Modeling (un)binding Kinetics of Biologically Relevant Systems Using Resampling of Ensembles by Variation Optimization

By

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Abstract

Conventional drug design optimizes binding affinity when designing molecules to maximize efficacy. However, recent studies show that taking kinetics into account when designing drugs is necessary in some systems where the drug efficacy does not correlate with binding affinity, instead correlating with residence time (RT). To maximize the RT, knowledge of the kinetic pathway is required, but not currently feasible to determine experimentally due to the instability of the transition state. Molecular dynamics (MD) allows us to simulate these pathways with atomic resolution. However, the rare events of interest often occur at timescales as long as milliseconds to hours, and most MD trajectories are computationally limited to the microsecond timescale. In this thesis we use a variant of the Weighted Ensemble (WE) enhanced sampling algorithm, Resampling of Ensembles by Variation Optimization (REVO), to overcome the limitations of MD. This approach is more computationally efficient than conventional MD and does not alter the system’s Hamiltonian nor does it affect the force field parameters used in simulation. We use REVO simulations to produce full binding and unbinding trajectories of biologically relevant systems such as the unbinding of a radioligand bound to Translocator Protein (18kDa) (TSPO), a potential drug target in the treatment of neurodegenerative diseases. We validate these pathways by predicting kinetic rate constants and binding free energies and comparing these results to experiment. Finally, we developed new distance metrics that use experimental data to help guide simulations to a desired conformation. We tested these new distance metrics using Hydrogen deuterium exchange (HDX) data to form the ternary complex between a ligase-proteolysis-targeting chimera (PROTAC) dimer and a target protein.

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