Investigating the conformational landscapes of FabH and Src kinase using all-atom molecular dynamics simulations

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All-atom molecular dynamics (MD) simulations are widely used to study the dynamic behavior of proteins. Here, all-atom MD has been used to investigate the conformational landscapes of two very different enzymes – FabH and Src tyrosine kinase. FabH is a dimeric bacterial ketosynthase involved in fatty acid synthesis. Experimental studies investigating the structure and catalytic behavior of FabH have revealed negative cooperativity between its two active sites. To investigate this functional asymmetry, microsecond timescale all-atom equilibrium MD was used. Initial results suggest that correlated behavior involving residues around the active site is observed in both monomers in the apo enzyme but disappears in one monomer when a substrate is present in the other active site. As most functionally relevant transitions occur on a timescale of several microseconds or longer, equilibrium MD is typically unable to sample all relevant conformations. Enhanced sampling methods bridge this gap by effectively extending the simulation timescale. To this end, an enhanced sampling technique called Adaptive Biased Path Optimization (ABPO) has been developed. ABPO has been used to identify the transition pathway between two known end conformations of Src tyrosine kinase in a reduced variable (RV) space. RVs are degrees of freedom that describe essential characteristics of biomolecular systems, allowing for exploration of complex conformational spaces. This technique employs unrestrained simulations to explore various conformations in the direction of the path, which may not be possible in other path-restricted methods. Insufficient sampling has been observed in different RV spaces, possibly due to the choice of RVs used for different combinations and the shape of the evolving path between the states. Identification of appropriate RV pairs to improve the sampling process is currently an area of focus. The long-term objective is to generalize the implementation of this method for various biomolecules with a more comprehensive workflow.