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Probing Biomolecular Machinery with Simulation Tools

By

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It is now well established that biomolecules undergo conformational fluctuations to perform a variety of cellular functions such as signal transduction, transport, and catalysis. Many experimental techniques such as X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, small-angle X-ray scattering (SAXS), and single-particle electron microscopy (EM) have indeed provided structural evidence at different resolutions to support the view of multiple functional states of biomolecules. Yet it remains difficult to characterize the vast conformational repertoire of biomolecules via experimental methods alone. Therefore, biophysical theory, modeling, and simulation techniques rooted in statistical mechanics are often useful for a detailed molecular understanding of biomolecular structures. Given the large number of degrees of freedom in biomolecules, conventional simulation approaches remain limited in providing information on conformational statistics, particularly metastable intermediates, at longer time-scales. Such information is often required for targeted therapeutic intervention in various disease states. Therefore, novel approaches are needed for extensive conformational sampling via biomolecular simulations. In this talk, I'll highlight the theory and applications of temperature-accelerated molecular dynamics (TAMD) in accelerating "slow" conformational changes in biomolecules via examples on enzymes, receptor proteins, and small molecule drugs. I'll also discuss how TAMD can be combined with state-of-the-art simulation methods to compute key thermodynamic properties such as the free-energy. In general, the simulation methodologies and concepts presented in this talk may have key implications for understanding biomolecular dynamics, enzyme catalysis, and solute transport at the molecular level.

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