Building Proteins in a Day: Efficient 3D Molecular Reconstruction

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Discovering the 3D atomic structure of molecules such as proteins and viruses is a fundamental research problem in biology and medicine. Electron Cryomicroscopy (Cryo-EM) is a promising vision-based technique for structure estimation which attempts to reconstruct 3D structures from 2D images. This paper addresses the challenging problem of 3D reconstruction from 2D Cryo-EM images. A new framework for estimation is introduced which relies on modern stochastic optimization techniques to scale to large datasets. We also introduce a novel technique which reduces the cost of evaluating the objective function during optimization by a factor of over 100,000. The net result is an approach capable of estimating 3D molecular structure from large scale datasets in about a day on a single workstation.

Biological macromolecules are composed of chains of simpler monomers, and the conformation or "folding" of these chains into a 3D structure is what gives each macromolecule its specific function and properties. The ability to routinely determine the 3D structure of such molecules would potentially revolutionize the process of drug development and accelerate research into fundamental biological processes. The Cryo-EM reconstruction technique is applicable to medium to large-sized molecules in their native state. This is in contrast to X-ray crystallography which requires a crystal of the target molecule, which are often impossible to grow or nuclear magnetic resonance (NMR) spectroscopy which is limited to smaller molecules.

The Cryo-EM reconstruction task is to estimate the 3D density of a target molecule from a large set of images of the molecule (called particle images). The problem is similar in spirit to multi-view scene carving [3, 6] and to large-scale, uncalibrated multi-view reconstruction [1]. Like multi-view scene carving, the goal is to estimate a dense 3D occupancy representation of shape from a set of different views, but unlike many approaches to scene carving, calibrated cameras cannot be assume, since the relative 3D poses of the molecules in different images are unknown. Like uncalibrated, multi-view reconstruction, we aim to use very large numbers of uncalibrated views to obtain high fidelity 3D reconstructions, but the low signal-to-noise levels in Cryo-EM, often as low as 0.05 [2] (see Fig. 1), and the different image formation model prevent the use of common feature matching techniques to establish correspondences. Computed Tomography (CT) [4, 5] uses a similar imaging model (orthographic integral projection) as Cryo-EM, however in CT the projection direction of each image is known. Existing Cryo-EM techniques suffer from two key problems. First, without good initialization, they converge to poor or incorrect solutions, often with little indication that something is wrong. Second, they are extremely slow, in some cases requiring hundreds of thousands of CPU hours for a single reconstruction.

We introduce a framework for Cryo-EM density estimation, formulating the problem as one of stochastic optimization to perform maximum-a-posteriori (MAP) estimation in a probabilistic model. The approach is remarkably efficient, providing useful low resolution density estimates in an hour. We also show that our stochastic optimization technique is insensitive to initialization, allowing the use of random initializations. We further introduce a novel importance sampling scheme that dramatically reduces the computational costs associated with high resolution reconstruction. This leads to speedups of 100,000-fold or more, allowing structures to be determined in a day on a modern workstation. In addition, the proposed framework is flexible, allowing parts of the model to be changed and improved without impacting the estimation; *e.g.*, we compare the use of three different priors. To demonstrate our method, we perform reconstructions on two real datasets and one synthetic dataset. We believe that Cryo-EM is an important and challenging problem which, with a few exceptions (*e.g.*, [7]), has seen little attention in the computer vision community. The approach proposed here represents a significant step forward, allowing high resolution reconstructions to be computed quickly and efficiently and without specific initialization.

This is an extended abstract. The full paper is available at the Computer Vision Foundation webpage.

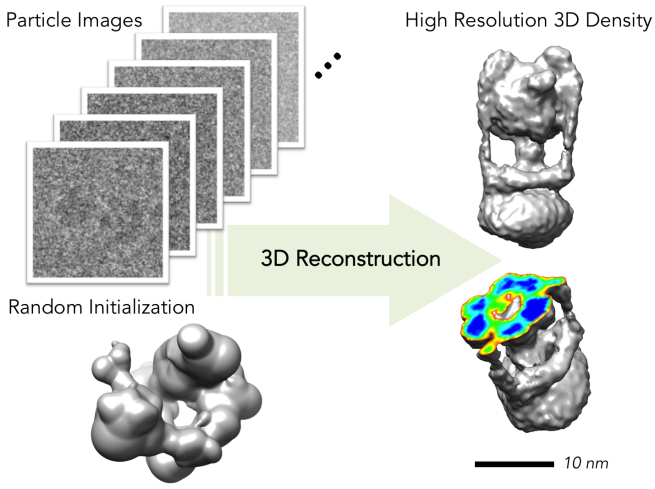

Figure 1: The goal is to reconstruct the 3D structure of a molecule (right), at nanometer scales, from a large number of noisy, uncalibrated 2D projections obtained from cryogenically frozen samples in an electron microscope (left).

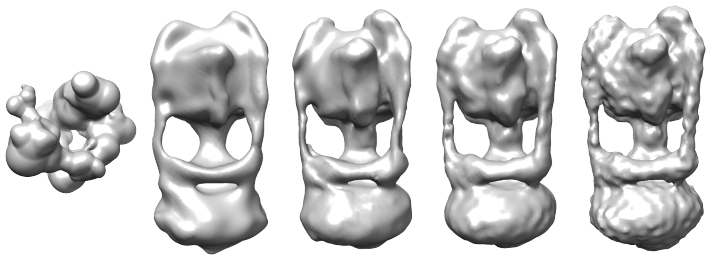

Figure 2: The random initialization (left) used in all experiments and reconstruction of the *thermus* dataset after various amounts of computation. Within an hour of computation, the gross structure is already well determined, after which fine details emerge gradually.

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