accelerated flip-flop (i.e., faster rates than were found just above the main transition temperature). We conclude that bilayer defects such as gel/fluid domain boundaries accelerate lipid flip-flop. We speculate that sample environment and measurement conditions that can alter the physical properties of bilayers have contributed to flip-flop discrepancies in literature.

862-Plat
Nanometer-Scale Lipid Clusters in Model Membranes Revealed by Atomic Recombination in Nanosims
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Much of what is known about the lateral organization of biological membranes is inferred from the analogy between phase diagrams of ternary mixtures of lipids and the plasma membrane of mammalian cells. However, the relevance of phase diagrams of simple lipid mixtures to the compositionally complex and dynamic plasma membrane has not yet been established. Additionally, the fluorescence and spin labels used to build phase diagrams often interact with lipid bilayers, and detecting nanometer-scale phases remains challenging. We have previously introduced atomic recombination in dynamic SIMS as a technique for detecting lateral heterogeneities that occur on the nanometer length scale, below the resolution of both fluorescence microscopy and conventional NanoSIMS imaging. In this method, the formation of $^{13}C^{15}N^-$ secondary ions from ^{13}C and ^{15}N atoms installed on different lipids only occurs if the isotopically-labeled lipids are within approximately 3 nm of each other. Isotope labels are desirable because they avoid problems caused by fluorescent dyes and because they directly report on the organization of the lipids of interest. Facile isotope-labeling chemistry allows the labels to be placed on any lipid of interest, allowing us to determine which lipids are clustering in complex mixtures. Here, we expand this technique to study the formation and composition of nanodomains of lipids in more complex mixtures for which phase diagrams have not been determined and would be too laborious to fully solve. Furthermore, we explore the formation of lipid clusters outside of phase boundaries, where lipids may still be inhomogenously distributed but display no first order phase transition. These more complex model membranes may be better models for lipid rafts given that lipids in the plasma membrane show no micrometer scale phase separation and no first order phase transition.

863-Plat
Effects of Silica Support on Dynamics of Transmembrane Peptides and Effective pK_a of Ionisable Sidechains
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Hybrid nanostructures composed of lipid bilayers and nanoparticles provide new avenues for biophysical studies as well as development of biotechnological platforms to interface manmade non-living systems with living organisms. At present, however, little is known about the influence of the nanostructured support and confinement on electrostatic properties of the membrane-protein interface. Here we report on spin-labeling EPR studies to 1) evaluate the effect of anionic lipid surface charge density on the effective pK_a of membrane-burred ionisable sidechains and 2) assess effects of the solid inorganic interface, specifically, silica support, on heterogeneous dielectric environment along the α-helix of a WALP peptide integrated in a lipid bilayer. The change in the protonation state of the pH-sensitive ionisable nitroxide label was directly observed by CW EPR. We have shown that the effective pK_a of the probe increases by 2.1 to 2.3 pH units (depending on the depth of the probe) upon replacing zwitterionic PC with anionic PG lipids, with almost 80% of that pK_a shift observed upon replacing only half of the PC with PG lipids. We have also shown that placing a lipid bilayer with integrated transmembrane α-helical WALP peptide on the surface of silica nanoparticles affects the peptide dynamics and shifts the effective pK_a of the probe in a membrane depth-dependent manner. The latter effect was attributed to the negative charge of the silica surface. Supported by NSF 1508607 to TIS.

864-Plat
Total Reflection X-Ray Fluorescence at the Air Water Interface using XeRay
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Total reflection x-ray fluorescence (TXRF) at the air/liquid interface is a widely applicable experimental technique for studying chemical elements accumulated at the air/liquid interface, with extremely high sensitivity at brilliant synchrotron x-ray sources. To promote and facilitate scientific discovery using this sensitive technique, we constructed an experimental setup for TXRF atop an existing liquid surface x-ray scattering spectrometer. We also developed a MATLAB-based software package with a graphical user interface (GUI), named *XeRay*, for quick, accurate, and intuitive data analysis. The experimental setup and software package have been tested in the study of Ca^{2+} accumulation at a Langmuir monolayer of an anionic lipid, 1-stearoyl-2-oleoyl-*sn*-glycero-3-phosphate (SOPA), on a buffer solution of 1mM $CaCl_2$ at pH 7.5. Analysis with *XeRay* has shown that each 1 nm^2 of interfacial area contains 1.23 Ca^{2+} ions, which corresponds to a 2:1 ratio between SOPA headgroups and Ca^{2+} ions, consistent with our intuition of a divalent ion bridging two singly charged lipids.

