Molecular Dynamics II

2918-Pos

A Study of Lipid Transferability of a Bottom-Up Implicit Solvent Coarse-Grained Model for Bilayer Membranes

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Compared to top-down solvent-free Coarse-Grained (CG) bilayer models, a Bottom-Up Solvent-Free (BUSF) CG bilayer model not only possesses an improved computational efficiency, but also preserves chemical specificity and quantitative accuracy of membrane structure. This permits extensive applications of BUSF CG models in simulations of specific rather than generic membranes. The ability to transfer parameters from one lipid to another is thus highly desirable, because otherwise too many CG force-field parametrizations would be required, and the predictive ability of a BUSF CG force field would be very limited. Recently, we have derived a BUSF CG model capable of reproducing Radial Distribution Functions (RDFs), density profiles and saturated area per lipid of a POPC bilayer obtained from All-Atom (AA) simulations and experiments. We now study the transferability of this POPC force field to DPPC and DOPC lipids. Instead of matching the structure of one particular type of lipid membrane between CG and AA simulations, we aim to balance the errors in the BUSF CG bilayer force field between different types of membranes. Beyond RDFs and density profiles, we focus on a minimized and balanced error in saturated areas per molecule between different types of lipids, which we achieve by adjusting the parameters in our force field that account for the absence of the solvent. This study will improve the reliability of BUSF CG bilayer force fields for simulating large-scale phenomena that require membranes with varied/multiple lipid composition.

2919-Pos

An NMR Data Base for Simulations of Membrane Dynamics

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Validation of molecular simulations requires comparison with experimental data to confirm and test computational predictions. One rich area of computational effort is in the field of membrane biophysics. Here we report a comprehensive NMR data base containing the results of ^{13}C and ^{2}H NMR spin-lattice relaxation times (T_{1Z}) and segmental order parameters (S_{CD}) for various saturated, unsaturated, and biological membrane phospholipids. Relaxation rates recorded as a function of field strength (Larmor frequency) provide information about molecular dynamics. Moreover, experimental measurements of segmental order parameters give direct information about the bilayer lipid areas and hydrocarbon thickness. To guide molecular simulations, we introduce simple specific models for segmental, molecular, and collective bilayer motions in closed form. At a model-free level, we utilize the rate/order profiles as an expedient means for presenting the T_{1Z} and S_{CD} values plotted against hydrocarbon position [1]. This is similar to studies of proteins where regions of dynamic flexibility along the polypeptide backbone, unobservable from high-resolution resonances alone, are identified. Further model-free reduction of the T_{1Z} studies in terms of a power-law formalism shows that the relaxation rate-frequency dispersion for unsaturated and saturated phosphatidylcholines follow a single frequency dispersive trend within the MHz regime. Interpretations using specific motional models suggest that anisotropic rotational diffusion and order fluctuations are implicitly governed by the viscoelastic nature of the liquid-crystalline lattice involving collective lipid interactions [2]. Theoretical reductions are presented in order to foster understanding of biomembrane structural dynamics through the synergy of NMR measurements and molecular simulations.
[1] M.F. Brown, S.I. Chan, *Encyclopedia of Nuclear Magnetic Resonance*, Wiley, New York 1996, 871-885. [2] M.F. Brown *et al.* (2002) *JACS* **124,** 8471-8484.

2920-Pos

Graphical Causal Modeling of Protein Structural and Dynamical Features

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The causal relationship between protein structural features and conformational dynamics is difficult to isolate experimentally because even seemingly small perturbations, such as point mutations, can simultaneously alter many physical properties of proteins. Using molecular dynamics simulation trajectories for a series of point mutations at a single solvent-exposed position on the protein GB1, for which experimental NMR spin relaxation data also are available [1], effects of various types of inter-residue interactions are isolated via a graph-theory-based approach to causal modeling [2] previously applied in the biological sciences mainly to functional MRI studies [3] and genomics [4]. This approach produces directed acyclic graphs (DAGs) in which protein structural features such as hydrogen bonds, inter-residue contacts, and order parameters are encoded as nodes; the presence of an edge in the graph implies a causal relationship between features and the directionality of the edge implies the direction of causation.
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2921-Pos

Automated and Optimized Embedding of Proteins into Membranes for Molecular Dynamics Simulations using Griffin

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As new atomic structures of membrane proteins are resolved, they reveal increasingly complex transmembrane topologies, and often highly irregular surfaces with crevices and pores. In many cases, specific interactions with the lipid membrane are formed and are functionally crucial, as is the overall lipid composition. Compounded with increasing protein size, these characteristics pose a challenge for the construction of high-quality simulation models of membrane proteins in lipid bilayers; that these models are sufficiently realistic is of obvious importance for the reliability of simulation-based studies of these systems. To automate and optimize this process, we have developed GRIFFIN (GRId-based Force-Field INput). In the initial steps of this embedding protocol, the program carves lipid and water molecules out of the protein volume as necessary to conserve the system density. In the main optimization phase GRIFFIN adds an implicit, grid-based protein force field to the molecular simulation of the carved membrane-water system. In this force field, molecules inside the implicit protein volume experience an outward force that will expel them from that volume, whereas molecules outside are subject to electrostatic and van-der-Waals attractive interactions with the implicit protein. At each step of the simulation, these are updated by GRIFFIN and combined with the intermolecular forces of the explicit membrane-water system, to derive a trajectory of the atomic positions. This procedure enables the construction of realistic and reproducible starting configurations of the protein-membrane interface within a reasonable timeframe and with minimal intervention. GRIFFIN is a standalone tool it is designed to work with any existing molecular dynamics package, such as NAMD or GROMACS. Examples of challenging applications are presented.

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Detection of Functional Modes in Protein Dynamics

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Proteins frequently accomplish their biological function by collective atomic motions. Yet the identification of a collective motions related to a specific protein function from, e.g. a molecular dynamics trajectory or an NMR ensemble, is often non-trivial. Here, we propose a novel technique termed 'functional mode analysis' that aims to detect the collective motion that is directly related to a particular protein function. Based on an ensemble of structures, together with an arbitrary 'functional quantity' that quantifies the functional state of the protein, the method detects the collective motion that is maximally correlated to the functional quantity. Both linear and non-linear correlation are considered by the technique. The functional quantity could, e.g., correspond to a geometric, electrostatic, or chemical observable, or any other variable that is relevant to the function of the protein. The new method is illustrated using various biomolecules, including T4 lysozyme, Trp-cage, and Leucine-binding protein. As an outlook, we show how the methodology can be utilized to detect the dihedral angles related to large conformational transitions, and hence, to describe and manipulate such transitions by internal degrees of freedom of the protein.
References: JS Hub & BL de Groot, Detection of functional modes in protein dynamics, PLoS Comp Biol 5(8), e1000480 (2009)

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Computational Insights into Retinal Dynamics in Rhodopsin

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Rhodopsin is one of the primary systems for computational studies of G-protein coupled receptor (GPCR) activation pathways [1,2]. Activation occurs through isomerization of its covalently bound ligand, retinal, from an 11-*cis* to an all-*trans* conformation. FTIR spectroscopy studies indicated the importance of retinal methyl groups, clearly demonstrating that retinal desmethyl analogs caused