Abstract

Understanding structural transitions and dynamics in biomolecules at a single molecule level

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Transition paths are fleeting events when a molecule crosses a barrier separating stable configurational basins. Recent advances in single molecule experiments, including optical tweezers-based force spectroscopy and FRET-based techniques, and data analysis methods have allowed detection of various statistical properties of transition paths. These observations have highlighted an important limitation in their current theoretical interpretation – a model of diffusive dynamics of the reaction coordinate along a one-dimensional free energy landscape is often unable to account for measurements of transition path time distributions in single molecule experiments. Here, we report similar observations in a long all-atom simulation of a small fast folding protein that exhibits multiple folding and unfolding transitions. Specifically, we discovered that the distribution of transition path times in this case is much broader than the prediction of the one-dimensional diffusion model. Moreover, direct analysis of the dynamics of the reaction coordinate in this simulation as well as in several other polypeptide simulations revealed that those dynamics are not diffusive, but subdiffusive. To explain these

observations, we developed and tested several non-Markovian models, which include memory effects in the dynamics of the reaction coordinate in the form of time-dependent transport coefficients. We invented a novel technique, based on an overdamped generalized Langevin equation, to extract conformational memory directly from one-dimensional trajectories in single molecule experiments and simulations. Finally, we tested our theories on loop formation kinetics in intrinsically disordered proteins and found that, while mean first passage times to loop closure are well described by both one-dimensional diffusion and generalized Langevin equation, neither of them can capture long-time tails observed in distributions of transition path times in all-atom simulations.