View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

2671-Pos Board B657
Quantitative Analysis of Membrane Deformation by Multi-Helical Transmembrane Proteins
Sayan Mondal, George Khelashvili, Jufang Shan, Lei Shi, Olaf Andersen, Harel Weinstein.
Increasing evidence suggests that the function of G-protein coupled receptors (GPCRs), ion channels, and other membrane proteins depends on their lipid membrane environments. Several such observations have been explained in terms of hydrophobic mismatch effects in protein/membrane interactions. We have developed a novel multi-scale approach to examine this problem, in which we combine the continuum elastic theory of membrane deformations with atomistic molecular dynamics (MD) simulations to quantify the hydrophobic mismatch-driven bilayer remodeling around membrane insertions, and calculate the corresponding energetics. Allowing for radially asymmetric bilayer deformations and for irregular membrane-protein boundary, our approach enables the study of membrane remodeling by multi-helical membrane proteins. The standard Euler-Lagrange formulation is used to calculate the equilibrium membrane shape that minimizes the system's free energy functional, with energy terms including membrane compression-expansion, splay-distortion and surface tension, as well as the residual mismatch energy contribution occurring from partial alleviation of the hydrophobic mismatch. We solve the partial differential equation self-consistently; the protein-membrane boundary contour, and the boundary conditions on bilayer thickness at the membrane/protein interface and in the ''bulk'' are obtained from cognate MD simulations. The approach is illustrated with calculations for rhodopsin in lipid bilayers of different thicknesses, for the serotonin 5-HT_{2A} GPCR in complex with different ligands, and the leucine transporter in its three key conformations viz., outward-facing, inward-facing, and occluded. Our analysis has identified quantitatively, for the first time, 1) the key role of the residual mismatch at specific transmembrane domains in hydrophobic mismatch-driven oligomerization of GPCRs; and 2) a new mechanistic hypothesis about the manner in which the distinct ligand or substrate-induced conformations of GPCRs, or transporters, can result in differential function of these proteins through differential effects on the membrane environment.

2672-Pos Board B658
Cholesterol Modulates the Membrane Effects and Spatial Organization of Membrane-Penetrating Ligands for G-Protein Coupled Receptors
George Khelashvili, Sayan Mondal, Olaf S. Andersen, Harel Weinstein.
The ligands of certain G-protein coupled receptors (GPCRs) reach their target from the lipid bilayer. We have probed the organization and dynamics of a such lipid bilayer-penetrating ligand, the endogeneous ligand for kappa-opioid receptor (KOR) dynorphin A (1-17) (DynA), using molecular dynamics (MD) simulations of DynA in cholesterol-depleted and cholesterol-enriched model membranes. DynA penetrates deep inside fluid dimyristoylphosphatidylcholine (DMPC) bilayers, and resides with its N-terminal helix at ~6Å away from the bilayer mid-plane, in a tilted orientation, at ~50°C angle with respect to membrane normal. In contrast, inside DMPC/Chol membranes with 20% cholesterol (DMPC/Chol) the DynA is situated ~5Å higher, i.e. closer to the lipid/water interface and in a relatively vertical orientation. Compared to the DMPC/Chol membranes, the DMPC membrane shows greater thinning around the insertion and permits a stronger influx of water inside the hydrocarbon. Relating these results to data about key GPCR residues that have been implicated in interactions with membrane-inserting GPCR ligands, we conclude that the position of DynA correlates with generally proposed GPCR ligand entry pathways in DMPC/Chol, but not in pure DMPC. Our predictions provide a possible mechanistic explanation as to why DynA binding to KOR, and the subsequent activation of the receptor, is facilitated in cholesterol-enriched environments. To obtain a quantitative description of DynA-induced membrane deformations we used a continuum theory of membrane deformations (CTMD) that is based on hydrophobic matching. Comparison with the MD results suggests that the lipid tail packing energy makes a significant contribution to predicting equilibrium membrane shape around DynA in the DMPC/Chol mixtures. This energy term was therefore introduced in the CTMD framework, thereby extending the applicability of the CTMD to quantify membrane remodeling by multi-helical proteins.

