Computational Challenges in Electron Microscopy of Macromolecules

Esmond G. Ng
Lawrence Berkeley National Laboratory

Abstract: Three-dimensional (3-D) density maps of biological molecules can be determined by merging a large number of two-dimensional (2-D) images taken by a low-dose electron microscope. The 2-D images are projections of a collection of randomly oriented 3-D molecules embedded in a thin layer of vitreous ice.

In order to recover the 3-D structure, one must first determine the relative orientations of projection images. Once the orientation parameters are obtained, the 3-D reconstruction can be carried out in the spatial domain by solving a large-scale linear least squares (LLS) problem iteratively. Because the angular coverage by 2-D projection images is limited, and because the projections are typically noisy, the LLS problem is ill-posed. Some type of regularization is required to enhance the fidelity of the reconstruction. Because the cost of matrix vector multiplication used in the iterative solver is fairly high, we would like to reduce the number of iterations through preconditioning.

The noisy nature of the 2-D projections makes it difficult to determine orientation parameters accurately in advance. As a result, an iterative procedure that simultaneously refines the orientation parameters and the 3-D structure of the molecule is often used to render the final structure of macromolecule.

In this talk, we will give an overview on the mathematical formulation of the image reconstruction problem, and discuss numerical techniques that can be employed to solve this problem. In particular, we will point out the important roles numerical linear algebra play in producing a high resolution 3-D images of biological macromolecules.