Furthermore, this water results in significant electrostatic screening, an important consideration when building theoretical and computational models of membrane remodeling. We suggest that this electrostatic screening is at least partly responsible for our observations that multiple, oligomerized N-BAR domains largely fail to bend flat membranes. Our results support the insertion of hydrophobic moieties as the major driving force of membrane remodeling by N-BAR domains.

2522-Pos

Mesoscopic Simulations of Membrane Protein Trafficking and Signal Transduction Across Membranes

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Palmitoylation is a frequent posttranslational modification that triggers the membrane association of soluble proteins. Besides those peripheral membrane proteins (PMPs) also many transmembrane proteins are subject to lipid modifications, hence indicating that these membrane anchors may also regulate the trafficking of transmembrane proteins. Using coarse-grained membrane simulations we find that palmitoylation indeed significantly alters the tilting of transmembrane proteins with respect to the bilayer normal. Cluster formation and partitioning behavior due to hydrophobic mismatching with the surrounding lipid bilayer is also altered, therefore allowing for ample possibilities to regulate the trafficking of transmembrane proteins via palmitoylation. Using the same simulation approach, we also have studied the trafficking of peripheral membrane proteins (PMPs). In particular, we have observed a cross-leaflet oligomerization of PMPs due to membrane mediated attraction. The strength of this effect is determined by the radii and membrane anchor lengths of the involved PMPs. Since both of these might be altered, for example by ligand binding, the observed cross-leaflet oligomerization may be the fundamental process by which PMPs can trigger an intracellular signalling cascade without the need for accessory transmembrane factors.

2523-Pos

Positioning of Proteins in Membranes of Variable Lipid Composition

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A novel anisotropic solvent model of the lipid bilayer has been developed and applied for calculating energetically optimal translational and rotational positions of proteins in different types of biological membranes. The spatial positions are refined for the entire set of ~900 distinct protein structures currently in the OPM (Orientations of Proteins in Membranes) database (http://opm.phar.umich.edu). The bilayer is represented as a fluid anisotropic solvent described by profiles of dielectric constant, solvatochromic dipolarity/polarizability parameter, and hydrogen bonding acidity and basicity parameters that change gradually along the bilayer normal, including the lipid head group region. The profiles of several artificial phospholipid bilayers have been calculated based on the published distributions of their molecular segments determined by neutron and X-ray scattering. The profiles were also simulated for biological membranes based on their lipid composition including eukaryotic plasma membrane and bacterial inner and outer membranes. Transfer energy of the protein includes a solvent accessible surface area-dependent contribution (first solvation shell energy) and a long-range electrostatic component for group dipole moments and ionized groups, as well as ionization energy. Application of this model to transmembrane and peripheral proteins from the OPM resulted in a more precise and reliable calculation of their spatial positions and membrane binding affinities. Membrane-binding regions of numerous peripheral proteins have been identified during Protein Data Bank screening. The analysis of membrane association for peripheral proteins from the Structural Genomics projects helps to assign their biological functions, as illustrated for proteins from calycin and SpoIIAA superfamiles.

2524-Pos

Modeling Lipid-Mediated Transmembrane Protein Aggregation

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Many transmembrane proteins play crucial roles in cell signaling, and lipid-mediated association of these proteins may well have a role to play in these pathways in addition to protein-specific interactions. We seek to gain insight into the large-scale aggregation effects induced by lipid-mediated hydrophobic driving forces previously revealed in coarse-grained molecular simulations [de Meyer, Venturoli, and Smit. Biophys J. (95) 2008]. The molecular coarse-grained model of transmembrane peptides and lipid bilayers focused on the impact of hydrophobicity and of simple molecular structures on the association between small numbers of peptides. We build on this previous work by developing a computationally feasible model of protein-protein interaction which captures the driving forces relevant for aggregation of small numbers of peptides as well as the highly non-additive effect of the surrounding lipid as the peptides further aggregate. Such a model is better able to capture large-scale aggregation and organization of proteins via the lipid bilayer and to explore the consequences of the driving forces of aggregation at the experimentally relevant time scales and length scales.

2525-Pos

Modeling the Membrane Role in Ca^{2+}-ATPase Catalytic Cycle

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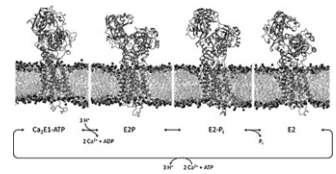
A deep understanding of the function of membrane proteins requires that we understand the direct and indirect effects of the lipid environment. Deformations of the bilayer to accommodate the protein induce energy penalties and potentially change the free energy between conformational states and thereby change the distribution of protein conformations. The lipid bilayer thus plays a regulatory role for the function of a membrane protein.

