Experimental studies of anionic membranes have generated several new and interesting information on their behavior under different pH, salt concentration and temperature conditions. However, good microscopic models is still lacking. We propose a generalization of the statistical model for neutral lipids to include the effect of the ionic charges. The ionization state of the lipid polar headgroup depends on the salt concentration, so one may have either dissociated (charged) or associated (neutral) gel/fluid phases, as well as semi-dissociated phases. The model order parameter, specific heat and conductivity are compared with experimental data of an aqueous dispersion of the phospholipid DMPG (dimyristoyl phosphatidylglycerol).

2366-Pos Board B336

Biophysical Characterization Of Phosphatidyl Alcohols In Model Membranes- Effects Of Headgroup Size

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The polymorphic phase behavior of different phospholipids depends strongly on fine details of their head group and backbone structures. Studies of phospholipid head group modification offers an attractive strategy in elucidating how structural elements of the head group effect membrane properties. We are investigating phosphatidyl alcohols with saturated fatty acyl chains and their interactions with phospholipids and sterols. Molecules of interest are dipalmitoyl glycerophospholipids with methanol, ethanol, propanol and butanol as different headgroups. These molecules can be formed from e.g., corresponding phosphatidylcholines due to the transphosphatidylation activity of phospholipase D. Phosphatidyl ethanol is of physiological relevance since it is increasingly formed in cells of chronic alcoholics. Thermodynamic properties such as phase transition temperatures, heat capacity of transitions and transition cooperativity have been studied with high sensitivity differential scanning calorimetry (DSC). The miscibility and effects of cholesterol on mixtures of these negatively charged phospholipids with high Tm and low Tm phospholipids have been determined using DSC, and with fluorescence spectroscopy using domain-selective lipid probes. The relative acyl-chain order in the bilayer membranes has been assessed using steady-state DPH anisotropy. We will report on the phase behavior of these molecules in simple and more complex bilayer systems. The formation, by the dipalmitoyl phosphatidyl alcohols, of sterol-enriched or ordered domains in fluid bilayer membranes will also be determined. Comparison of the properties of these phosphatidyl alcohols with molecules having closely related structures will help in understanding the relationships between the chemical structures, physical properties and functional properties of the phospholipid molecules in model as well as biological membranes.

2367-Pos Board B337

Measurements of Electrostatic Interactions between Charged Membranes

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Neighboring lipid membranes experience attractive and repulsive forces. The attractive (van der Waals) force is due to induced change fluctuations and it acts even between neutral membranes. Repulsive forces arise from the tendency of lipids to stay hydrated and can include electrostatic interactions due to accumulation of membrane surface charge. When the attractive vdW force is balanced by repulsive forces, an equilibrium spacing between lamellae is established, as measured by X-ray scattering. This is often the case for neutral membranes. By contrast, lipid bilayers made entirely of charged lipid species such as the negatively charge phosphatidylserine (PS) swell indefinitely (‘‘unbind’’) in the absence of salt indicating the dominance of electrostatic repulsion. To measure the strength of electrostatic interactions in solution, we manipulate membrane charge in two simple ways: by adsorbing ‘‘sticky’’ ions such as bromide onto neutral phosphatidylcholine lipids, and by mixing-in charged lipid species. We will present results and discuss in what conditions membrane electrostatics can lead to unbinding.

2368-Pos Board B338

The Role of Sedimentation and Osmotic Stress in the Regulation of Surface Drag for GUVs Moving in an Electric Field

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Giant unilamellar vesicles (GUVs) suffer variations in shape when exposed to changes in osmotic stress. These shape variations should alter their drag properties when moving close to a surface by inducing a change in the lubrication drag between the surface and the vesicle due to an excess surface area. Using POPC vesicles labeled with NBD-PE we study the influence that osmotic pressure and sedimentation conditions produce on the dynamics of vesicles moving under the influence of a lateral electric field. As a result we find that vesicles in the 5 - 15 μm size range reach a higher terminal velocity in hypotonic compared to hypertonic conditions. This difference decreases for larger diameters. Confocal fluorescence microscopy is used to measure the shape of the vesicles for different osmotic conditions in order to relate the deformability of the vesicle to the terminal velocities. Additionally, we obtain preliminary measurements on the thickness of the water layer that separates the vesicles from the glass surface, which determines the lubricating drag force. For GUVs that remain mobile this distance ranges between 0.5-3 μm. Variations in the drag conditions are studied using finite element simulations through a 3-D boundary integral method which models the approach of the vesicle to the glass surface. Through this method we study the vesicle deformability, and the limiting value of the water thickness. We relate these results to the movement of the vesicles due to an applied constant force. The theoretical and experimental results are compared using the dimensionless Bond and capillary numbers.

