the proximal leaflet and lack of appropriate protein insertions but also to understand the bilayer-nanoparticle interactions. Here, we demonstrate the formation of multiphase lipid bilayers on nanoporous silica xerogels and compare it with mica supported bilayers. It was observed that the lipid bilayer follows the surface contours by AFM (Atomic Force Microscopy). This was also confirmed by the quantitative fluorescence analysis. The lateral diffusion coefficient of the lipids on silica xerogel was found to be lower than on mica by both FRAP (Fluorescence Recovery After Photobleaching) and FCS (Fluorescence Correlation Spectroscopy) experiments. The basic reason for this reduction was the bilayer following the surface contours. The domains on silica xerogel were observed to be symmetric and larger than the domains on mica. This reflects the possible effect of the support on the phase behavior of the lipid mixture. Ternary mixtures containing cholesterol were also prepared and the substrate effect on phase behavior was investigated.

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Understanding The Nucleation and Growth of Lipid-Lipid Phase Separation at Nanometer-Length-Scale: A Small Angle Neutron Scattering Study

Sumit Garg[1], Lionel Porcar[2], Paul Butler[3], Ursula A. Perez-Salas[1].
[1]Argonne National Laboratory, Argonne, IL, USA, [2]Institut Laue-Langevin, Grenoble, France, [3]National Institute of Standards and Technology, Gaithersburg, MD, USA.

Although lipid-lipid phase separation has been studied extensively in model lipid membranes, most of the available information is limited to micron-size domains. Lack of information on the nanometer-length-scale is a big hurdle in understanding the fundamental basis for lipid domain nucleation, in the first place, and growth. How do small unstable domains grow? What is the effect of temperature and membrane curvature? To answer these questions, this work presents Small Angle Neutron Scattering (SANS) studies on small Unilemellar Vesicles (ULVs) (diameter varying from 30nm to 400nm) made of 1:1 and 3:7 ratios of deuterated DPPC (dDPPC) and hydrogenated DLPC respectively. Small vesicles with varying sizes not only provide a means to control the curvature, but also limit the amount of available lipids for domain growth. Experiments were performed in contrast matched conditions, such that the scattering length density of the solvent and that of the homogeneous lipid vesicle (above the melting transition temperature, Tm, of the mixture) were exactly equal. As the sample temperature was lowered below Tm, the lipids started to phase separate and an excess scattering characteristic of lipid segregation into nano-size domains was observed. Notable trends were observed in the scattering curves as the temperature was lowered below the Tm of the mixtures. Interestingly, these results show that the phase separation behavior varies significantly between the small and large size vesicles. Insight in to the basic mechanism for the formation of lipid-lipid phase separation as a function of temperature and curvature will be discussed based on the analysis of the scattering intensities and Differential Scanning Calorimetry experiments.

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Cholesterol Displacement By Ceramide In Sphingomyelin-containing Liquid-ordered Domains, And Generation Of Gel Regions In Giant Lipidic Vesicles

Jesús Sot[1], Maitane Ibarguren[1,2], Jon V. Busto[1,3], Ruth L. Montes[1], **Felix M Goni**[1,3], Alicia Alonso[1,3].
[1]Unidad de Biofisica (CSIC-UPV/EHU), Leioa, Spain, [2]Departamento de Bioquímica y Biología molecular, Leioa, Spain, [3]Departamento de Bioquímica y Biología Molecular. Universidad del País Vasco, Leioa, Spain.

Fluorescence confocal microscopy and differential scanning calorimetry are used in combination to study the phase behaviour of bilayers composed of PC:PE:SM:Chol equimolecular mixtures, in the presence or absence of 10 mol% egg ceramide. In the absence of ceramide, separate liquid-ordered and liquid-disordered domains are observed in giant unilamellar vesicles. In the presence of ceramide, gel-like domains appear within the liquid-ordered regions. The melting properties of these gel-like domains resemble those of SM:ceramide binary mixtures, suggesting Chol displacement by ceramide from SM:Chol-rich liquid-ordered regions. Thus three kinds of domains coexist within a single vesicle in the presence of ceramide: gel, liquid-ordered, and liquid-disordered. In contrast, when 10 mol% egg diacylglycerol is added instead of ceramide, homogeneous vesicles, consisting only of liquid-disordered bilayers, are observed.

