siRNA as a therapeutic technology. A key limitation to the widespread implementation of siRNA techniques is the difficulty of delivering siRNA-based drugs to cells. We have examined structural and mechanical barriers to siRNA passage across a phospholipid bilayer using all-atom molecular dynamics (MD) simulations. We find that the electrostatic interaction between the anionic siRNA and zwitterionic head groups of phospholipid molecules induces a liquid crystalline-to-gel phase transformation. The gel phase consists of a major region of interdigitated lipid molecules and a patch of noninterdigitated lipids. Large compressive lateral stresses in the hydrocarbon chains of lipid molecules present a considerable barrier to siRNA passage across the bilayer. Steered MD simulations reveal that the siRNA transfection through the bilayer gel phase requires a force of ~ 2 nN. We will discuss the role of multivalent cations in lowering transfection barriers.

3408-Pos Board B563
Fusion Proteins - Different Tools for Different Jobs?
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SNARE molecules and influenza hemagglutinin are thought to facilitate a similar fusion mechanism. Yet, fusion occurs under different physiological conditions and time-scales, and thus the underlying free-energy landscapes and reaction pathways might be rather different. Here, we have applied CG-MD simulations to elucidate how these different fusion proteins overcome the molecular barriers in membrane fusion. We demonstrate that SNARE molecules, in addition to merely triggering fusion by forcing the opposing membranes into close proximity, actively guide the fusion reaction up to the expansion of the fusion pore [1]. ATR-IR spectroscopy [2], as well as atomistic- and coarse-grained simulations [2,3], suggest that the influenza fusion peptides assemble into a compact bundle prior to membrane merger. In agreement with recent fluorescence spectroscopy and electron cryo-tomography studies [4], we demonstrate that such a bundle stabilizes the formed stalk and facilitates an alternative transition into a hemifusion diaphragm. Finally, we reproduce the effect of point mutations known to corrupt the fusion reaction.

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[3]Risselada H.J. et al, PLoS ONE, 7(6), e38302 (2012)
[4]Lee K.K., EMBO 29, 1299-1311 (2010)
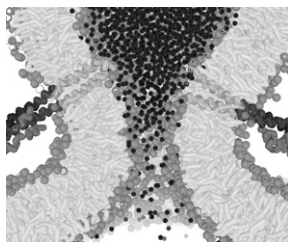
3409-Pos Board B564
Effects of the Midspan Arginine on the Interactions between a Solvated Lipid Bilayer and the HIV-1 Gp41 Membrane Spanning Domain
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The membrane spanning domain (MSD) of HIV-1 gp41 has been shown experimentally to anchor envelope protein gp41 in the viral membrane and to play a role in fusion/infection. One conserved structural motif of the MSD is a midspan arginine, probably charged, located in the hydrophobic lipid bilayer core. It has therefore been postulated that the positively-charged guanidino sidegroup of the midspan arginine (R694) snorkels to negatively-charged headgroups in the membrane. The configurational differences between the wild-type (WT) MSD and a fusion-impaired mutant (R694L) MSD are studied here using molecular dynamics (MD). The conformational distribution and PMF of the R694L MSD peptide were compared with that of the WT MSD peptide using the technique of metadynamics. The mutant and WT peptides both have stable, alpha-helical conformations. Equilibrium properties of these stable, alpha-helical conformations were studied by long (300ns) MD. The presence of greater water around the C-terminal and the greater tilt of the WT MSD indicates that perhaps a role of the charged midspan arginine is partial solvation of the C-terminal, which may function to hold the viral membrane in a metastable prefusion state.

3410-Pos Board B565
All Atom Molecular Dynamics Simulations of pH Dependent Surfactants
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Molecular dynamics simulations have been widely applied to study surfactant systems. However, traditional methods do not capture the effect of changing pH, as all molecules have a fixed protonation state. Continuous constant pH molecular dynamics (CpHMD), however, allows for atomistic study of pH-coupled phenomena, and has been successfully applied to study proteins. In this work we use CpHMD with pH-based replica exchange to study pH-sensitive surfactants in aqueous solution. Lauric acid, a twelve-carbon fatty acid, self-assembles in a pH-dependent manner, with a bilayer to micelle transition seen near the aggregate's pKa. The calculated pKa of a 0.5 M lauric acid solution is 7.0, in good agreement with the experimental value of 7.5. Decreasing the tail length by four carbons decreases the pKa by ~0.5 units, in qualitative agreement with experiment. The effect of aggregate size and concentration was also examined. We have also simulated the titration of fatty acids in fully-solvated detergent bilayers, which sets the stage for exploring proton-coupled biological processes in cellular environments.
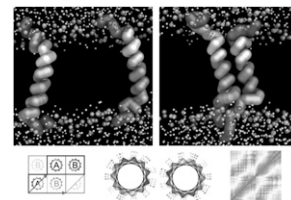
3411-Pos Board B566
The Daft Approach for in Silico Prediction of Transmembrane Peptide Complexes
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Transmembrane helix-helix interactions play a vital role in signaling, and the details of the complexes involved are a valuable complement to biochemical studies. Unfortunately, it is difficult to obtain structural models experimentally, and computational approaches such as protein-protein docking are problematic due to the membrane environment. Here we present an innovative method that combines coarse-grained molecular dynamics simulations, without biasing potentials, with a docking approach to quickly sample the interaction energy landscape. Starting structures are set up using schemes specific for the number of components, promoting encounters, and processed using a fully automated MARTINI-based workflow, facilitating high-throughput simulations.
The method has been applied to ErbB1/ErbB2 homo- and heterodimers, validating the results against available experimental data. In addition, the method was used to investigate temperature controlled signaling by the DesK derived minimal sensor, and to provide a view on the interplay of TM dimers and trimers involved in TNF receptor activation. The results give insight in the mechanisms underlying signaling by simple transmembrane helix systems. This insight offers opportunities for the design of custom membrane-based sensor systems and for assessment of signaling by more complicated helix based systems.

3412-Pos Board B567
Atomistic Simulations of Functional Gold Nanoparticles Au144(Sr)60 Interacting with Membranes
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Gold nanoparticles (AuNps) are used in nanomedicine in, e.g., drug delivery and bio-imaging. However, it is regrettable that the understanding of nanoparticle properties in cellular surroundings is incompletely understood. Here, we have complemented our previous studies [1] by performing extensive atomistic molecular dynamics simulations of lipid membranes interacting with charged gold nanoparticles. We have elucidated the action of these nanoparticles on membranes characterized by lipid compositional asymmetry in the two leaflets, thereby unraveling the interactions of AuNPs with both the extracellular and the cytosolic sides of plasma membranes of eukaryotic cells. We have found that there is an appealing interplay between AuNps and the two membrane leaflets, where both the membrane leaflet composition and the charged nature of the nanoparticle (cationic vs. anionic) play a role. Here we discuss the resulting effects from both structural and dynamical points of view, and highlight the role of electrostatics in nanoparticle-membrane interactions.

[1] E. Heikkila, et al. 2012. J. Phys. Chem. C 116: 9805-9815.
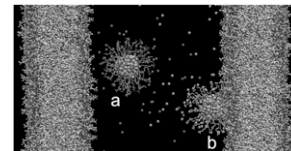

Figure 1. Visualization of (a) anionic AuNP with the extracellular and (b) cationic AuNP with the cytosolic leaflet.