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“Graph-Driven Methods for Exploring Protein Folding Mechanisms and Kinetics”

Thanks to AlphaFold, we can now predict native protein structures with remarkable accuracy. However, knowing the folded state alone provides limited insight into the folding process itself. Crucially, understanding the thermodynamic and kinetic properties of folding pathways, as well as the intermediate structures formed along the way, is key to revealing folding dynamics and mechanisms by which folding can fail as well.

Enhanced sampling simulations have long been valuable computational tools for exploring protein folding. Ideally, these methods should uncover both the folding mechanism and the kinetics of the process. Most approaches rely, to varying degrees, on molecular dynamics simulations. Here, we introduce a graph-based enhanced sampling methodology for studying protein folding that, notably, does not depend on molecular dynamics. Thanks to this framework, we can also construct Markov-state models without relying on MD simulations (well, almost).

Though still in early development, this method has shown promise on increasingly complex proteins, successfully tackling the challenging problem of multiple folding pathways and identifying previously unexplored kinetic traps. This work is part of a broader effort in our group to harness graph theory and network science as alternative tools for investigating the physical chemistry of molecular systems and condensed matter.