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The Threshold Force for Membrane Tether Formation Depends Strongly on Loading Rate
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Tethers are thin tubes of lipid (~200 nm in diameter) that form when membranes are subjected to a point force. Tether dynamics are important to a myriad of biological processes including white blood cell adhesion and transport of intracellular material between neighboring cells. To understand the dynamics of tether formation more fully, we investigated the dependence of the force needed to create a tether on the rate of force change (loading rate). To conduct these experiments, a microfabricated magnetic force transducer was used to generate well-controlled and localized magnetic force profiles. Tethers were formed off the surface of microsuspended giant unilamellar vesicles (GVUs) attached to magnetic beads. We discovered a strong correlation between the threshold force of tether formation and the applied force ramp, with the force changing from <10 pN at low loading rates to ~50 pN at high loading rates. At slow loading rates, the threshold force changes weakly with ln (loading rate), while at high loading rates a steeper dependence is observed. The experimental data can be fit to a energetic model based on Kramer’s theory, similar to models used to describe membrane rupture. The model predicts that tether formation involves passage over two energy barriers and enables characterization of the characteristic forces and timescales associated with these barriers. This new tool for dynamic studies of membrane mechanics may further be extended to study how tethers form off of flowing cells or how phase regimes, induced by the presence of cholesterol, influence membrane dynamics.

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Solid-State 2H NMR Reveals Changes in Membrane Flexibility Due to Osmotic Pressure
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1Department of Chemistry and Biochemistry, University of Arizona, Tucson, AZ, USA, 2Department of Physics, University of Arizona, Tucson, AZ, USA. Cellular membrane properties are sensitive to pressure, temperature, and dehy-dration as well as lipid composition, which can affect function through non-specific lipid-protein interactions [1]. Functional lipid rafts in cellular membranes may correspond to detergent-resistant domains due to the presence of cholesterol. Changes in swelling and stiffening of pure lipid bilayers in the liquid-crystalline phase have been observed [2-4] with addition of detergent and cholesterol. Here we show how structure and associated dynamics of mixed-lipid bilayers are affected by osmotic pressure. Determinations of area per lipid and motional parameters of DMPC membranes in the presence of detergent (C12E8) or cholesterol utilize 2H NMR together with a mean-torque model for interpreting acyl-chain order parameters (SCD) [5]. Swelling by addi-tion of detergent is due to enhanced membrane flexibility, and is counteracted by applying osmotic pressure to the lipid dispersion. By contrast, reduced swelling has been observed for whole cell membranes when cholesterol is reinforced by osmotic pressure. In both cases the membrane area compressibility modulus Ks is calculated from SCD order parameters. We propose that apparent Ks values differ with osmotic pressure for both systems due to changes in the hierarchy of forces and motions. Calculation of the bilayer bending rigidity and the area elastic modulus provides a basis for molecular dynamics simulations of membrane deformations at the atomistic and mesoscopic levels. Osmotic pressure-induced deformation of membranes reveals how lipid-protein interactions can play key roles in biological functions of pressure-sensitive proteins and channels. [1] K.J. Mallikarjunaiah et al. (2011) BJ 100, 98-107 [2] M.F. Brown et al. (2002) JACS 124, 8471-8474. [3] D. Otten et al. (2000) JPC 104, 12119-12129. [4] G.V. Martinez et al. (2002) PREE 66, 050902. [5] H.I. Petrache et al. (2000) BJ 79, 3172-3192.

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Inhibition of the Peroxidation of Liposomal Lipids by Uric Acid Requires Tocopherol
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Urate is the major water-soluble low molecular weight antioxidant in serum, contributing about 50% to the antioxidative potential of the serum. Unexpectedly, both urate, as well as the other major antioxidant ascorbate, promote the copper-induced peroxidation of liposomal PUFA. In a previous study it has been shown that ascorbate inhibits copper-induced oxidation of liposomal lipids when the liposomes contain Tocopherol, whereas urate does not. In an attempt to explain these findings we studied the temporal order of events, by monitoring continuously and simultaneously the time-course of formation of oxidation products and the consumption of the various components of the system. The resultant kinetic profiles show that: 1. Both water-soluble antioxidants slightly inhibit the oxidation of tocopherol; 2. Ascorbate becomes oxidized very rapidly (much faster than tocopherol), whereas urate and tocopherol become oxidized at similar rates. 3. GDP bound to, and bridges, the cytoplasmic sides of myelin membranes. Tetc the major one arising from the dedicated protein - myelin basic protein (MBP) - which binds to, and bridges, the cytoplasmic sides of myelin membranes via a depletion mechanism similar to hydrophilic polymers (like PEG). On the other hand, triblocks copolymers with two