Structures of the Ca^{2+}-ATPase from sarcoplasmic reticulum, SERCA, have been determined by X-ray crystallography in several different functional states. These structures have provided a unique opportunity to study how the protein interacts with the membrane throughout the functional cycle by all-atom molecular dynamics (MD) simulations.

MD simulations have been performed with four different structures of SERCA representing a Ca^{2+}- and ATP-bound state (Ca_2E1-ATP); a state with the luminal Ca^{2+}-exit path open and the protein phosphorylated (E2P); and two dephosphorylated occluded states with bound protons, one with inorganic phosphor still bound (E2-Pi) and one without (E2). Our results show how the POPC-membrane and the protein in different functional states undergo mutual adaption (see figure) and how the hydrophobic mismatch and protein area profile change during the functional cycle.



2526-Pos

Monte-Carlo Simulations of Peptide-Membrane Interactions: Web-Server

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Short peptides interact with biological membranes in many ways. For example, antimicrobial peptides destabilize bacterial cell membrane, while fusion peptides of viral proteins promote membrane fusion. Short peptides may mimic the interaction of integral membrane proteins with the membrane and thus are a convenient model system to study the folding and insertion of membrane proteins into the hydrophobic environment of the membrane. Along with various experimental techniques, computational methods are also used in research of peptides-membranes interactions. We have previously developed a Monte Carlo (MC) simulations model for the investigation of linear α-helical peptides with membranes. This model was tested on an assortment of peptides, such as Magainin2, penetratine, M2δ peptide (a transmembrane segment from the acetylcholine receptor δ-subunit), melittin and NK-2 and its derivatives. The results of the simulations correlated very well with empiric data. Moreover, these computations were used to guide further experimental efforts. Encouraged by these studies, we are establishing a web-server to allow external users to perform simulations of their peptides of interest in membrane and water environments. The server will provide a possibility to choose the amino acid sequence of the peptide, the ratio of zwitterionic-to-acidic lipids and width of the bilayer, and the ionic strength. The results will include the free energy of membrane-association of the peptide, its helical content upon membrane interaction as well as its predicted location in the membrane.

Membrane Structure II

2527-Pos

Probing the Membrane Deformations Induced by Binding of Membrane Proteins: Alpha-Synuclein and CRAC

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Using a combination of all-atom and coarse-grained molecular dynamics simulations to interpret a range of x-ray scattering experiments, we aim to understand the role of membrane deformation in the action of the Parkinson's Disease protein, α-Synuclein. Our simulation results have led to the hypothesis that αS flattens curved membranes by screening the repulsive interactions between negatively charged, acidic headgroups, thereby reducing the effective area per headgroup and relieving the inherent positive curvature of the lipids on the outer leaflet of synaptic vesicles. We hope to address the question of whether αS influences a membrane's mechanical properties as a route to evaluating this hypothesis. Additionally, we aim to understand the role of αS in recruiting sub-domains of positively charged lipids. A second, smaller peptide (the CRAC motif from gp41) is also studied in an effort to build the computational tools necessary for matching the x-ray data that is used for calculating a membrane's material properties.

2528-Pos

Effects of Subphase on Collapse Behavior of Lung Surfactant

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The phase behavior of binary fluids next to interfaces can be complex. If one fluid has a more favored interaction with the interface the fluids can phase separate in some interfacial region extending into the bulk. Using neutron and x-ray reflectivity, we show phase separation of water/glycerol mixtures next to lipid monolayer interfaces. The glycerol forms a thin layer ten angstroms deep underneath the monolayer. This non-equillibrium interfacial phase separation greatly impacts the mechanical properties of the lipid monolayer. Moreover, the thermodynamic driving force for this de-mixing is complex. Usually such de-mixing is observed when two miscible fluids have significantly different surface tensions at a given interface. However glycerol and water are miscible and have nearly identical surface tensions at the air/water interface. Our work probes what surface tension and interfacial free energy mean in the setting of more complex interfaces. The preference partitioning of glycerol to the interface affects the collapse behavior of the lipid film and has implications on the collapse mechanism of lung surfactant which sits atop an alveolar lining fluid enriched in sugar biopolymers.

