Conformational Transition of Protein through Multiple Pathways: Insight from Adenylate Kinase

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Conformational change of protein, especially the transition between functional states, is usually critical for biological processes. Therefore, understanding this dynamic process is critical for understanding protein function. However, conformational transitions in proteins are usually not easy to be well characterized by experimental protocols, mainly because of their inadequate temporal and spatial resolution. By providing time-dependent structural information at atomic level, molecular dynamics (MD) simulations serve as a potential tool to dissect the dynamic process of conformational transition of protein, though the sampling of configuration space is still a great challenge. In this work, we proposed a robust and unbiased enhanced conformational sampling protocol with combined MD simulations and principal component analysis, and applied it to explore the conformational transition of adenylate kinase (ADK), a model system with well characterized open and closed state structures. This protocol drives the switching between the open and the closed states of ADK within tens of ns. By analyzing the ensemble of hundreds of one-direction transition in ADK, we reproduced different mechanisms and the associated multiple pathways for domain motion of ADK reported in literature, and further identified the correlation between the probability of transition pathway and the free energy. Therefore, our work provides a strong evidence for the funnel landscape model, which predicts that protein folding proceeds through multiple kinetically distinct pathways. This reliable and efficient enhanced conformational sampling protocol could be employed to study the dynamics between different functional states of a broad spectrum of proteins and biomolecular machines.