1493-Pos Board B263
From Thermodynamic States to Biological Function by Einstein’s Approach to Statistical Physics
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Einstein founded statistical physics on an important generalization of the Boltzmann principle: Einstein’s reversion, where not the model but the law of entropy is placed first. The advantage is that it assures the 2nd Law and requires no model assumptions. In particular, the existence of a complete molecular mechanism is not necessary. However, if the empirical behavior of a system is known, the entropy and the corresponding probability of the thermodynamic states can be directly derived. With his approach Einstein successfully explained Brownian motion, wave-particle dualism, quantum transitions as well as the Bose-Einstein condensation. Impossible to find in any textbook, we outline Einstein’s approach and apply it to soft interfaces. The introduction of their proper entropy potential, its first, and its second derivatives predicts interfacial nonequilibrium excitation, propagation, and fluctuations, respectively. Experimental observations of the phenomenon of the membrane susceptibilities allow quantitative predictions. The propagation of waves as well as the existence of channel-like fluctuations are experimentally confirmed and compared to measurements on living systems. Finally, we present experiments that confirm Einstein’s approach to the interfacial reaction coordinate. Here the phenomenon of the system is derived from a proper entropy law even though hidden from direct observation. Not structure of molecules but entropy of the aqueous interfaces turns out to be the origin of catalysis and the associated surprising increase in reaction rate. Simultaneous specificity and activity appears now predictable and no more paradox. The theory derived from K.K. in 1999 is briefly outlined and confirmed in experiments. A general approach to model synthesis is presented. Since enzyme activity is controlled from remote by these continuous layers, our results predict the ubiquitous, integrative action in biology of the excitatory hydration interface.
Membrane Structure I

1495-Pos Board B265
Temperature Behavior of Nanometer-Size Lipid Domains in DPPC:DLPC Model Membranes Studied by Small Angle Neutron Scattering
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Membrane cellular domains are no longer viewed as a heterogeneous mix of lipids and proteins, but rather as having distinct lipid domains which are key for many biological processes. Each domain is characterized by an inherent microscopic local composition and structure, self assembly and interactions with complex biomembranes.

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Physical Properties of Lipid Membranes Containing Sterol Studied by Deuterium NMR and Fluorescence Microscopy
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We study the physical properties of model membranes composed of phosphatidylcholines and sterol. The morphology and phase behavior of membranes were investigated by deuterium NMR and fluorescence microscopy. In binary mixtures, coexistence of solid-ordered and liquid-disordered phases was observed in a wide temperature and composition range. The results for ternary mixtures containing sterol show that addition of sterol promotes the formation of the liquid-ordered phase. Sterol has strong influence on the morphology and the phase behavior of membranes. A partial phase diagram will be presented.

Role of Curvature to Produce Modulated Patterns of Lo + Ld Phases on GUV Surfaces
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GUV studies of the three component lipid system DSPC/DOPC/CHOL show macroscopic phase separation of Ld + Lo phase domains. In contrast, GUV’s of DSPC/POPC/CHOL appear uniform in the Ld + Lo region, but show nanometer-scale phase separation in FRET and ESR studies. Examination of the four component system DSPC/DOPC/POPC/CHOL enables study of macroscopic-to-nanostructural transition as composition (DOPC/POPC ratio) is changed. The transition is observed to be rather abrupt, and reveals “modulated phase” patterning on the GUV in a small window of compositions. The patterns show stripe, bubble, and honeycomb structures. Following Helrich, we attempt to explain these patterns through the energetics of curvature. We perform calculations and simulations to determine whether a heterogeneous membrane can stabilize modulated phases, subject only to a line tension and a bending rigidity. We also explore the energetic stability, shape, and size scales of these patterns.