Multi-ensemble Markov model approaches to model ligand binding

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Markov models describe molecular dynamics as a kinetic network of transitions between metastable states. These models use detailed balance to leverage kinetic information from ensembles of short trajectories to make estimates of transition rates and equilibrium populations, and have been used with great success to model long-timescale conformational changes. Modeling protein-ligand binding reactions with slow dissociation rates, however, is much more challenging, requiring some kind of enhanced sampling to observe unbinding transitions. In this talk I will discuss our group's recent work to address this challenge using two different multi-ensemble approaches—one based on the TRAM estimator, and another based on the principle of maximum-caliber. We apply these methods in toy models of ligand binding [JCP (2022) 156 (13): 134115], as well as in large-scale simulations of protein folding, coupled folding-and-binding of cyclic peptides to protein receptors [JCIM (2021) 61 (5): 2353–2367], and *de novo* designed mini-proteins to therapeutic targets.