Enhanced Sampling and Reweighting Methods to Understand Rare-Event Kinetics of Cyclic Peptides

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Cyclic peptides are promising therapeutic candidates for targets with large and flat binding sites. Depending on their chemical structure and related dynamical properties, many cyclic peptides suffer, however, from low permeability across cellular membrane. We simulate the conformational dynamics of cyclic peptides in order to rationalize their membrane permeability and extract design principles. A recurring challenge is that the most interesting dynamics are slow and difficult to access within current simulation timescales. To overcome this limitation, methods that enhance the sampling efficiency can be employed but at the cost of altering the kinetics. Here, we aim to recover the original kinetics and metastable states by subsequent reweighting of the simulations based on path- and transition-probabilities. This method combination will allow us to study the slow interconversion between conformational states of cyclic peptides with significantly reduced simulation time.