Computational Methods

2077-Pos Board B47

Coarse Graining Methodology for the Multiscale Simulation of Complex Biological Systems

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Computer simulation holds the promise of revealing the mechanisms of biological processes in their ultimate detail. Although atomistic molecular dynamics (MD) simulation using molecular mechanics potential functions has provided crucial insight into many aspects of chemical and biophysical systems, the characteristic times of biologically relevant processes remain out of reach. Here, a coarse graining methodology is presented for extending the size and timescale of the systems to be simulated. The multiscale development involves, (1) coarse graining via implicit solvent using Langevin equation, and (2) that of atomistic potential function onto residue-scale force field via our REACH method.

The two methods follow the same scheme in that mapping on the coarse-grained model is performed using all-atom MD simulation based on the all-atom potential energy function. In (1), the velocity autocorrelation function for each normal mode calculated from the atomistic MD was fitted to that from the Langevin equation, leading to a friction coefficient. The atomistic frictions were then derived from the solution and vacuum MD, allowing the solvent contribution to the friction to be examined. Langevin dynamics MD was performed to examine whether the implicit solvent MD including the derived atom-dependent frictions can reproduce the solution MD result. In (2), the residue-scale elastic network force constants were calculated from the atomistic MD for three proteins to show the transferability of the REACH method. The REACH force field was extended by combining with a double-well potential, allowing structural changes of the ligand-unbound adenylate kinase to be represented via residue-scale coarse-grained MD.

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Multiscale Simulation of Nucleation-limited Viral Capsid Assembly

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Viral capsids provide a striking example of the complexity and diversity in self-assembled biological systems. Computer simulations of capsids therefore serve as a valuable test bed for understanding and predicting the behavior of complicated macromolecular self-assembly in general. Previous work in our lab has focused on investigating pathway usage in model capsid assembly systems across broad parameter ranges primarily using models based on the stochastic simulation algorithm (SSA). The standard SSA, though, can become highly inefficient for multi-timescale problems, where important events occur in parallel and at a much slower rate than other relatively unimportant events. Recently, we have devised two new algorithms based on the spectral analysis of Continuous Time Markov Model (CTMM) graphs to accelerate sampling of rare events in SSA models. These methods are well suited for simulating a broad class of ''stiff'' reaction networks, including some important parameter domains for modeling self-assembly of nucleation-limited systems. We demonstrate these methods for use in modeling nucleation events and multi-bond dissociation events, important issues in accurately modeling capsid-like assembly near the critical concentration. We are now applying these methods to develop more accurate and efficient models of capsid assembly at low (*in vitro*) concentrations.

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Improved Coarse Grained Force-Field Parameters for Biomembranes

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Coarse-grained (CG) simulation method provides an important step in understanding cell fusion process. Based on the CG Martini force-field model (S. J. Marrink et al., J. Phys. Chem. B 2007, 111, 7812-7824), we are refining and reparameterizing the force-field parameters for the smaller molecules that are components of phospholipid membranes. For united-atom model, we have recently shown this from-the-ground-up derived force fields for the hydrocarbons and the smaller organic compounds are completely transferable to simulation of phospholipid bilayers, as evidenced by the recreation of x-ray form factors with a high degree of fidelity (S.-W. Chiu et al., manuscript submitted to J. Phys. Chem B.)

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Hierarchical Reduction Method of Protein Structures for Understanding Protein Dynamics

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Understanding protein dynamics is prerequisite for investigating the biological functions of proteins. Protein Dynamics has been understood based on atomistic model for protein structure. However, atomistic model has been computationally limited for large protein dynamics. In this talk, we address how to computationally solve the large protein dynamics problem by implementing the component mode synthesis method which allows the computations on low-frequency modes of large proteins. Specifically, component mode synthesis allows us to consider the vibration motion of each protein domain instead of whole protein structure, and then the dynamic characterization of each domain is assembled to provide the insight into dynamics of whole protein structure. (see Fig. 1) Hemoglobin was chosen as one of the model proteins in present study. Fig. 2(a) represents Hemoglobin model, Fig. 2(b) displays constraint points at boundaries between adjacent components. The mean-square fluctuations of model proteins are compared by both GNM and component mode synthesis in Fig. 3. It is remarkable that component mode synthesis provides the mean-square fluctuation qualitatively comparable to the one obtained by both GNM and experiment one, even though component allows one to reduce the computational burden on the mean-square fluctuation.

This suggests that the proposed method may allow for gaining insight into dynamics of supramolecules with computational efficiency.

Fig. 1. Configuration of a structure with components
(a) Hemoglobin(pdb code: 1a3n)
(b) Constraint points (dotted points) and four components (different colors)
Fig. 2 Hemoglobin target model
Fig. 3 Comparison of mean square fluctuation of X-ray crystallography, GNM modeling and component mode synthesis.

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Coarse-grained Molecular Dynamics of lipid bilayer membranes with multiple components

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Lipid bilayer membranes formed from multiple components can separate into coexisting liquid domains with distinct compositions. The formation of stripe and circular domains, curvature-dependent domain sorting, and membrane fission into separate vesicles have been observed experimentally.

We have developed a novel solvent-free coarse-grained model that allows free diffusion of membrane agents to simulate the phase separation and morphological evolution in the two-component liquid membranes. Depending on the line energy between the domains, a vesicle with uniform composition can undergo phase separation accompanied by the formation of stripe or circular domains. The formation of the complete spherical buds and the fission into separate vesicles at domain boundaries are also observed in our simulation. The distinct curvatures for phase-separated domains are apparent during the evolution of the vesicles. Our simulations are in agreement with several recent experimental observations.

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Prediction of Membrane Binding, Orientation and Permeability of Peptide-like Molecules Using a Continuum Model of the Lipid Bilayer

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The reliable prediction of membrane permeability of active compounds is essential for the success or failure in preclinical drug development. A new computational method for simulation of partition and transfer across cellular membranes of peptides and drug-like peptidomimetics has been developed. This method combines an all-atom representation of a solute and an implicit solvent model of the lipid bilayer, where lipid head groups, interfacial mid-polar and hydrocarbon core regions are represented by layers with distinct dielectrics and water permeation profiles. Parameters of these profiles were derived form published spin-labeling data, statistical distributions of membrane protein groups along the bilayer normal, and from modeling of energy profiles of 20 amino acid residue types included in an alpha-helical fragment that is gradually immersed into the lipid bilayer. The calculations account for atomic solvation, ionization, ionic and dipole interactions of the molecules with different membrane regions. The model combines an accessible surface area-based approach and the Born model. The required atomic solvation parameters and the electrostatic transfer energy costs have been derived from transfer energies of ~100 small organic molecules from water to five organic solvents. The method