2369-Pos Board B339

Interaction of Buffers with Lipid Membranes

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Common buffers including Tris, MES, and MOPS are used to control the pH values of aqueous solutions. The pH, in turn, determines the charged (protonation) state of macromolecules such as proteins, lipids, and DNA. We have investigated the effect of common buffers on the charged state on lipid aggregates. Immersed in water, common lipids often form multilamellar structures. The extremely uniform interlamellar spacings (measurable by X-ray scattering) depend critically on the chemical nature (composition) of the solvent, including the presence of buffers. Multilamellar structures shrink or expand (swell) depending on how interlamellar forces are modified. We present measurements on the modification of lipid interactions by buffers and discuss specific buffer effects that go beyond the non-specific effect of pH.

2370-Pos Board B340

Lipid Gymnastics: Complete Acyl Chain Reversal in Oxidized Phospholipids: Evidence from Molecular Simulations

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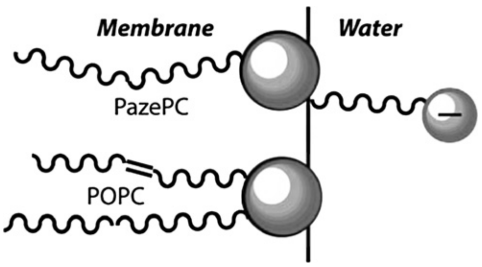
Biological membranes in oxidative environments can contain oxidized phospholipids (OXPLs) with short, polar acyl chains. Two lipid oxidation products of POPC are PoxnoPC and PazePC, which have a carbonyl and an anionic carboxyl group pendant at the end of the short oxidized acyl chain respectively. We have used Molecular Dynamics simulations to investigate the possibility of chain reversal in OXPLs in POPC-OXPL mixtures. The polar azelaoyl chain of PazePC undergoes complete chain reversal without compromising the lipid bilayer integrity at concentrations up to 25% OXPL. The carboxyl group points into the aqueous phase. The carbonyl-containing chain of PoxnoPC is oriented perpendicular to the bilayer normal; and perturbed the lipid packing arrangement more strongly. This work provides molecular evidence of the ‘‘extended lipid conformation’’ in phospholipid membranes. OXPLs are implicated in diseases including cancer and heart disease. The simulations present a clear structural model, using which it will be possible to investigate the interactions of OXPLs with various membrane hosts, ranging from single ions to large proteins. This will ultimately lead to a better understanding of how OXPLs participate in the genesis of diseased states.



2371-Pos Board B341

Headgroup Conformations of Phospholipids from Molecular Dynamics Simulation: Sampling Challenges and Comparison to Experiment

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The preferred conformations of the glycerol region of a phospholipid have been explored using replica exchange molecular dynamics (MD) simulations and compared with the results of standard molecular dynamics approaches and with experiment. We find that due to isomerization rates in key torsions that are slow on the timescale of atomistic molecular dynamics simulations, standard MD is not able to produce accurate equilibrium conformer distributions from reasonable trajectory lengths (~ 100 ns). Replica exchange MD, however, results in quite efficient sampling due to the rapid increase in isomerization rate with temperature. The equilibrium distributions obtained from the replica exchange MD have been compared with the results of experimental nuclear magnetic resonance (NMR) observables providing a valuable tool in the refinement of force fields for membrane simulation.

2372-Pos Board B342

Self-assembly and Equilibration of Bolalipid Membranes Studied by Molecular Dynamics Simulations

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Bolalipids are bi-polar lipids, consisting of two mono-polar lipids chemically linked together at either one or both of the lipid tails. Membranes formed by these lipids or by their mixtures with mono-polar lipids are known to have additional mechanical stability while retaining membrane fluidity. This is traditionally attributed to the fact that bolalipids can span the bilayer with their two polar heads positioned at opposite membrane-water interfaces. Our primary interest is to confirm this hypothesis by studying the relation between bolalipid configurations inside the membrane and the structural and mechanical properties of the membrane.

To this end, we performed molecular dynamics simulations using the coarse grained MARTINI force field [1]. We start with self-assembly simulations of bolalipids in mixtures with mono-polar lipids, to elucidate the preferred orientation of the bolalipids, i.e. spanning versus a looping configuration in which both head groups reside in the same monolayer. To assure proper equilibration between the spanning and looping conformations, we introduce artificial pores in the membrane to allow lipid flip-flops. We consider different types of linkage, including also bi-polar lipids attached at head group level for which spanning configurations are inaccessible.

After equilibration, the membrane properties are characterized in terms of a variety of structural properties and the lateral pressure profile. The resistance of the membrane to mechanical rupture is also investigated. We find that both the spanning/looping ratio and the stability of the membrane depend strongly on the type of crosslink, as well as on the concentration of bolalipids and length of the lipid tails. Our study can help designing new artificial membranes, with higher stability under a variety of extreme conditions.

[1] S.J. Marrink, H.J. Risselada, S. Yefimov, D.P. Tieleman, A.H. de Vries, J. Phys. Chem. B 111 (2007) 7812-7824.

