# Exploring Conformational Landscape of Cryo-EM Using Energy-aware Path Finding Algorithm

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## Abstract

Single-particle cryo-electron microscopy (cryo-EM) is a powerful tool for determining the structure of dynamic macromolecular machines at near-atomic resolution. Recently, various reconstruction models have successfully extracted structural heterogeneity from noisy images, potentially allowing for the identification of kinetically preferred sequences of transitions between two conformational states in dynamic processes. Typically, these sequences are addressed using pathfinding algorithms on a two-dimensional energy landscape. However, it is not clear how to construct a high-dimensional energy landscape and search for a kinetically preferred path on it. Therefore, it is a challenge to implement previous algorithms on recent leading models like cryoDRGN, which represent structural heterogeneity using a latent space higher than two dimensions. Here, we introduce a novel method for finding the kinetically preferred path in the high-dimensional latent space. This method searches for the shortest path in a graph that defines the edge weights based on free-energy difference for each point. We demonstrate that the proposed method can reveal the correct transition state in synthetic data with continuous conformational changes and can find the stable pathway in different noise levels.

Keywords: cryo-EM, free-energy landscape, manifold embedding, graph traversal, pathfinding.