing through a random part of the molecular reciprocal space containing the origin. In principle, these portions can be "patched together" to extract the 3-dimensional diffracted intensity distribution of the molecule. The problem is to identify each measured pixel of a 2-dimensional diffraction pattern produced by a molecule of unknown orientation with a unique position in the 3D reciprocal space representing the Fourier Transform of the molecule's electron density. Methods for identifying relative molecular orientations from a set of projected images have been developed for 3D electron microscopy [1]. However, the absence of phase information in diffraction patterns causes additional difficulties, including "Friedel pair" ambiguities. Nevertheless, inspired by 3D electron microscopy, we have explored two different approaches to this problem: the method of common lines [2]; and a projection matching method [3]. We will describe the extent to which such approaches, combined with an iterative phase recovery algorithm [4] may be expected to yield the electron density distribution, and hence the structure of individual biological molecules.

[1] J. Frank, Three-Dimensional Electron Microscopy of Macromolecular Assemblies, Oxford University Press, 2006.
[2] A. B. Goncharov *et al.*, Sov. Phys. Crystallogr. **32**, 504 (1987).
[3] P. Penczek *et al.*, Ultramicroscopy **40**, 33 (1994). [4] e.g. J. R. Fienup, Appl. Optics **21**, 2758 (1982)

[1]With Valentin Shneerson and Abbas Ourmazd (see http://hermes.phys.uwm.edu)