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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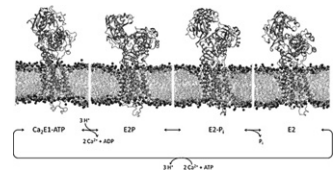
A deep understanding of the function of membrane proteins requires that we understand the direct and indirect effects of the lipid environment. Deformations of the bilayer to accommodate the protein induce energy penalties and potentially change the free energy between conformational states and thereby 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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