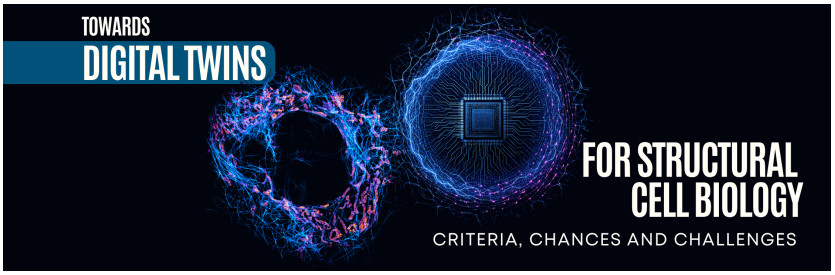

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Follow the MEP: Scalable Neural Representations for Minimum-Energy Path Discovery in Molecular Systems

Characterizing conformational transitions in physical systems remains a fundamental challenge, as traditional sampling methods struggle with the high-dimensional nature of molecular systems and high-energy barriers between stable states. These rare events often represent the most biologically significant processes, yet may require months of continuous simulation to observe. One way to understand the function and mechanics of such systems is through the minimum energy path (MEP), which represents the most probable transition pathway between stable states in the high-friction, low-temperature limit. We present a method that reformulates MEP discovery as a fast and scalable neural optimization problem. By representing paths as implicit neural representations and training with differentiable molecular force fields, our method discovers transition pathways without expensive sampling. Our approach scales to large biomolecular systems through a simple loss function derived from the path's likelihood via the Onsager-Machlup action and a scalable new architecture, AdaPath. We demonstrate this approach using four proteins, including an explicitly hydrated BPTI system with over 3,500 atoms. Our method identifies a MEP that captures the same conformational change observed in a millisecond-scale molecular dynamics (MD) simulation, obtaining this pathway in minutes on a standard GPU, rather than the weeks required on a specialized cluster.

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