Mechanical forces generated by cells mediate shape changes that occur during essential life processes including polarization, division and spreading. While the cell cytoskeleton is recognized for its myriad contributions to force generation, the mechanisms by which the cell membrane may also generate forces are often overlooked. Therefore, we explore the potential that membrane generates mechanical tension on cellular length scales by measuring the traction stresses generated during liposome adhesion and spreading on compliant substrates. We find that giant liposomes devoid of a cytoskeleton generate contractile traction stresses on par with those exerted by living cells. These stresses result from the equilibration of internal, hydrostatic pressures elevated by the membrane tension built by strong adhesion to the substrate. These results highlight the active role of membranes in the generation of mechanical stresses on cellular length scales. Furthermore, it uncovers that the modulation of hydrostatic pressure via membrane tension and adhesion can be channeled to perform mechanical work on the environment, providing a more comprehensive description of cell contractility and force generation.

915-Plat

Determining Material Elastic Properties of Arbitrarily-Shaped Membranes using Molecular Dynamics Simulations with Application to the Inverted Hexagonal Phase

Niklaus B. Johner[1], Daniel Harries[2], George Khelashvili[3].
[1]Biozentrum, Basel Universität, Basel, Switzerland, [2]Institute of Chemistry and the Fritz Haber Research Center, The Hebrew University, Jerusalem, Israel, [3]Physiology and biophysics, Weill Medical college of Cornell University, New York, NY, USA.

Accumulating evidence indicates that diverse physiological processes are influenced by the lipid composition of the membrane and by its material properties. This has notably been shown for the function of diverse proteins and their oligomerization, and processes on larger scales such as membrane reshaping and fusion. Determination of the elastic properties of lipidic membranes is therefore of great importance to our understanding of these processes. Experimental approaches to determine the material properties of lipids remain challenging and usually rely on their study in a relaxed environment or in flat bilayers, although it is widely accepted that cell membranes can be under considerable stress and frustration as well as high local curvature. Whether this impacts the measured properties is a matter of debate so that studying membranes under more realistic conditions is key for our understanding how these material properties impact different physiological processes. In this context, we propose a computational method to determine the elastic properties of lipid assemblies of arbitrarily shaped interfaces and use it to study the impact of the curvature of a membrane on its elastic properties. Specifically, we apply the methodology to mixtures of DOPE (dioleoylphosphatidylethanolamine) lipids and cholesterol in the inverted-hexagonal and lamellar phases and find that the bending rigidity for a particular lipid composition critically depends on the geometry of the lipidic system. This dependence correlates on the molecular level to the changes in lipid chain order imposed by the membrane curvature, implying that these results should pertain to other situations where the membrane is deformed, stressed or frustrated that notably emerge around integral membrane proteins or during membrane remodeling processes such as budding.

916-Plat

Mobility of Single-File Water Molecules in Aquaporins

Andreas Horner[1], Florian Zocher[1], Johannes Preiner[1], Nicole Ollinger[1], Christine Siligan[1], Sergey A. Akimov[2], **Peter Pohl**[1].
[1]Biophysics, Johannes Kepler University, Linz, Austria, [2]Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences, Moscow, Russian Federation.

Confined water is an important element in protein structure and function, yet its physical properties are notoriously difficult to assess. Here we show that the mobility of single-file waters inside aquaporins reaches bulk water mobility. Our assessment is based on measurements of the unitary water channel permeability, p_f [1]. We used stopped-flow experiments to determine the per channel increment in proteoliposome water permeability as a function of protein abundance. Therefore, we substituted (i) semi empirical relationships between vesicle volume and scattered light intensity for an adaptation of the Rayleigh-Gans-Debye equation and (ii) analytically solved the differential equation for the time dependence of vesicle volume on water efflux. Both fluorescence correlation spectroscopy and high speed atomic force microscopy served to determine the exact number of water channels per vesicle. p_f increased in this order: aquaporin-Z [2], aquaporin-1 [3], and GlpF (*E.coli* glycerol facilitator) [4]. The maximal turnover number was equal to $5x10^{10}$ s^{-1}, it thus exceeded previous estimates by as much as 50-fold. The high mobility is consistent with previous reports on the low number of hydrogen bonds formed by the single-file waters in the channel and the distorted geometry of those bonds.

