Molecular Dynamics II

2918-Pos

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

Zun-Jing Wang, Markus Deserno.
Carnegie Mellon University, Pittsburgh, PA, USA.

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

Avigdor Leftin, Michael F. Brown.
University of Arizona, Tucson, AZ, USA.

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.
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2920-Pos

Graphical Causal Modeling of Protein Structural and Dynamical Features

Kate A. Stafford, Arthur G. Palmer, III.
Columbia University, New York City, NY, USA.

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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[2] Pearl, J. (2000). Cambridge University Press, London; Pearl, J. (2009). Statistics Surveys. 3:96-146; Spirtes et al. (2000). MIT Press, Cambridge.
[3] Eichler, M. (2005). Phil. Trans. R. Soc. B. 360(1457): 953-967.
[4] Maathius, MH et al. (2009). Ann. Stat. 37(6A): 3133-3164.

2921-Pos

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

René Staritzbichler, **Lucy R. Forrest**, José D. Faraldo-Gómez.
Max Planck Institute for Biophysics, Frankfurt, Germany.

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.

2922-Pos

Detection of Functional Modes in Protein Dynamics

Jochen S. Hub[1], David Van der Spoel[1], Bert L. de Groot[2].
[1]Uppsala University, Uppsala, Sweden, [2]MPI for Biophysical Chemstry, Göttingen, Germany.

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)

2923-Pos

Computational Insights into Retinal Dynamics in Rhodopsin

Blake Mertz[1], Scott E. Feller[2], Michael F. Brown[1].
[1]University of Arizona, Tucson, AZ, USA, [2]Wabash College, Crawfordsville, IN, USA.

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

a backshift in the activation pathway [3]. Additionally, recent ^{2}H nuclear magnetic resonance (NMR) studies on retinal bound to rhodopsin hint towards a much lower methyl rotation activation barrier than observed in previous MD simulations [4]. Here we report quantum chemical calculations of torsional surfaces of model compounds and molecular dynamics (MD) simulations of the proteolipid complex in full atomic detail, to aid in the interpretation of the body of experimental data. Specifically, by using larger retinal fragments and a higher level of theory (MP2/cc-pVDZ), we are able to accurately reproduce the rotational behavior observed from ^{2}H NMR relaxation data [4]. For example, the relaxation data indicate an unusually low activation energy (E_a) for C9-methyl rotation, due to intraretinal interactions with H7 and H11 of the retinal polyene chain. These results in turn should lead to the ability to begin to simulate the coupling of small- to large-scale motions in rhodopsin activation. Ultimately, these efforts are aimed towards modeling more accurate comparisons to other GPCR proteins. [1] P.-W. Lau *et al*. (2007) *J. Mol. Biol.* 372(4) 906-917. [2] K. Martínez-Mayorga *et al*. (2006) *J. Amer. Chem. Soc.* 128(51) 16502-16503. [3] R. Vogel *et al.* (2006) *Biochemistry* 45(6), 1640-1652. [4] M.F. Brown *et al.* (2009) *Biochim. Biophys. Acta*, in press.

2924-Pos

Towards a Computational Model of Lignocellulose: Molecular Simulation of Lignin

Loukas Petridis, Jeremy C. Smith.
Oak Ridge National Lab, Oak Ridge, TN, USA.

Atomic-detailed computational models of lignocellulose can complement experiments in understanding its structure and dynamics. Here, we present results of Molecular Dynamics simulation of the plant cell wall polymer lignin. Polymer theory is employed to interpret these results. Finally the steps towards a realistic model of lignocellulose are discussed.

1. L. Petridis and J.C. Smith (2009); A molecular mechanics force field for lignin; Journal of Computational Chemistry 30 457-467
2. R. Shulz, B. Lindner, L. Petridis and J.C. Smith (in print); Scaling of Multimillion-atom Biological Molecular Dynamics Simulation on a Petascale Supercomputer; DOI: 10.1021/ct900292r

2925-Pos

Molecular Simulations of Dodecyl-D-Maltoside Micelles in Water: Influence of the Headgroup Conformation and the Force Field Parameters

Stéphane Abel[1], François Yves Dupradeau[2], E. Prabhu Rahman[3], Alexander D. Mackerell Jr.[3], Marchi Massimo[1].
[1]Commissariat à l'Energie Atomique, DSV/iBiTEC-S/SB2SM/LBMS, Saclay, France, [2]Laboratoire des glucides, UMR CNRS 6219, Amiens, France, [3]Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, MD, USA.