2373-Pos Board B343

Mean Field Based Coarse-Grained Simulations of Ternary Mixtures

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Traditional methods of bilayer simulation at an atomistic level fail to capture length and time scales of biological interest. For example, the formation of lipid rafts in ternary mixtures is not observable with Molecular Dynamics (MD) simulations. To address this fundamental problem we have developed a coarse-grained model to simulate lipid bilayers based on self-consistent mean-field theory (SCMFT) that uses MD trajectories to extract simulation parameters, and a library of chain states that is used for statistical mechanical calculations. We have applied this model to two ternary mixtures: DOPC, SM and Cholesterol and POPC, SM and cholesterol. The thermodynamic behavior of these two systems is of interest because they are known from experiment to exhibit coexisting regions of lipid order and disorder, related to lipid rafts, at certain temperatures and concentrations. In this poster we describe predictions of the SCMFT model for both ternary mixtures, over a range of mixture concentrations, and over microsecond time scales. The existence of the single double bond in POPC influences packing among neighboring lipids differently from two double bonds of DOPC, and this has an effect on the system-wide level of lateral organization. The two systems are compared with experiments conducted with these mixtures.

2374-Pos Board B344

Molecular Dynamics simulations of mixture of POPC and PIP2 bilayer

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PI(4,5)P2 is a phospholipid that plays a role in a wide variety of cellular signaling processes. We have developed force field parameters for the molecular dynamics simulations of PI(4,5)P2 that are consistent with the modified GROMACS parameters 43A1-S3. Furthermore, we performed a long time simulation of hydrated bilayers of mixtures of POPC and 5 mol% PIP2 lipids. The simulated system consists of 800 POPC molecules. This is system is large enough to demonstrate the effect of small quantities of PIP2 and yet small enough to be trackable for molecular dynamics techniques. In this simulation we study the structural properties of poly-unsaturated chains of PIP2 molecules and electrostatic interactions at the bilayer-water interface that enable PIP2 to play significant roles in singling processes.

2375-Pos Board B345

Coarse-Grained Molecular Dynamics Simulations of an Inhomogeneous Ternary Lipid Bilayer

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Lateral, phase-separated microdomains form in model membranes composed of multi-component lipid mixtures. Similar structures are hypothesized to be of significant functional relevance in biological membranes. Though intensely studied, the molecular-level structures of these domains as yet remain unclear. We present coarse-grained molecular dynamics simulations (employing the MARTINI force-field) of a bilayer containing a ternary mixture of glycerophospholipids (saturated DPPC and unsaturated DOPC) and cholesterol. On the microsecond timescale we observe inhomogeneous mixing, with the saturated and unsaturated lipids showing preferential self-interaction. This simulation of the early stages of domain formation provides insight into the interactions that favor lateral domains, the dynamics of lateral separation, and the molecular-level structure and biophysical properties of the lateral domain.

2376-Pos Board B346

Molecular Dynamics simulation of a large asymmetric lipid bilayer

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Many factors are responsible for the curvature of lipid membranes. In this work we use very large scale Molecular Dynamics (MD) to investigate asymmetry in lipid composition as one of the factors that can induce curvature in bilayers. A very large MD simulation can begin to address this issue since larger boundaries permits longer wavelength undulation fluctuations. The simulation we describe on this poster consists of a hydrated bilayer with lipids of composition that mimics inner and outer leaflet compositions of biological membranes, viz, a 20 mol% mixture of cholesterol in 1500 POPE molecules in one leaflet and a 20 mol% mixture of cholesterol in 1500 POPC lipids in the second leaflet. The simulated system is large enough and compositionally heterogeneous enough to demonstrate undulation and curvature within the periodic boundaries. We study the bending modulus and compressibility of the system along with structural properties such as fluctuations in head group areas and order parameters. Other structural properties and in-plane radial distribution function data will also be presented. In this poster we present re simulation results and compare the model predictions with experimental structural and mechanical data.

2377-Pos Board B347

Critical Instability Leads To Labyrinthine Transition In Binary Lipid/Polymer Monolayers

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Near critical points, the microscopic structures of fluid mixtures become unimportant and systems are characterized by strong susceptibility to small perturbations, large fluctuations and mesoscopic ordering. In biological membranes, these fluctuations in physical properties (composition, density, and curvature) may provide a spatially and temporally defined structural means to organize important functions such as formation of lipid rafts, caveolar invaginations or molecular colocalization. We report an observation of characteristic critical fluctuations in lipid monolayers composed of binary mixtures of 1,2 dipalmitoyl-sn-glycerol-3-phosphocholine (DPPC) and polyoxyethylene stearate (PegxS of varying PEG chain length) confined to an air/water interface. Using fluorescence and Brewster angle microscopy, compositional changes that occur during the expansion of an initially phase-separated binary monolayer reveal a passage through a critical composition at vanishing lateral surface pressure. The corresponding morphological transformation from an optically homogeneous liquid expanded state to a gas bubble phase via a striped, labyrinthine phase reflects the competition between long-range electrostatic repulsion and line tension forces caused by interactions between DPPC and PegxS.