Linking structural ensembles from simulations to the analysis of individual cryo-EM images

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Cryo-electron microscopy has revolutionized structural biology by providing atomic-level resolution structures of biomolecules that are difficult to characterize using X-ray crystallography or nuclear magnetic resonance. However, despite many improvements, there are still several scenarios in which cryo-EM face challenges, e.g., when the particle-images acquire preferred orientations or for analyzing highly disordered systems.

To harness the power of cryo-EM's near-native conditions and single-molecule character, we developed a method to extract structural information from individual EM images of dynamic molecular assemblies. The Bayesian inference of EM (BioEM)[1] method uses a likelihood-based probabilistic measure to quantify the degree of consistency between each EM image and given model ensembles. These structural models can be constructed using hybrid-modeling or obtained from molecular dynamics simulations. To analyze EM images of highly flexible molecules, we propose an ensemble refinement procedure, and validate it with weighted ensembles from simulations and synthetic images of the ESCRT I-II supercomplex. Both the size of the ensemble and its structural members are identified correctly.

The BioEM posterior calculation is performed with a highly parallelized, GPU-accelerated computer software[2] resulting in a nearly ideal scaling both on pure CPU and on CPU+GPU architectures. This enables Bayesian analysis of tens of thousands of images in a reasonable time, and offers an alternative to 3D-reconstruction methods by its ability to extract accurate population distributions for highly flexible structures and their assemblies.

[1] Cossio, Hummer. (2013) J. Struct. Biol. 184: 427-37.
[2] Cossio, et al. (2017) Compu. Phys. Commun. 210, 163-171.