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Weighted ensemble milestoning (WEM): A combined approach for rare event simulations

Dhiman Ray [1], Ioan Andricioaei [1]

Affiliations

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Abstract

To directly simulate rare events using atomistic molecular dynamics is a significant challenge in computational biophysics. Well-established enhanced-sampling techniques do exist to obtain the thermodynamic functions for such systems. However, developing methods for obtaining the kinetics of long timescale processes from simulation at atomic detail is comparatively less developed an area. Milestoning and the weighted ensemble (WE) method are two different stratification strategies; both have shown promise for computing long timescales of complex biomolecular processes. Nevertheless, both require a significant investment of computational resources. We have combined WE and milestoning to calculate observables in orders-of-magnitude less central processing unit and wall-clock time. Our weighted ensemble milestoning method (WEM) uses WE simulation to converge the transition probability and first passage times between milestones, followed by the utilization of the theoretical framework of milestoning to extract thermodynamic and kinetic properties of the entire process. We tested our method for a simple one-dimensional double-well potential, for an eleven-dimensional potential energy surface with energy barrier, and on the biomolecular model system alanine dipeptide. We were able to recover the free energy profiles, time correlation functions, and mean first passage times for barrier crossing events at a significantly small computational cost. WEM promises to extend the applicability of molecular dynamics simulation to slow dynamics of large systems that are well beyond the scope of present day brute-force computations.