2529-Pos

Oxygen Diffusion Through Lung Surfactant Layers

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Pulmonary surfactant, a lipid-protein complex covering the air-liquid interface of alveoli, is essential for preventing alveolar collapse at the end of expiration. To do so, surfactant reduces surface tension by forming a surface-active interfacial film, which has to be crossed by oxygen to reach the pulmonary epithelium and the capillary. The effect of the presence of the pulmonary surfactant layer in oxygen diffusion has not been properly evaluated.
Here we have developed a special setup using luminescent Rutenium-containing organo-metallic oxygen sensors to measure oxygen diffusion rates through capillary water layers containing different concentrations of pulmonary surfactant lipid or lipid-protein preparations.
The potential role of surfactant and the structure of surfactant membrane network in terms of facilitating oxygen diffusion through the air-water respiratory interface will be discussed.

2530-Pos

Molecular Organization of the Tear Film Lipid Layer

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Purpose. To describe the molecular organization of the anterior lipid layer of the tear film.
Methods. Artificial tear fluid lipid layers (ATLL) were deposited on the air-water interface and their physico-chemical behavior was compared to egg-yolk phosphatidylcholine (eggPC) monolayers by using Langmuir-film balance techniques, X-ray diffraction, atomic force microscopy, and Brewster angle microscopy. These experimental approaches were complemented by *in silico* molecular level simulations.
Results. In contrast to eggPC monolayers compression isotherms of the ATLL suggested that at higher surface pressures the ATLL films were no longer monolayers. ATLL films had a lower compressibility compared to eggPC lipid films. At π=20 mN/m both samples or part of the samples were in the condensed phase. Brewster angle microscopy suggested that in the case of ATLL a clear phase separation was observed. Atomic force microscopy preformed at π=20 mN/m showed only a smooth surface for eggPC, whereas for ATLL lipoprotein-like particles were protruding from the otherwise smooth lipid film. Computer simulations on eggPC and ATLL yielded a detailed picture of the atomic level organization of eggPC and ATLL residing on the air-water interface and supported the experimental findings.
Conclusions. Here we provide detailed structural analysis of eggPC and ATLL films deposited on the air-water interface. The results are discussed in the context of *in vivo* function of the tear fluid.

2531-Pos

Molecular Scale Texture and Topological Defects in Lipid Membranes: A New Liquid Crystalline Phase

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Lipid membranes are self-organizing structures that define intercellular and intracellular interfaces in biological systems. Grazing incidence x-ray diffraction (GIXD), provides a sensitive probe of the local, molecular structure and packing of lipid molecules within single membranes. For example, diffraction clearly establishes that dipalmitoyl-phosphatidylcholine (DPPC) membrane leaflets are always coupled across the bilayer, and that even when leaflets are deposited independently the membrane rapidly self-organizes so that opposing lipid tails scatter as one entity. Variation in the azimuthal tilt direction of the lipid tails was required to reproduce the diffraction data indicating an orientational texture of lipid molecules and smectic domains formation identical to larger scale textures observed in many 2-D liquid crystalline systems, but at a molecular scale.
A similar phenomenon is also observed when proteins bind to membrane receptors. The interplay between lipids and proteins is complex: lipids can influence the structure and function of membrane proteins and at the same time proteins can impact lipid organization. In this example, lipid monolayers at the air-water interface containing the ganglioside GM1 were studied in the absence and presence of cholera toxin. At low surface pressures, protein binding perturbed the lipid order such that the molecules were no longer close packed, creating topological defects and lipid-protein domains with orientational texture. This new lipid phase may be a mechanism for toxin penetration and potentially has far broader implications in biological signaling.

2532-Pos

Calculation of Interleaflet Domain Coupling in Mixed Lipid Bilayers

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The coupling between the physical states of the two leaflets (monolayers) of a lipid bilayer is a subject of current interest in relation to both the biology of lipid rafts and the physics of model membranes capable of liquid-liquid phase separation. In these model systems there is experimental evidence of a large coupling which maintains micron-scale registry between domains in the two leaflets. Nevertheless, the mechanism of this coupling has been unclear. We have performed a mean-field calculation with molecular detail to evaluate the contribution to this coupling due only to lipid tail interdigitation. By comparing the free energies of symmetric and asymmetric lipid compositions, we obtain a coupling strength of 0.2 kT per square nanometer. This is enough to account for micron-scale domain registry and is in favorable agreement with a recent estimate from a coarse-grained molecular dynamics simulation. Our result supports the hypothesis that lipid interdigitation is the dominant mechanism for interleaflet domain coupling in model membranes capable of liquid-liquid phase separation.

2533-Pos

Assembly of Lipid Bilayers in Large Scaffold Arrays

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