The Hybridization of Generative Diffusion Models With Molecular Dynamics Simulations: a Novel Method to Accelerate Drug Discovery

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Drug discovery requires an understanding of protein conformations and ligand binding poses. Classical molecular dynamics (MD) can provide this understanding, but it is too slow to sample essential rare events like cryptic pocket opening, allosteric transitions, and ligand binding. I created diffusion-hybridized MD (dhMD), a method that intermittently proposes backbone torsion updates from a generative diffusion model and screens them with a Metropolis-Hastings criterion to preserve the equilibrium distribution. The method was evaluated in five 80 ns replicas of classical MD and dhMD on alanine dipeptide, a common benchmark system. dhMD trajectories achieved a 68-fold improvement (p=0.00755) in effective sample size per GPU-hour for the slow phi dihedral relative to classical MD. Equilibrium basin populations agreed within =5% across three low free energy basins. Accurate ligand binding mode populations are required for determining thermodynamic stability and binding affinity of protein-ligand complexes. I integrated diffusion into Binding Modes of Ligands Using Enhanced Sampling (BLUES), a method that uses random ligand rotations to accelerate sampling. Diffusion-hybridized BLUES converged to equilibrium ligand binding mode populations 4.22-times faster than BLUES on the T4-lysozyme and toluene system. This work shows that the integration of diffusion models into MD can achieve large gains in efficiency without distorting thermodynamic properties. Diffusion-hybridized methods have implications for the field of drug discovery, allowing for faster, more accurate, and more informative simulations. Future work will extend diffusion-hybridization to coupled protein, ligand, and solvent moves to accelerate coordinated rare events.

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