2673-Pos Board B659
Large-Scale Computational Analysis of Protein Arrangement in the Lipid Bilayer
Andrei L. Lomize, Irina Pogozheva, Henry I. Mosberg.
Spatial arrangements in the lipid bilayer of more than 1500 integral and peripheral membrane proteins with known 3D structures were calculated using a new continuum anisotopic solvent model of the lipid bilayer. The new model accounts for hydrophobic, hydrogen bonding, and long-range electrostatic solute-solvent interactions and includes the preferential solvation of protein groups by water. The model implements empirical dependencies of atomic solvation parameters and electrostatic energy terms on the bulk solvent properties including its dielectric constant (ϵ), hydrogen bonding acidity and basicity (α, β) and dipolarity/polarizability parameter (π^*). The dependencies were determined from 1269 partition coefficients of neutral molecules and ions from water to 19 solvents. The transmembrane profiles of polarity parameters (ϵ, α, β, π^*) in DOPC and DOPS bilayers were calculated based on published distributions of lipid fragments and water along the bilayer normal obtained in X-ray diffraction, neutron scattering and ESR studies. The obtained profiles indicate the existence of a "mid-polar" region (9 to 16 Å from the membrane center) that provides a significant energy gain from the hydrophobic interactions of nonpolar groups, but only a small electrostatic energy penalty associated with transfer of polar hydrogen-bonding groups and dipoles from water to this region. This explains the preferential accumulation of protein ''hydrophobic dipoles'' (aromatic rings of Trp and Tyr residues) in the "mid-polar" region. The results of the calculations have been included in the second version of the OPM database at opm.phar.umich.edu. The developed method and the database were applied for identification and functional assignment of potential membrane-associated proteins, planning mutagenesis experiments to verify the predicted membrane binding mode of peripheral proteins, prediction and interpretation of experimental membrane binding data.

2674-Pos Board B660
Effective Field Theory Approach to Membrane-Mediated Interactions
Cem Yolcu, Markus Deserno.
Many cellular processes rely on the interactions between membrane-bound proteins. In the case of bilayer remodeling events it has been suggested that forces between the membrane-sculpting proteins driven by the very curvature they induce affect their overall aggregation behavior. To lowest order in a distance-expansion these interactions have been previously worked out, including their thermal fluctuation (Casimir) contribution. Once proteins get closer, it is unclear how accurate such asymptotic results remain, but the current theoretical approaches are difficult or tedious to push to higher order. Here we show that such interactions can be calculated efficiently and to arbitrary order in an effective field theory (EFT) formalism. All known results follow readily as the first terms in a systematic double-expansion in gradients and cumulants. Higher order terms always have multiple origins (e.g. low in gradient expansion but high in the cumulant, or vice versa), and we show that previous attempts at deriving the next corrections have missed some of these contributions. The formalism is extremely versatile and can also handle multibody terms, anisotropic perturbations, or nonlinear corrections. Here we apply it to curvature-mediated interactions between membrane inclusions and discuss the implications of the higher order corrections to the remodeling problem.

2675-Pos Board B661
Possible Membrane-Segragation of PPI/PC Membranes Induced by Calcium Ions
Shinpei Ohki.
Abstract
Calcium-Dependent possible membrane segregation in PPI/PC membranes was studied by using NBD-labeled various phosphoinositides (PPIs). The NBD fluoropore is known that its fluorescence emission signal is reduced as the fluorophore concentration increases. Using this effect, we try to interpret the NBD-incorporated PPIs accumulation in the PC membrane by calcium ions. Either small or large unilamellar lipid vesicles composed of phosphatidylcholine (PC) and NBD-incorporated various phospoinositides (PI, PIP or PIP_2) at different molar ratios were suspended in 0.1 M NaCl/10 mM Hepes at pH 7.4. Then, different concentrations of calcium chloride were made in each vesicle suspension and the NBD emission signals of these phospholipid vesicles were measured by use of a fluorimeter in time at room temperature. As a reference experiment, the vesicle suspension containing 40 μM EDTA without additi of Ca^{2+} was also measured. The molar concentrations of PPIs in PC membrane were 4% and 8% (mole ratio of PPI to PC). The NBD emission signal decreases took rather long time. The higher molar ratio of PPI in PC gave shorter time course. The larger signal decreases were observed at higher concentrations of Ca^{2+} and the vesicle suspension containing EDTA gave more or less a constant and the highest emission signal. The reduction of NBD emission signals was also dependent on the different types of PIPs used. The PIP_2 containing PC membrane showed the largest changes in the fluorescence signal decreases. The order was $PIP_2 > PIP > PI$. Form these results, we interpret that PPIs in PC membranes are segragated by themselves with Ca^{2+}.