

## A Curvilinear-Path Umbrella Sampling Approach to Characterizing Thermodynamics and Mechanisms of Biomolecular Interactions

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Protein-protein and protein-ligand interactions are central in biological mechanisms. These interactions can be classified into thermodynamics and mechanistic pathways. Estimating accurate and reliable interaction energetics along the thermodynamic pathway is one of the ongoing challenges in computational biophysics. Umbrella sampling simulation-based potential of mean force calculations is one of the methods to estimate the interaction energetics. Previously this method was implemented by first choosing a predefined path of dissociation, which is often chosen as a straight-line/vectorial path. However, there are several unresolved issues such as choices of predefined direction, corrections of potential of mean force to standard free energy of binding, etc. To unleash these limitations, we developed a curvilinear-path umbrella sampling molecular dynamics (MD) simulation approach to address some of the issues. We have applied the new method for evaluating the standard free energy of binding for the barnase-barstar protein-protein system and then on a protein-ligand system, where the interaction energetics of FKBP12-rapamycin protein-ligand system is estimated. The computed energetics for both systems are in good agreement with the experimental values. The revealed mechanistic insight for the protein-protein complex matches very well with the computationally expensive adaptive biasing MD based brute-force methods. Further, we also conducted the simulations of dissociation reactions of ternary complex FKBP12-rapalog-FRB, which indeed demonstrated a tug-of-war between FRBP12 and FRB to bind with the rapamycin, and revealed that the rapamycin prefers to bind with FKBP12 more than FRB. Thus, the glue-like molecule rapamycin and other rapalogs seem to follow a step-wise path of forming FKBP12-rapalog complex first and then the ternary complex with FRB. Thus, the developed curvilinear-path approach offers accurate and reliable binding energetics, is sensitive enough to distinguish the change in interaction energetics upon mutations, and can reliably reveal mechanistic details towards the fulfillment of the characterization.

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