Extracting free-energy profiles from cryo-electron microscopy experiments

Pilar Cossio[1]

[1]*N/A*

pcossio@flatironinstitute.org

Understanding the molecular mechanisms of biomolecules involves characterizing at atomic detail conformational states, extracting probability distributions of the conformations and elucidating the time to transition between states, among others. Cryo-electron microscopy (cryo-EM) is an experimental technique that measures single-particle projections of biomolecules. Although single-particle cryo-EM is widely used for 3D reconstruction, it has the potential to provide information about a biomolecule's conformational variability, which leads to the underlying free-energy landscape of the system. However, cryo-EM images are challenging to analyze due to their low signal-to-noise ratio. To address these issue, we developed the cryo-BIFE method, which uses a path collective variable together with a Bayesian approach to infer free-energy profiles and their uncertainties from cryo-EM particles. We applied the method over a diverse set of synthetic and real systems, finding that the signal-to-noise ratio and pose estimate as key determinants to extracting accurate profiles.