Exploring the conformational landscape of cryo-EM using a density-aware path-finding algorithm

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Abstract

To understand the protein's functionality, cryo-electron microscopy (cryo-EM) has become the mainstream technique to resolve the associate conformation landscape. A key aspect of the cryo-EM workflow is identifying trajectories within this landscape, which relies on the results of 3D conformation analysis. Despite its importance, there is a lack of literature addressing the evaluation and validation of these trajectories. Establishing benchmarks for such trajectories is crucial for increasing confidence in using computational tools to uncover protein functionality and understanding their limitations, as opposed to traditional labor-intensive experimental methods. This presentation will introduce a preliminary framework for trajectory validation. Specifically, I will delve into a synthetic dataset generation workflow capable of producing datasets featuring two or three major conformational motions, along with proposed metrics for benchmarking the resulting trajectories. Furthermore, I will elaborate on a method that integrates novel statistical measures of local density into the objective function when searching for trajectories. Lastly, ongoing research directions in this area will be discussed. The results are expected to contribute to the advancement of the cryo-EM field and offer valuable insights for dynamic protein studies, ultimately aiding in drug and vaccine development. (This is joint work with Teng-Yu Lin)

Keywords: Cryogenic electron microscopy, minimum energy path, dimension reduction, manifold learning, graph traversal