[1] S. M. Saparov *et al.*, Phys. Rev. Lett. **96,** 148101 (2006).
[2] P. Pohl, S. M. Saparov, M. J. Borgnia, and P. Agre, Proc. Natl. Acad. Sci. U. S. A. **98,** 9624 (2001).
[3] S. M. Saparov *et al.*, J. Biol. Chem. **276,** 31515 (2001).
[4] S. M. Saparov, S. P. Tsunoda, and P. Pohl, Biol. Cell **97,** 545 (2005).

Platform: Computational and Simulation Methods

917-Plat

Adaptive Boundaries in Multi-Resolution Simulations

Jason A. Wagoner[1], Ken Dill[1], Vijay Pande[2].
[1]Laufer Center for Physical and Quantitative Biology, Stony Brook University, Stony Brook, NY, USA, [2]Department of Chemistry, Stanford University, Stanford, CA, USA.

Biomolecular simulations generally require a compromise between forcefield resolution and computational efficiency. Methods that combine multiple levels of resolution promise to extend the ability of simulations to handle bigger systems and more complex processes.
We have developed an explicit/continuum solvent model that is able to reproduce the effects of explicit biomolecular solvation while only including a fraction of the molecules that would otherwise be required. We are extending this approach as a general multi-resolution model where both solvent and other, more complex, molecules change representation as they move across the boundaries of the explicit and continuum domains.
This model includes: (1) new boundary methods that accurately reproduce thermodynamic and kinetic properties in the explicit region exactly, within statistical error, as if they were taken from large, fully explicit simulations; (2) adaptive boundaries that spatially alter the level of detail in response to an evolving molecular environment; and (3) a grand canonical control of molecular components, relaxing the density of chemical species as the simulation progresses (important for studies in crystallization, assembly, etc.).
Our current work is aimed at surmounting a considerable challenge facing all multi-resolution models: transferability to new systems and arbitrary geometries. Overcoming this challenge will be essential in making these multi-resolution models ready to be used 'out of the box' for a range of problems in biophysics.

918-Plat

To Bayes, or Not to Bayes, Information is the Answer

Paul A. Wiggins.
University of Washington, Seattle, WA, USA.

Biological systems are inherently noisy on a molecular scale. The problem of determining the true state of a system and characterizing the transitions between states whose observables are corrupted by noise is a canonical problem in statistics with a rich history. There has recently been a significant renaissance in the application of Bayesian Statistics (for instance variational Bayes and the use of the Bayesian Information Criterion) to analyze single-molecule biophysics and cell-biology problems. Although these Bayesian techniques regularize the model selection problem to prevent over-fitting through the introduction of a prior probability distribution, Bayesian techniques typically significantly underestimate the complexity that can be resolved by information-based and frequentist analyses and often require the introduction of ad hoc prior distributions. We demonstrate the application of information-based statistics (both canonical and novel) in the analyses of several distinct biological measurements from our laboratory ranging from single-molecule techniques including stoichiometry by bleaching and tether-particle motion to cell biology problems including characterizing cell motility. In each case we compare the resolution of the Bayesian and information-based approaches to demonstrate the increased resolving power of information-based techniques.

919-Plat

Benchmarking and Optimizing Atomistic Forcefields with Density Measurements

Kyle A. Beauchamp, Julie M. Behr, Patrick B. Grinaway, Arien S. Rustenburg, John D. Chodera.
Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

Predictive biophysical models of drug binding and selectivity could accelerate drug discovery. However, a limited understanding of molecular-scale phenomena currently prevents biophysical models from impacting drug design. To assess the quality of the GAFF small molecule forcefield, we have performed