Parallel search for competing molecular transition pathways in high-dimensional free energy landscapes

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In molecular dynamics simulations, insight often comes from free energy landscapes—with interpretable stable states, transition pathways and barriers—projected onto key system descriptors, or collective variables (CVs). However, the computational cost of rendering these landscapes scales exponentially with the number of CVs, limiting our ability to analyze complex transitions. To circumvent this issue, path-based methods—like our in-house developed path-metadynamics (PMD)—calculate a 1D free energy profile along an adaptive curve connecting two stable states in CV-space. This approach delivers the minimum free energy path (MFEP) in terms of the CVs, but is conditioned by the initial guess, and neglects alternative mechanisms that might contribute to the overall rate. Here, we extend the PMD framework to perform simultaneous calculations along multiple paths, and thus find the mechanisms and probabilities of competing pathways. Our framework relies on a multiple-walker multiple-path implementation in which the walkers are grouped to sample different pathways concurrently. To discourage that the different groups localize into the same, most likely, pathway, each group contains a special, non-metadynamics, walker that repels those from the other groups, or pinpoints a distinctive landmark. We illustrate the framework for two C7eq-to-C7ax paths in alanine dipeptide, and for six PPI-to-PPII paths in tetrameric polyproline, as well as for the more challenging Watson–Crick–Franklin-to-Hoogsteen base pairing transition in different DNA sequences. The scheme is highly flexible regarding the number of paths and repellers, the nature of the repulsive potential, and the choice of the biasing method along the paths. Our setup enables a parallel search for routes beyond the MFEP, broadening our perspective on complex transitions with many CVs, whose determination we also work on automating. Complementarily, we propose a scheme to render the free energy between the located paths, a measure of the probability of switching between mechanisms.

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