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Learning Biomolecular Ensembles from Experimental Cryo-EM Data

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Biomolecules are inherently flexible, continuously transitioning between conformations to carry out their cellular functions. Cryo-electron microscopy (cryo-EM) enables us to image individual biomolecules at near-atomic resolution. As a result, an image dataset can capture the entire biomolecular ensemble at once. By comparing cryo-EM images to structural hypotheses, one can identify the structure that best matches each image. In principle, this allows us to identify the structures in the images and infer the underlying ensemble. However, performing these exhaustive comparisons is computationally very expensive. To tackle this problem, we introduce simulation-based inference for Cryo-EM (CryoSBI), a novel method that utilizes simulation-based inference to infer biomolecular conformation from individual cryo-EM images. Our approach uses neural posterior estimation, a technique that directly approximates the Bayesian posterior using a simulator and a density estimator. Training is performed only once using simulated data generated with the simulator. Afterward, inference for each particle requires just a single forward pass through the neural network. This eliminates the need to estimate particle pose and imaging parameters for each observation, delivering substantial computational speedups compared to traditional explicit likelihood methods. We demonstrate this approach through experiments on real cryo-EM data, where cryoSBI successfully extracts molecular conformations with reliable confidence measures. In addition, we combine cryoSBI with established ensemble reweighting techniques to infer biomolecular ensembles directly from entire cryo-EM image datasets. This enables the recovery of population distributions over conformational states. We demonstrate this capability by reweighing p4p6-conformational ensembles using cryo-EM data collected under different environmental conditions, revealing how changes in the experimental environment modify the underlying ensemble.

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