Dodecyl-D-maltoside (DDM) is a non-ionic glycolipid detergent with a maltose headgoup and a dodecan chain. It is used for the extraction and purification of membrane proteins from their natural environment. DDM has two anomers: one with a linear conformation (beta) and one with a right angle bend between the headgoup and the alkyl tail (alpha). Experiments show that the headgroup conformations change the micelle properties. However, little is known about the influence of the surfactant conformation on the micelle internal structure and hydration properties. To examine these aspects, we have used molecular dynamics (MD). MD was performed with micelles containing 75 and 132 alpha-DDM and beta-DDM monomers, respectively, at ambient conditions with different parameters (CHARMM22 and a newly developed force field (ff) compatible with GLYCAM06). We analyse the simulations in terms of the aggregate structure, surfactant conformations and interfacial water dynamic properties. Our results show that micelle properties vary with the force field used and that the simulations performed with the GLYCAM reproduce better the experimental findings from SANS or NMR. The micelles are slightly ellipsoidal with dimensions around 20.0 and 26.4 Å. The structures of the aggregate do not change significantly with the ff. Surfactant and the headgroup conformations show similar behaviour with an exception for the ether link between the headgroup and the tail. The dynamics of the interfacial water are 7-10 times slower than that of bulk water and seem, surprisingly, to be independent of the headgroup conformation. Finally, to evaluate the robustness of the simulations, we also performed additional runs with a new release of the CHARMM ff for disaccharide with new optimized parameters for the ether link. Comparison of these runs with the preceding simulations will be presented.

2926-Pos

Dynamics in Tethered Particle Motion: Interpreting the Observations

Sanneke Brinkers[1], Heidelinde R.C. Dietrich[1], Jurriaan J. Mes[2], Sjoerd Stallinga[1], Bernd Rieger[1].
[1]Delft University of Technology, Delft, Netherlands, [2]Wageningen UR, Wageningen, Netherlands.

Tethered Particle Motion (TPM) enables the researcher to examine the properties of semi-flexible polymers at the single molecule level. In TPM, a small reporter particle is tethered to a substrate using the polymer of interest. The particle motion reflects the mechanical properties of the tethering polymer.
We will present a framework in which the influence of the different experimental aspects on the measurement outcome are quantified. The key elements are tether length, particle size, exposure time, fluid properties and frame rate.
Here, we use 80 nanometer diameter gold particles, tethered to a glass slide by double stranded DNA, that are visualized by dark field microscopy. The recorded images of these highly scattering particles have a high contrast and signal-to-noise ratio; therefore the particle can be tracked with high spatial resolution (5-20 nm).
High temporal resolution is necessary to distinguish between different diffusion regimes. At very short time scales the particle is freely diffusing and on longer time scales its motion is influenced and eventually restricted by the retracting harmonic force of the tether. We will show that the diffusion coefficient of the free motion on short time scales is composed of the diffusion properties of both the particle and tether and that the harmonic potential stems from the entropic elasticity of the tether molecule. Motion blur caused by the finite exposure time has to be considered for computing the diffusion constant. Lastly, the choice of tether length and particle size play an important role as well. They determine how often the particle will be in proximity of the substrate where particle-substrate interactions such as van-der-Waals and electrostatic forces play a bigger role.

2927-Pos

Md-Based Method for Computing Configuration Integrals Provides Ability to Test Force Fields

Gevorg Grigoryan.
University of Pennsylvania, Philadelphia, PA, USA.

Modern force fields allow the study of biological molecules in atomistic detail. However, too often computational limitations prohibit one from computing many biologically relevant measures such as folding energies and rates, differential population of alternate biological states, and binding affinities. This makes it difficult to test and improve upon the accuracy of force fields for such thermodynamic applications. In this work, new methods are presented for computing the configuration integral of biological molecules both around specific structural states as well as over all of phase space. These methods are based on Molecular Dynamics simulations and can be applied with any force field, including ones with explicit solvent. The methods are applied to study several problems. First, as a proxy for the random-coil state, free energies of hexa- and hepta- peptides are studied as a function of their sequence. Surprisingly, it is demonstrated that the Random Energy Model describes quite well the relationship between sequence and energy, indicating that individual amino acids contribute to the overall free energy largely in a context-independent manner. Second, the ability of EEF1 force field to reproduce experimental helix propensities is studied by computing relative helix folding energies of short peptides. Values computed for polar and non-polar amino acids, separately, show moderate correlation with experimental data. However, the two groups are out of scale with one another, indicating an imbalance between polar and hydrophobic interactions in the force field. Further, each group has two clear outliers - Val/Ile for non-polar amino acids and Lys/Arg for polar ones, suggesting additional avenues for improvement of EEF1. The success of the presented methods has far reaching implications not only for force field development and validation, but also for such areas as computational protein design and drug discovery.

2928-Pos

Molecular Dynamics Simulations of the AAA Protein P97

Jeff Wereszczynski, James Andrew McCammon.
University of California, San Diego, La Jolla, CA, USA.

The mechanocoupling of energy stored in triphosphate nucleosides provide the power necessary for many fundamental *in vivo* processes. The highly abundant protein p97 (also known as valosin-containing protein) is one of the most widely studied members of the AAA protein family (ATPases Associated with various cellular Activities), and is involved in numerous cellular functions such as nuclear envelope assembly, retrotranslocation of misfolded proteins from the endoplasmic reticulum to the cytosol, reformation of the Golgi following mitosis, and the IκBα pathway. Structurally, each monomer is composed of two hydrolysis domains (D1 and D2 with only D2 being catalytically active under standard cellular conditions), an N-terminal domain that interacts with effector proteins, a C-terminal domain, and linker regions between them. In solution, proteins hexamerize into stacked-ring shaped complexes with rings formed by each of the hydrolysis domains. Here, we present results from molecular dynamics simulations on each of the four predominant hydrolysis states