A Bayesian View on Cryo-EM Structure Determination.

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Three-dimensional (3D) structure determination by single-particle analysis of cryo-electron microscopy (cryo-EM) images requires many parameters to be determined from extremely noisy data. This makes the method prone to overfitting, that is, when structures describe noise rather than signal, in particular near their resolution limit where noise levels are highest. Cryo-EM structures are typically filtered using ad hoc procedures to prevent overfitting, but the tuning of arbitrary parameters may lead to subjectivity in the results. I describe a Bayesian interpretation of cryo-EM structure determination, where smoothness in the reconstructed density is imposed through a Gaussian prior in the Fourier domain. The statistical framework dictates how data and prior knowledge should be combined, so that the optimal 3D linear filter is obtained without the need for arbitrariness and objective resolution estimates may be obtained. Application to experimental data indicates that the statistical approach yields more reliable structures than existing methods and is capable of detecting smaller classes in data sets that contain multiple different structures.