

Crystallography without Crystals: Structure from Diffraction Patterns of Randomly Oriented Molecules

V. L. Shneerson, A. Ourmazd, *D. K. Saldin*

Department of Physics, University of Wisconsin-Milwaukee

Amongst the promised capabilities of fourth generation x-ray sources currently under construction is the ability to record diffraction patterns from individual biological molecules. One version of such an experiment would involve directing a stream of such molecules into the X-ray beam and sequentially recording the scattering from each molecule of a short, but intense, pulse of radiation. Due to the shortness of the pulse, the diffraction patterns may be thought of as arising from molecules of different, frozen, random orientations. It has been proposed that the data from such diffraction patterns may be pooled to reveal the 3D structure of the molecular species. However, to this date, there has been no demonstration of such an algorithm.

We propose an algorithm based on the method of “common lines”, first developed for 3D electron microscopy. In that field, the raw data are projections of electron microscope images of “identical” objects in multiple orientations. In our problem the available data are a set of diffraction patterns from unknown orientations of an object. Due to the absence of direct phase information, there is less information in the diffraction patterns, resulting in a “Friedel Law ambiguity” in the determination of common-line directions by comparison of sinograms from different diffraction patterns. We show that this ambiguity may be removed by imposition of consistency relations amongst different diffraction patterns, a process that ensures that the common-line directions are determined by more than just the data from two diffraction patterns. The common-line directions determine two of the three Euler angles specifying the relative orientations of any two diffraction patterns in reciprocal space. Given three or more diffraction patterns, the remaining “hinge” Euler angle may be determined by a formula derivable from spherical trigonometry. By systematically cycling through all available diffraction patterns, we will show that it is possible to correctly orient the majority of these in 3D reciprocal space.

A gridding algorithm then interpolates the diffracted intensity data onto a regular Cartesian grid in reciprocal space at a sampling frequency greater than the Nyquist frequency for the expected size of the object. An iterative algorithm, which cycles between reciprocal and real space, applying appropriate constraints in each, is then able to determine the phases associated with the reciprocal space amplitudes, and simultaneously the electron density of the object under investigation.

We will demonstrate this algorithm for simulated diffraction patterns from a small protein. The molecular electron density is recovered with excellent fidelity. We have also investigated other methods of structure solution, e.g. one based on a “projection matching” approach, progress on which will also be reported.