

Membranes are vital components in cellular regulatory system, upon which many metal ion molecules act as messengers of intracellular signaling and mediators for membrane protein association. In particular, anionic lipid phosphatidylserine (PS) is involved in a wide range of biological processes such as blood coagulation, membrane fusion and cell apoptosis in cooperation with calcium-binding proteins. Although it is commonly acknowledged that calcium ions interact with PS to form complexes that induce the phase separation in mixed bilayers, the PS domain formation has not yet been observed in molecular dynamics (MD) simulations. The effect of monovalent ( $M^I$ ) and divalent ( $M^{II}$ ) cationic radii is explored on lipid domain formation in mixed zwitterionic-anionic lipid bilayers. We propose a mechanism of the formation of divalent-cation induced lipid domains based on the results of a series of MD simulations with our Water-Explicit Polarizable MEMbrane (WPEMEM) coarse-grained model, which uses phosphatidylcholine (PC) as a model for zwitterionic and phosphatidylserine for anionic lipids. The network of gel-like PS aggregates is only observed with both monovalent and divalent metal ions of appropriate radii. More ordering and closer packing of PS lipids are observed within the domains, which correlates with bilayer thickness, curvature and asymmetry in lipid compositions of both leaflets. The results of the simulations reveal that the PS domain consists of  $M^{II}$ -mediated PS dimer/trimer complexes bridged by monovalent ions  $M^I$  and provide a stereochemical insight in understanding calcium-induced phase separation.

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##### Mixed Phosphoinositide/Lipid Langmuir Films in the Presence of Bivalent Cations

**Katrice E. King**, Arne Gericke.

Chemistry and Biochemistry, Worcester Polytechnic Institute, Worcester, MA, USA.

Local accumulation of phosphoinositides (domain formation, phosphoinositide gradients) have been linked to a broad range of physiological processes. The interaction of phosphoinositides (PIPs) with bivalent cations, cationic peptides or cationic patches in proteins has been shown to promote formation of PIP enriched domains. Our study aims to investigate how the cation/PIP interaction is modulated by the presence of lipids capable of forming hydrogen bonds with PIPs, namely phosphatidylethanolamine (PE), phosphatidylinositol (PI) or cholesterol (chol).

We have investigated mixed phosphatidylinositol-4,5-bisphosphate (PI(4,5)P<sub>2</sub>)/PE monolayers at the air/water interface (Langmuir films) in the presence and absence of calcium. Both 1:1 and 4:1 mixtures of PE:PI(4,5)P<sub>2</sub> in the absence of calcium lead to an expansion of the monolayer while the addition of relatively small amounts of calcium lead to a significant condensation. While for DOPC/PI(4,5)P<sub>2</sub> monolayers epifluorescence microscopy revealed domain formation at low surface pressures in the presence of Ca<sup>2+</sup>, DOPE/PI(4,5)P<sub>2</sub> monolayer did not exhibit domains even in the presence of Ca<sup>2+</sup>. These data in combination with previously published results (Graber et al. *Chem. Phys. Lipids* 165 (2012) 696) suggest that PE in the absence of Ca<sup>2+</sup> inserts between PI(4,5)P<sub>2</sub> and forms hydrogen bonds with the PI(4,5)P<sub>2</sub> headgroup. The addition of Ca<sup>2+</sup> to this PI(4,5)P<sub>2</sub>/PE complex results in a further condensation, presumably due to a Ca<sup>2+</sup> bridging of the PI(4,5)P<sub>2</sub> headgroups. These results will be compared to those obtained for PE/PI and PI/PI(4,5)P<sub>2</sub> monolayers.

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##### Presence of Salt and Solution Asymmetry Across Charged Membranes Influences Their Phase State

**Bastian Kubsch**, Tom Robinson, Reinhard Lipowsky, Rumiana Dimova. Theory and Bio-Systems, Max Planck Institute of Colloids and Interfaces, Potsdam, Germany.

Liquid-liquid phase separation in giant unilamellar vesicles (GUVs) leads to the formation of intramembrane domains or lipid rafts. In order to mimic charged biological membranes, we studied phase separation and domain formation in GUVs of ternary lipid mixtures, composed of egg sphingomyelin (eSM), cholesterol (Chol) and the negatively charged lipid dioleoylphosphatidylglycerol (DOPG). The GUVs were exposed to solutions of sucrose and high-saline buffer. The phase diagram was mapped using epifluorescence microscopy for vesicle populations with symmetric and asymmetric solution compositions across the membrane. Interestingly, solution asymmetry was also found to affect the membrane phase state. Furthermore, compared to the case of symmetric sucrose conditions, the phase diagram in the presence of high-saline buffer (both symmetrically or asymmetrically distributed across the membrane) was found to exhibit a significantly extended coexistence region for liquid ordered (Lo) and liquid disordered (Ld) phases. These observations were confirmed on single GUVs using microfluidics and confocal laser scanning microscopy. Moreover, we showed that the miscibility temperatures markedly increased for vesicles in the presence of symmetric and asymmetric salt

solutions. Our results indicate a substantial effect of salt on the phase behavior of charged membranes and demonstrate that one has to control the solution conditions in order to appropriately map the phase diagram of lipid mixtures.

