SH2 and SH3. X-ray crystal structures of c-Src kinase are available for the inactive assembled state and an active-like re-assembled state, but the transition pathway and its dependence on the configuration of the SH2 and SH3 regulatory modules is still largely unsolved. Using molecular dynamics simulations and the string method with swarms-of-trajectories we have determined the transition pathway in both the assembled and re-assembled active-like conformations of the SH2/SH3 domains. Comparison of the active-like conformation of the catalytic domain in the two SH2/SH3 states shows that the re-assembled SH2/SH3 promotes a further opening of the catalytic site. The mechanism of the A-loop opening is also influenced by the SH2/SH3 domains. The calculated pathway provides novel insight into the influence of the regulatory models on kinase activation.

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Exploring pK_a Values for Buried Residues in Membrane Bilayers using Constant pH Molecular Dynamics Simulations

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Environmental conditions such as pH are considered to play profound roles in determining proteins' structures and functions. In recent years, several experimental and computational techniques have been developed to improve our understanding of the effects of pH on proteins. However, the implicit representation of solvents in the current constant pH molecular dynamics (CpHMD) methods can lead to undesirable side effects in calculating pK_a values of titratable side chains. These effects can be even more pronounced for membrane proteins where the rigid nature of the current implicit membrane models causes unrealistic pK_a shifts in favor of neutral states. Inspired by recently published pK_a values for Lys residues in model transmembrane peptides (Gleason NJ et al. (2013) PNAS 110:1692-1695), here we explore a newly developed CpHMD technique based on an all-atom representation of solvent/lipid molecules and proteins for simple transmembrane peptide models with a titratable side chain. The pK_a values of the side chains along with the pH dependent configuration of these peptides in the membrane bilayer are investigated and compared with the available experimental values. Motivated by the excellent agreement between the calculated pK_a values and the experiment for model peptides, the purely explicit CpHMD is also applied to study the pK_a values of titratable side chains of influenza A proton channel (M2) and its pH dependent structural change in the membrane bilayer.

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Robust Estimation of Diffusion-Optimized Ensembles for Enhanced Sampling

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Molecular dynamics and Monte Carlo simulation can provide detailed structural insights into biological systems by exploring the distribution of accessible conformational states. However, due to the rough free energy landscapes characterizing many systems, obtaining converged statistics in such simulation remains an important challenge. In order to address this issue, over the past decades, a number of enhanced sampling strategies have been proposed, including methods like simulated annealing, replica exchange, metadynamics and generalized ensemble approaches such as multicanonical (flat histogram) sampling. Most of these methods were designed to soften the landscape, making it easier to overcome the free energy barriers. Recently, it was proposed that additional performance gains could be obtained by taking the position-dependent diffusion coefficient along the reaction coordinate into account, thus placing greater emphasis on regions diffusing slowly so that the round trip rate is maximized (Trebst et al. 2004. 10.1103/PhysRevE.70.046701). Although the diffusion-optimized ensemble approach has shown great promise, the practical application of it has been hindered by the serious challenge of estimating the diffusion coefficient accurately, especially at the preliminary stage of a simulation when only a small part of the phase space has been explored. In this study, a simple yet robust solution to this problem is presented. We propose replacing the standard global estimation procedure with a local estimation technique that was previously introduced in the context of trajectory analysis and reaction coordinate optimization (Krivov et al. 2008. 10.1073/pnas.0800228105). We demonstrate that the precision of the proposed estimation method is dramatically increased, requiring considerable fewer data compared to current state-of-the-art procedures. Finally, we show that with our method, diffusion-optimized sampling arises as a natural generalization of the standard multicanonical ensemble, estimating a simple histogram of transitions rather than the usual histogram of states.

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Driven Adaptive-Bias Scheme: A Hybrid Free Energy Method for Biomolecular Systems with Complex Energy Landscapes

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We present a hybrid free energy calculation method that integrates two distinct classes of nonequilibrium sampling techniques, namely, driven and adaptive-bias molecular dynamics (MD) methods. We design a biasing protocol with an explicitly time- and history-dependent bias that uses on-the-fly work measurements to gradually flatten the free-energy surface. The scheme is general in that any variation of driven MD, e.g., steered MD (SMD) or targeted MD (TMD), can be integrated into any variation of adaptive-bias MD, e.g., metadynamics (MetaD) or adaptive biasing force (ABF). Two variations will be discussed in particular: (i) driven metadynamics (D-MetaD) and (ii) driven ABF (D-ABF) that use history-dependent biasing potential and force, respectively, in order to adaptively bias the system towards a flattened free energy landscape. The asymptotic convergence of both D-MetaD and D-ABF methods is discussed in the context of nonequilibrium work relations such as Jarzynski and Hummer-Szabo relations. We show that the adaptive term of the bias in both D-MetaD and D-ABF methods converges to the same stationary state as in their non-driven counterparts, if the convergence is reached. Employing nonequilibrium work relations, a method is proposed for accurate free energy reconstruction and error estimation. Several prototypical examples including polyalanine and polyproline peptides are used to numerically illustrate the superior efficiency and faster convergence of the method compared with its adaptive-bias and driven components in isolation. We show that driven adaptive-bias scheme is particularly useful to study systems with complex free energy landscapes such as those with multiple high free energy barriers in which non-driven adaptive-bias methods fail to converge in an achievable timescale. A publication introducing D-MetaD method recently appeared in J. Phys. Chem. Lett. (JPCL 4:1882, 2013).

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Going Backward: An Efficient Multiscale Approach using Reverse Transformation

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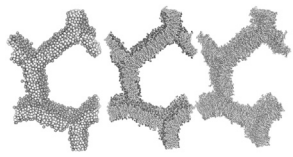
The conversion from coarse-grained to atomistic models is an important step in obtaining insight about atomistic scale processes from coarse-grained simulations. Here we present a new method for this conversion, combining geometric projection and force-field based relaxation. The projection is based on simple mapping definitions, describing the correspondence between particles. For the backbone reconstruction from a coarse-grained model a new algorithm is used, which, unlike most other methods, is geometrical, rather than statistical. The method is generic and can be used to map between any two particle based representations, provided that a mapping can be written. The method was tested on systems ranging from simple, single-component bilayers to a large protein-membrane-solvent complex.

We here show a simulation of 2006 lipid molecules, using the Cooke three-bead model, in which an inverted hexagonal phase is formed. The system is first converted to MARTINI representation, and subsequently converted to full atomistic detail, yielding a system of 1.8M atoms. In addition, we show how a large, fully solvated membrane-protein complex is converted from MARTINI to atomistic representation, allowing investigation of protein-lipid interactions at atomistic resolution after binding has occurred on the coarse-grained level.



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Mixing and Matching Simulations at Different Resolutions

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In multiscale molecular dynamics simulations the accuracy of detailed models is combined with the efficiency of a reduced representation.

For several applications _ namely those of sampling enhancement _ it is desirable to combine fine-grain (FG) and coarse-grained approaches into a single hybrid approach with an adjustable mixing parameter.

We present a benchmark of three such schemes _ multigraining, temperature-scaling, and mass-scaling. These algorithms use different approaches for