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A novel replica exchange molecular dynamics variant for efficient conformational sampling and free energy calculations

Molecular dynamics (MD) simulations are routinely used to study the atomistic behavior of molecular systems. Unfortunately, conventional MD simulations often struggle to adequately sample the full configurational space of the process of interest because the requisite timescales exceed practical computational limits. To overcome this, enhanced sampling techniques such as replica exchange molecular dynamics (REMD) are increasingly employed to accelerate free-energy barrier crossing and enrich configurational sampling. Over the past decade a host of REMD variants has emerged, among which multi-dimensional exchange schemes and hybrid approaches combining REMD with metadynamics or accelerated MD. The proliferation of these variants reflects both the diversity of molecular systems (from small peptides in explicit solvent to larger macromolecular systems) and the continual drive to balance sampling efficiency against computational cost [1,2,3,4].

REMD involves running multiple simulations of the system in different thermodynamic states (e.g., different temperatures or Hamiltonians) in parallel, periodically exchanging the conformations among them. This exchange reduces correlation times and improves sampling efficiency by allowing the system to overcome kinetic barriers through transitions into neighboring states with lower barriers. Effective REMD requires moderate overlap in configuration space between neighboring states to facilitate these exchanges. Typically, exchanges occur at predefined intervals by attempting to swap the "final" configurations, including all atomic positions and momenta, between the neighboring thermodynamic states [1,2]. This approach implies a trade-off between the number of replicas spanning a given range of thermodynamic states and the phase space overlap, potentially leading to situations where the "final" conformations from the neighboring states exhibit a smaller-than ideal configurational overlap, thereby hindering efficient conformational sampling. Conversely, many closely spaced thermodynamic states are required to achieve optimal exchange rates in traditional REMD, partially negating its computational advantage.

In the present work, we introduce a new REMD variant that employs fewer thermodynamic states while maximizing exchange rates and therefore sampling efficiency. While we conceived this novel approach for the purpose of calculating adsorption free energies for disordered adsorbants, we demonstrate the method's validity by obtaining accurate solvation free energies for small molecules and accurate sampling of the conformational ensembles of short peptides.

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