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#### 2046-Pos Board B190

##### Influence of Charge on the Elastic Properties of Lipid Membranes

**Elizabeth G. Kelley**<sup>1</sup>, Michihiro Nagao<sup>1,2</sup>, Robert D. Bradbury<sup>1,2</sup>, Paul D. Butler<sup>1,3</sup>.

<sup>1</sup>Center for Neutron Research, NIST, Gaithersburg, MD, USA, <sup>2</sup>Center for Exploration of Energy and Matter, Indiana University, Bloomington, IN, USA, <sup>3</sup>Chemical and Biomolecular Engineering, University of Delaware, Newark, DE, USA.

Lipid membrane elastic properties play an important role in the membrane deformations and dynamic morphological transitions necessary for cell function. A key elastic property underlying these dynamics is the bending rigidity, motivating significant research efforts to quantify the effects of lipid structure and additives on the membrane bending modulus. To date, the majority of experimental research has focused on the dynamics of model membrane systems composed of zwitterionic lipids; however, most biomembranes are negatively charged at physiological conditions due to the presence of charged lipid headgroups. Here we study the bending dynamics of negatively-charged phosphatidylglycerol (PG) bilayers using neutron spin echo spectroscopy. Our results show that the charged lipid bilayers are softer than analogous zwitterionic phosphatidylcholine (PC) bilayers in both the gel and fluid phases at low ionic strength conditions. Interestingly, theoretical predictions indicate that the opposite should be true and that the bending rigidity should increase with increasing surface charge. We propose that this discrepancy is due to charge-related differences in the area per headgroup and lipid hydration between PG and PC bilayers that are not considered by existing theoretical models. Our results provide new insights into the influence of charge on the membrane elastic properties and demonstrate how these dynamics are coupled to charge effects on the membrane structure.

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##### Molecular Simulation of Lipids and Water: Atomistic, Coarse-Grained, and Mixed Resolutions

**Mario Orsi**, Wei Ding, Michail Palaiokostas, Wen Wang.

Queen Mary University of London, London, United Kingdom.

Lipids and water are fundamental ingredients of living matter. Lipids form membranes which are employed by living organisms to enclose cells and organelles, transmit information, control molecular transport, and store energy. Water is the universal biological solvent. This presentation will focus on the investigation of lipid and water systems using different molecular dynamics simulation approaches. We will show results from all-atom simulations of mixed bilayers composed of lamellar and nonlamellar lipids. In particular, a quantitative characterisation has been obtained of the internal distributions (profiles) of lateral pressure, electric field, and dipole potential. These properties, very difficult to measure experimentally, are thought to play key roles in many membrane phenomena, including nonspecific lipid-mediated mechanisms of protein regulation. We will also describe the development of coarse-grained models, that are simplified representations in which entire groups of several nearby atoms are reduced to single particles. In particular, we will present recent results on the ELBA water model, where a water molecule is reduced to a single sphere embedded with a point dipole [1,2]. The ELBA model is remarkably accurate, and can be combined directly with atomistic force fields in mixed resolution systems [3]; however, recent results also highlight a number of issues in relation to ionic screening and phase behavior. Finally, we will report on ongoing efforts to develop a new "ultra coarse-grained" model for lipids and water, aimed at further increasing computational efficiency while retaining only the essential underlying physics.

[1] M. Orsi, *Mol. Phys.* (2014), 112, 1566-1576.

[2] W. Ding, M. Palaiokostas, M. Orsi, *Mol. Simulat.* (2015), <http://dx.doi.org/10.1080/08927022.2015.1047367>.

[3] M. Orsi, W. Ding, M. Palaiokostas, *J. Chem. Theory Comput.* (2014), 10, 4684-4693.

#### 2048-Pos Board B192

##### Structure and Dynamics of Bio-Membranes and their Hydration Water in Water Solution of Room Temperature Ionic Liquids: An Experimental and Computational Study

**Antonio Benedetto**<sup>1</sup>, Pietro Ballone<sup>2</sup>.

<sup>1</sup>Laboratory for Neutron Scattering and Imaging, Paul Scherrer Institut, Villigen, Switzerland, <sup>2</sup>Istituto Italiano di Tecnologia, Pisa, Italy.