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Automatic Projective Model Estimation and Reconstruction in Cryogenic Electron Tomography

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Abstract

In recent years there has been increasing interest in using cryo TEM tomography to study cells in close to their “native” environment. One limitation of this technique is the relatively low signal to noise ratio in each of the TEM images, since the total electron dose through the sample must be constrained to limit structure damage to the cell. Even with gold markers added to the sample, robust automatic alignment of the TEM slice data for reconstruction remains difficult. We have tried to address this problem by leveraging recent work in probabilistic analysis, and have constructed a prototype alignment system using *Markov random fields (MRF's)* for alignment, and *robust optimization methods* for projective model estimation.

With markers, there are three basic steps required to align the TEM dataset: marker feature identification, correspondence and tracking of these features throughout the image set, and projective model estimation from these feature tracks. In our framework, features are extracted initially using standard template matching techniques like cross correlation. Feature correspondence and tracking is accomplished by constructing a Markov random field (MRF) probabilistic model where contour labels are random variables which take on values of candidate marker feature locations. We use mutual information and the relative geometric positions to estimate a priori marker correspondence probabilities between two images. An approximate probabilistic inference technique called loopy belief propagation (LBP) is then used to calculate the maximum a posteriori assignment of features to contours in the image set. In this technique, rather than a joint distribution (whose complexity is exponential in the number of random variables), a collection of singleton and pairwise distributions is maintained in a special data structure. This data structure contains cycles, and is called a *cluster graph*. The a priori estimates for these distributions (initial beliefs) are refined by belief propagation, until they converge to roughly the true pairwise distributions (final beliefs). The correspondences of candidate markers to contours are taken directly from these beliefs.

Errors in the correspondence are possible due to feature location mistakes as well as inaccurate inference results. Therefore, the projective model estimation uses a robust fitting method as opposed to least squares (the traditionally applied fitting) and is tolerant to outliers. Once we have an estimate of the projective model, the model is iterated using

expectation maximization (EM) to re-estimate perceived outliers with improved reprojection data from the current model. This iteration is performed as many times as necessary before a stopping criterion is satisfied, but in our example a small number of iterations is needed (often only one).

This robust framework has allowed us to fully automatically recover dozens of contours (both complete and piecewise) with subpixel accuracy from several challenging cryo datasets of bacteria *Caulobacter crescentus*. The results were used to create 3D reconstructions comparable to results previously obtainable only by extensive manual intervention.