Membrane Dynamics & Bilayer Probes II

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Lipid-Protein Interactions of Rhodopsin Investigated by Molecular Dynamics Simulations

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Rhodopsin is currently one of two proteins of the G protein-coupled receptor (GPCR) family for which an atomic-resolution structure is available and therefore it serves as a prototypical GPCR. Over 50% of recently launched drugs are targeted to GPCRs so that these proteins are of outstanding pharmaceutical interest. Yet many aspects of the structure-function relations of rhodopsin are only poorly understood. Especially interesting is the important role played by highly unsaturated lipids in achieving full functionality. In this study we investigated lipid-protein interactions of rhodopsin through a series of molecular dynamics (MD) simulations. Rhodopsin was inserted into a membrane consisting of a 2:2:1 mixture of 18:0,22:6n3PE, 18:0,22:6n3PC, and cholesterol. MD simulations with a total trajectory of ~4 microseconds were conducted on the IBM Blue Gene/L supercomputer. Additional simulations were carried out for rhodopsin in membranes consisting of 18:0,18:1PC and 14:0,14:1PC. This allowed direct comparison of the lipid-protein interactions of rhodopsin in monounsaturated and polyunsaturated environments as well as bilayers of varying thickness. Our analysis focuses on the palmitoylations of two adjacent cysteins in helix 8 of rhodopsin which are a common structural motif in many proteins related to signal transduction. As seen in our earlier studies on lipid modifications of smaller proteins, these are generally highly flexible and best characterized by their dynamical structure. We calculated order parameters and correlation functions from the simulation trajectories and compared them to experimentally obtained results on lipid modifications of other proteins. In general we find the that the palmitoyl modifications of rhodopsin are highly flexible which can affect the binding free energy of the polypeptide to the membrane surface. Entropic contributions due to the configurational disorder of the posttranslational modifications reduce the binding energy so that doubly palmitoylated modifications are needed.

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Dynamic Structure Factors From Lipid Membrane Molecular Dynamics Simulations

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The dynamics of biological membranes is present on many time- and length scales, from the pico-second vibrations of single lipid tail groups to micro-second collective undulations of hundreds of lipid molecules. These motions can be probed as local density fluctuations, and characterized and measured in different ways. Inelastic scattering experiments as well as computer simulations of biological membranes are usually theoretically interpreted within the framework of generalized hydrodynamics, where the dynamic structure factor, S(k,w), is the quantity of interest. S(k,w) is the space and time Fourier transform of the density-density correlation function and contains all the relevant information about the dynamics of a liquid system. We have performed large-scale molecular dynamics simulations from which we have calculated the dynamic structure factors for a lipid bilayer in the high temperature phase, enabling a thorough test of theoretical predictions, especially in the hydrodynamic limit of low wave vectors. The frequency and wave vector resolutions are considerably improved compared to traditional experiments, which make it possible to directly resolve the lines of the power spectrum. Membrane material constants have been determined and compared in fair agreement to experimental data. In addition, from the power spectrum we can distinguish two dispersive contributions to the elastic scattering. These correspond to two exponential relaxation processes on separate time scales. For low wave vectors, this analysis was impossible due to insufficient frequency resolution. To be able to fully decouple and analyze the nature of these dispersive modes from simulations, longer trajectories are required.

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Anomalous Diffusion Of Lipid Atoms And Molecules In Phospholipid Bilayers: A Combined Molecular Dynamics And Theoretical Study

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Individual atoms and lipid molecules in biologically relevant phospholipid bilayers have an extremely rich dynamics that extend on a wide range of time and length scales. Computer modeling and simulations can be used effectively both to investigate the dynamics of such complex systems and to interpret the results from a variety of experimental techniques employed to probe such systems. Here we present an all-atom molecular dynamics (MD) simulation, combined with theoretical modeling, to investigate the dynamics of selected lipid atoms and lipid molecules in a hydrated diyristoyl-phosphatidylcholine (DMPC) lipid bilayer. From the analysis of a 0.1 microsecond MD trajectory we find that the time evolution of the mean square displacement (MSD) of lipid atoms and molecules exhibits three well separated dynamical regions: (1) for short times ($t <$ 10 fs) the motion is ballistic with a quadratic in time MSD; (2) for intermediate times (10 ps $<t$ 30 ns) the MSD is linear in time, corresponding to ordinary Fickian diffusion. The origin of the extended anomalous, sub-diffusive region is attributed to the polymeric nature of the lipid molecules, characterized by connectivity and flexibility. We propose a memory function approach for calculating the MSD over the entire time range, from the ballistic to the Fickian diffusion regimes. The lateral self-diffusion coefficient of lipid molecules determined by employing the memory function approach is found to be in good agreement with the one calculated directly from the long time MD trajectory of the lipid bilayer. The proposed memory function approach is a useful tool for interpreting neutron scattering experiments on lipid membranes.
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Fusion of Biomimetic 'Stealth' Probes into Lipid Bilayer Cores

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The ability to specifically and non-destructively incorporate inorganic structures into or through biological membranes is essential to realizing full bio-inorganic integration. This research explores a new method for interfacing inorganic structures with cellular membranes using nanometer-scale hydrophobic bands to specifically interact with the lipid bilayer core. Similar to the structure of transmembrane proteins, thin hydrophobic bands allow targeted formation of interfaces between lipid bilayers and macroscopic inorganic objects.
In this work, we show that by fabricating custom atomic force microscopy (AFM) probes that possess 2-10 nm hydrophobic bands formed through molecular self assembly, specific interaction with the hydrophobic core of lipid bilayers can be achieved. When hydrophilic probes are penetrated through stacks of lipid bilayers they exhibit distinct breakthrough distances of 2.9 +/− 0.3nm, corresponding to the hydrophobic core thickness of 2:1 SOPC:Cholesterol bilayers, followed by linear relaxation through the water layer between bilayers. In contrast, 'stealth' probes possessing a thin hydrophobic band exhibit strong association with the bilayer core, ''jumping'' 5.6 +/− 0.6nm from bilayer core to bilayer core, which corresponds to the compressed lamellar spacing of the bilayer stacks.
In addition, by using AFM, it is possible to examine how the properties of the hydrophobic band affect the adhesion strength between the bilayer and stealth probe. Molecular mobility, hydrophobicity, and orientation all have a role in determining the interface behavior, and in turn the potential applications for a given surface functionalization.

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Simulations of the Morphological Evolution of Lipid Bilayer Membranes Using a Phase-Field Method

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We present a continuum-level simulation method for modeling phase separation and morphological evolution of multicomponent lipid bilayer membranes. Our objective is to investigate how various physical parameters input into the model, such as spontaneous curvature, phase fraction, and interleaflet coupling strength, affect the dynamics and equilibrium morphological phases formed in two-phase lipid bilayer membrane systems. The model applies to membranes with planar and spherical background geometries, simulating a nearly planar portion of membrane or entire vesicle, respectively. The compositions and shape of the membrane are coupled through a modified Helfrich free energy. The planar model treats the composition of each leaflet, and thus includes a term coupling these compositions across the bilayer. The compositional evolution is modeled using a phase-field method and is described by a Cahn-Hilliard-type equation, while shape changes are described by relaxation dynamics. For nearly planar bilayer systems with each leaflet having the same phase fraction, we find that domains in both leaflets align to reduce the interaction energy, as expected. When the coupling effect is stronger, this alignment occurs more