Learning Protocols for Non-Equilibrium Conformational Free-Energy Estimation Using Optimal Transport and Conditional Flow Matching

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Abstract

Accurate estimation of conformational free-energy differences is crucial in drug discovery, particularly for understanding protein-ligand stability and transitions that dictate drug binding and selectivity. Despite its importance, machine learning (ML) applications in this area remain limited, with existing methods relying on exhaustive equilibrium sampling of the Boltzmann distribution. We present an alternative approach using the Generalised Jarzynski Equality from non-equilibrium thermodynamics to estimate free-energy differences without equilibrium sampling. Specifically, we focus on deriving optimal minimal work protocols to switch between conformational states, leveraging Optimal Transport theory and proposing an efficient Conditional Flow Matching-based method to learn these protocols. Our experiments demonstrate the effectiveness of this approach in accurately estimating conformational free energies. Future work will aim to scale this method to larger, more complex systems relevant to drug development.

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