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How Membrane Curvature Can Sort Proteins

Stefan Semrau, Timon Idema, Cornelis Storm, Thomas Schmidt.
Leiden University, Leiden, Netherlands.

While it is a well known fact that membrane proteins interact via electrostatic, hydrophobic and van der Waals forces, only recently attention was drawn to a new kind of fundamental interaction that is mediated by the membrane itself. Proteins that locally impose a membrane curvature create a deformation that is probed by other, similar proteins. Since it is very difficult to quantitatively measure and discriminate the different types of interactions in the case of proteins, we study a model system which allows the exclusive observation of membrane mediated interactions alone. Building on our earlier experiments on fully phase separated vesicles (Semrau et al., PRL, 2008) we study biomimetic vesicles with bulging liquid ordered domains. These domains deform the surrounding membrane and create a repulsive force between them. This leads to a wealth of measurable effects: we observe hindered domain fusion, a preferred domain size and, most importantly, an intriguing sorting mechanism. Domains of different sizes spontaneously demix and form regions of equally sized domains. Quantitative measurements of the repulsive force allow us to build a model for the sorting that is independently confirmed in Monte Carlo simulations. The observed sorting provides a new mechanism for protein sorting in the endoplasmic reticulum and for membrane mediated protein aggregation.

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Lateral Stress and Spontaneous Curvature in Mixed Membranes

Horia I. Petrache[1], Michael F. Brown[2].
[1]Indiana University Purdue University Indianapolis, Indianapolis, IN, USA, [2]University of Arizona, Tucson, AZ, USA.

A key aspect of membrane mechanics is the balance of attractive and repulsive forces involving lipid head groups and acyl chains [1]. In particular, demethylation of PC lipids and addition of polyunsaturated chains [2] have been shown to alter substantially the activity of membrane receptors [3, 4] and of ion channels. How to best describe membrane forces? An appealing theoretical description is the lateral stress profile, which is easily calculated from computer simulations. However the lateral stress profile is not yet accessible experimentally. Experimental observables (which can be related to the lateral pressure profile if desired) are (i) the *spontaneous curvature* values as obtained from X-ray scattering, and (ii) the lateral *mean-torque profile* obtained from solid-state ^{2}H NMR [1]. We report and analyze experimental data on PE/PC and saturated-polyunsaturated lipid mixtures to show how measured shifts in the chain mean-torque profiles correspond to shifts in the balance of forces between headgroups and acyl chains. We first determine changes in the mean-torque profile caused by variations in lipid composition. We then determine a geometric parameter called the projected segmental area, directly related to the spontaneous curvature of individual monolayers. Last, we show that lateral compression energies are sufficiently large to provide a thermodynamic driving force for protein conformational changes. Our approach reveals that a universal chain packing profile exists for saturated acyl chains, and that the measurable shift in the force balance gives rise to the observable membrane mechanics. This approach provides a new framework for relating lipid composition to membrane function.

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Platform AB: Molecular Dynamics

1873-Plat

Automated Event Detection and Activity Monitoring in Long Time-Scale Molecular Dynamics

Willy Wriggers[1], Kate A. Stafford[1], Yibing Shan[1], Stefano Piana-Agostinetti[1], Paul Maragakis[1], Kresten Lindorff-Larsen[1], Patrick J. Miller[1], Michael P. Eastwood[1], Ron O. Dror[1], David E. Shaw[1,2].
[1]D. E. Shaw Research, New York, NY, USA, [2]Center for Computational Biology and Bioinformatics, Columbia University, New York, NY, USA.

Molecular dynamics trajectories of biological systems contain many events of great scientific interest, including conformational transitions, folding processes, and translocations of ligands and reaction products. In proteins these events often correspond to high-level tertiary or quaternary structure rearrangements, which alter the contacts between amino acid residues. Due to advances in computer architecture and software, molecular dynamics trajectories representing such structure-changing events have become easy to generate, but their length complicates scientific interpretation. The goal of this work is to simplify an important part of the analysis workflow (and to complement traditional visual inspection) by automating the mining of long trajectories. We present