Integrating Unbiased Path Sampling with Biased Enhanced Sampling for Rare-event Kinetics

Dhiman Ray [1]

[1]*Department of Chemistry and Biochemistry, University of Oregon, Eugene, OR, USA*

Studying the kinetics of long-timescale rare events is a fundamental challenge in molecular simulation. To address this problem, we integrate two different rare-event sampling philosophies: biased enhanced sampling and unbiased path sampling. Enhanced sampling methods, e.g., metadynamics, can facilitate enthalpic barrier crossing by applying an external bias potential. On the contrary, path sampling methods like weighted ensemble (WE) lack explicit mechanisms to overcome energetic barriers. However, they can accelerate the exploration of rugged free energy surfaces through trajectory resampling. We show that a judicious combination of the weighted ensemble with a metadynamics-like algorithm, OPES flooding, can synergize the strengths and mitigate the deficiencies of path sampling and enhanced sampling approaches. The resulting integrated sampling algorithm improves the computational efficiency of calculating the kinetics of conformational transitions in alanine dipeptide, protein unfolding, and the dissociation of a ligand-receptor complex. Furthermore, our approach can direct sampling along the minimum free energy pathway even when the collective variable used for biasing is suboptimal. These advantages make the integrated sampling algorithm suitable for studying the kinetics of complex molecular systems of biological and pharmaceutical relevance.

[1] “Integrating path sampling with enhanced sampling for rare-event kinetics”, Dhiman Ray. *The Journal of Chemical Physics*, 161(22) (2024).