Abstract

Gaining a detailed insight into the molecular kinetics of the biomolecular systems is the fundamental step to comprehend the human health. In the present thesis, our focus is on the development of a new class of enhanced kinetic sampling methods for construction of the kinetic network of biomolecular systems using Markov State Model (MSM) approach. Here a new concept of validity time is introduced to address the uncertainty/error in an MSM due to missing states/pathways and a theoretical framework for calculation of validity time is provided to quantify the completeness of an MSM. An efficient and accurate construction of MSM with desired validity time is accomplished by a suite of new algorithmic developments: namely Swarm MD, State-constrained MD (SC-MD) and Programmed state-constrained MD (PSC-MD). The newly developed methods and concepts are used to construct MSM for Single Molecule Force Spectroscopy (SMFS) experiments with the objective of rapidly construction of kinetic network using a stretching force to accelerate rare conformational transitions of biomolecules involving multiple states and kinetic pathways. An idea of Master-MSM for constant-probe separation experiments in a Force-Spectroscopy (FS) setup is proposed to predict the connection between topologically different kinetic networks constructed at distinct trap separations. On the basis of the idea of Master-MSM, a Time-Dependent MSM (TD-MSM) formalism is developed where the external stretching force to the system is a function of time. The TD-MSM approach enables us to get the new molecular insights into the kinetic, thermodynamics and mechanical properties of the system. Finally, we extend the Master-MSM method at constant-probe separation to constant-force experiment to predict the intrinsic kinetic properties (kinetic rates at zero-force conditions) of slow transitions at lower computational cost by a handful of simulations at various stretching forces.