Enhanced sampling for rare event kinetics with Milestoning

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Milestoning is an exact and efficient method for rare event kinetics calculation based on parallelization of short trajectory ensemble. Its accuracy depends on the initial distribution of these short trajectories and the ergodicity of trajectory sampling. We propose an enhanced sampling algorithm to improve the ergodicity of trajectory sampling by applying a biasing force. We derive exact expressions for underdamped and overdamped Langevin dynamics to reweight biased trajectories and examine its efficiency for a simple model system (Mueller's potential) and for bond breaking in solution. The use of a biasing force significantly enhances the sampling of otherwise rare trajectories but also introduces an exponential weight to the trajectories that significantly impact the value of the statistics. In our examples, computing averages and standard deviations are not better using the biasing force compared to straightforward Milestoning. However, the biasing force is useful for highly steep energy landscapes. On these landscapes, the probability of sampling straightforward Milestoning trajectories, which overcome the barrier, is low and the biasing force enables the observations of these rare events.