Have you tried turning it off and on again? Stochastic resetting for enhanced sampling

Barak Hirshberg
School of Chemistry, Tel Aviv University, Tel Aviv 6997801, Israel.

June 29, 2025

Molecular dynamics simulations are widely used across chemistry, physics, and biology, providing quantitative insight into complex processes with atomic detail. However, their limited timescale of a few microseconds is a significant obstacle in describing processes such as conformational transitions of biomolecules and polymorphism in molecular crystals. Enhanced sampling algorithms like Metadynamics bias the system in the direction of a chosen collective variable that ideally describes the slowest modes of the process. However, identifying collective variables in condensed phases is difficult, and the bias distorts the system's natural dynamics, making it hard to infer kinetic observables. I will present an alternative approach using stochastic resetting. It requires no prior knowledge, minimally perturbs the natural dynamics of the system, and provides a framework for inferring the system's unbiased kinetics. Metadynamics and resetting can be combined synergistically for conformational sampling of biomolecules, leading to higher acceleration than either approach separately and a more accurate prediction of unbiased mean first-passage times. I will also show how to design adaptive resetting strategies that further accelerate the sampling and are ideal for inferring another important kinetic observable called the direct transit time. In that case, Metadynamics with informed resetting leads to two to three orders of magnitude speedups over unbiased simulations with almost no loss of accuracy.

1. O. Blumer, S. Reuveni, and B. Hirshberg, J. Phys. Chem. Lett. 13, 11230 (2022).

2. O. Blumer, S. Reuveni, and B. Hirshberg, Nat. Commun. 15, 240 (2024).

3. J. R. Church, O. Blumer, T. D. Keidar, L. Ploutno, S. Reuveni, and B. Hirshberg, J. Chem. Theory Comput. 21, 605 (2025).

4. T. D. Keidar, O. Blumer, B. Hirshberg and S. Reuveni, arXiv:2409.14419.