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.

2078-Pos Board B48
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.

2079-Pos Board B49
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.)

2080-Pos Board B50
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.

2081-Pos Board B51
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.

2082-Pos Board B52
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

calculates the binding affinity of a solute molecule, its preferred spatial arrangement, lowest energy path and energy barriers along the membrane normal using solute 3D structure and pKa together with parameters of the membrane, such as surface, transmembrane potentials and pH values on both sides of the membrane. The method was tested for series of peripheral proteins, peptides and small molecules experimentally studied in lipid bilayers. Some of the results have been deposited in the Orientations of Proteins in Membranes database (http://opm.phar.umich.edu). The predicted membrane permeability of potential anticancer drugs, proapoptotic peptidomimetics correlates with their cellular activities.

2083-Pos Board B53
Generic Coarse-Grained Model for Protein Folding and Aggregation
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The complexity involved in protein structure is not only due to the rich variety of amino acids, consistent with the random heteropolymer picture, but also the weak interactions involved, comparable to thermal energy, and important cooperative phenomena. This presents a challenge in computer simulations, as it is associated with high-dimensionality and ruggedness of the free energy landscape as well as long equilibration times, frequently exceeding what can be handled in atomistic studies. We have recently developed a coarse-grained (CG) implicit solvent peptide model which has been designed to reproduce key consequences of the abovementioned weak interactions. Its intermediate level of resolution, four beads per amino acid, allows for accurate sampling of local conformations, in particular secondary structure, by designing a force field that relies on simple interactions (e.g. hydrogen bonds, hydrophobicity). A realistic ratio of alpha-helix to beta-sheet content is achieved by mimicking a nearest-neighbor dipolar interaction.
In the present study, we tune the model in order to fold helical proteins while systematically comparing the structure with NMR data. Very good agreement is achieved for proteins that have simple tertiary structures, which implies that the force field is able to reproduce important cooperativity features between amino acids. We further probe these effects by looking at peptide aggregation scenarios. Hydrophobic peptide fragments cooperatively form largescale beta-sheet structures. The model is able to reproduce features from atomistic simulations on a qualitative basis. The large-scale and long-term regime that this CG model offers, coupled with our design criteria (folding and realistic alpha/beta content), make it very suitable for many biological processes, such as misfolding and oligomerization involved in neurodegenerative diseases.

2084-Pos Board B54
Martini Force Field: Extension To Carbohydrates
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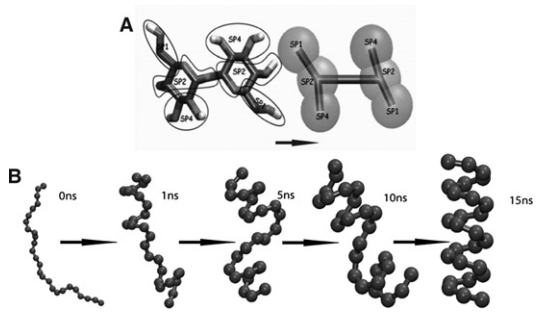
MARTINI force field: extension to carbohydrates
We present an extension of the coarse grained (CG) MARTINI force field (1) to carbohydrates. In line with the MARTINI force field development, the coarse grained model for carbohydrates has been systematically parameterized based on reproduction of experimental partitioning free energies in combination with mimicking the behaviour seen in atomistic simulations. Parameters were derived for all common mono- and disaccharides, considering the different ways of linking for monosaccharide units. The model has been tested on a number of small polysaccharides. For instance, the folding of a 26 (α 1-4) D-glucopyranose amylose chain was simulated both in a non-polar (nonane) and polar (water) environment. The folded structure is found to be similar for the CG and the all-atom model.



Coarse grain mapping of trehalose (A) and simulation of the folding of a CG 26-glucose amylose chain in nonane (B). For representation just the backbone beads are shown
The CG carbohydrate model is fully compatible with the previously parameterized lipid and protein models, and opens up the way to study a large variety of biological systems in which carbohydrates are important.
(1) S.J. Marrink, H.J. et al, JPC-B, 111:7812-7824, 2007.

2085-Pos Board B55
Scaal: A Robust, Accurate, And High-efficient All-atomistic Protein Reconstruction Method From Low-resolution Protein Models
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In the quest to develop multiscale molecular simulation methods for complex protein dynamics that fuse high-resolution and low-resolution protein representations, it is important to investigate the required information of reconstruction of all-atomistic proteins from low resolution ones with manageable uncertainly. In this paper, we introduce a robust, accurate, and fast reconstruction method (SCAAL) that produces reliable all-atomistic protein structure by taking few beads from a coarse-grained model with at least one side chain bead and one Cα bead in the backbone (Side chain-Cα Model, SCM) into accounts. Our algorithm (SCAAL) is compared with SCWRL3.0 and it excels in robustness and is more accurate in the reconstruction of large amino acids. In addition, we further test SCAAL in the reconstruction of a complete protein folding trajectory from SCM coarse-grained models. We show that the efficiency, accuracy, and robustness of SCAAL as leverage for multi-scale simulations are excellent in terms of low root mean square deviations that lie within 1Å resolution.

2086-Pos Board B56
Self-Learning Multiscale Simulation
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Molecular dynamics (MD) simulation plays more and more crucial roles in understanding the underlying molecular mechanisms of many biological processes. Unfortunately, due to the large number of degrees of freedom involved and inherently rugged energy surface, the time scale currently reachable by accurate all-atom (AA) simulation is far below typical biologically relevant time scale. Coarse graining the molecular representation can accelerate sampling, but the coarse grained (CG) simulation is unavoidably less accurate in energy estimate. To surmount these problems, a number of strategies have been proposed to integrate the AA and CG simulations, which is often called multiscale simulations. However, traditional multiscale methods heavily rely on the accuracy of the CG model. If the CG potential has its major basins different from those of AA potential, the multiscale simulation is not efficient and sometimes even bias the sampling. Here, we propose a new multiscale simulation method, self-learning multiscale molecular dynamics (SLMS-MD), which can achieve high accuracy and high sampling efficiency simultaneously. Based on the resolution exchange MD between atomistic and CG replicas, a self-learning strategy is introduced to progressively improve the initial CG potential by an iterative way based on the previously sampled CG conformations and their corresponding AA energies. The CG simulation ensures the efficient and broad sampling, and simultaneously the AA energies shape up the accuracy of the CG potential. Testing results show that the SLMS-MD can optimally combine the advantages of the AA and CG simulations, and achieve accurate and efficient multiscale simulations even when the initial CG potential is very poor. The resulting free energy converged to the exact result much faster than that by the replica exchange method. This method is generic and can be applied to many biological as well as non-biological problems.

2087-Pos Board B57
Simultaneous Use Of Class-i And Class-ii Force Fields In CHARMM For Solid-liquid Multiphase Simulation Of Protein-surface Interaction
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An appropriate understanding of conformational and behavioral changes of proteins upon their adsorption to synthetic surfaces is of crucial importance in the development of biomaterials because the changes play a governing role in determining cellular responses to implanted materials and substrates for tissue engineering. A detailed analysis of molecular behavior is key to such an understanding, and classical molecular dynamic (MD) simulation is one of the direct methods of addressing this issue. However, one of the challenges in using MD simulation is that class-I force fields (CHARMM, AMBER, OPLS, etc.) that have been parameterized for proteins are not suitable for