Platform: Molecular Dynamics I

865-Plat
Developing Force Fields for the Accurate Simulation of Both Ordered and Disordered Protein States
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Molecular dynamics (MD) simulation can serve as a valuable complementary tool to experiments in characterizing the structural and dynamic properties of ordered and disordered proteins. The utility of MD simulation depends, however, on the accuracy of the underlying physical models (''force fields''). We present here an extensive benchmark study to systematically assess the ability of commonly used MD force fields to reproduce NMR, SAXS, and FRET data for a number of ordered and disordered proteins. We found that, while the properties of folded proteins are generally well described in simulation, large discrepancies exist between simulation and experiment for disordered proteins, which is significant given that a large fraction of proteins are partially or completely disordered under physiological conditions. We subsequently developed a new water model, TIP4P-D, that better balances electrostatic and dispersion interactions, resulting in significantly improved accuracy in the description of disordered states, but slightly degraded results for ordered proteins. Guided by experimental measurements from folded proteins, fast-folding proteins, weakly structured peptides, and disordered proteins, we are further optimizing force fields to more accurately simulate proteins across the order-to-disorder spectrum.

866-Plat
CHARMM36: An Improved Force Field for Folded and Intrinsically Disordered Proteins
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There is increasing interest in intrinsically disordered peptides and proteins (IDPs) due to their abundance and functional importance in eukaryotes, as well as their association with various human diseases ranging from cancer to neurodegenerative diseases. Instead of folding into a single, well-defined three-dimensional structure, an IDP fluctuates between an ensemble of interconverting conformational states, which allows some IDPs to interact with several different binding partners, thereby functioning in protein-protein interaction networks. Recent advances in hardware and software allow molecular simulations to reach relevant timescales for sampling IDP conformations, but a major limiting factor lies in the accuracy of their underlying models, typically empirical force fields (FFs). Protein FFs were mostly developed targeting folded proteins and their accuracy in modeling IDPs needs to be scrutinized and improved. In a recent benchmark study on the structural ensembles of a disordered arginine/serine (RS) peptide obtained with different force fields, the CHARMM36 (C36) protein FF was found to generate a high population of left-handed alpha-helix (alphaL), inconsistent with nuclear magnetic resonance and small-angle X-ray scattering experimental measurements. Here, we report an improved version of the C36 FF that overcomes this bias towards alphaL-helix and yields more accurate conformational sampling of IDPs. Specifically, we present an improved C36 FF based on a refined backbone CMAP potential derived from a reweighting calculation and a better description of specific salt bridge interactions. The modified FF, which will be referred to as CHARMM36m (C36m), is validated using a comprehensive set of 15 peptides and 20 proteins with a cumulative simulation time of more than 500 microseconds. The extensive validation

simulations illustrate that the improved force field is suitable for MD simulations of both folded and disordered proteins.

867-Plat
Verifying Self-Consistency of Protein Structure and Dynamics through MD Simulation and WAXS
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Molecular Dynamics (MD) simulations based on a crystal structure and selected force field represent a powerful approach to generate models for the internal motions of a protein in order to interpret the results of biological experiments and model the interactions between proteins and ligands. However, there are relatively few experimental probes that can be used to verify the results of MD, particularly with regard to slow, correlated motions of loops, folds or domains. Wide-angle X-ray solution scattering (WAXS) is sensitive to protein structure and dynamics including secondary, tertiary and quaternary structure and slow, correlated motions. Here, we present a method to utilize the crystal structure of a protein and its corresponding MD simulation to predict WAXS data from a protein. First, the WAXS pattern of a rigid protein is calculated using an explicit atom model of the hydration layer with the software package, XS. Second, MD trajectories are utilized to calculate a sigma-r plot (the standard deviation of interatomic distances averaged as a function of interatomic distance) which is subsequently combined with the results of the XS calculation to predict the scattering pattern of the dynamic protein. The difference between observed and calculated intensities is minimized by scaling the sigma-r plot with a single variable factor which provides a measure of the discrepancy between experimental and computational characterization of global dynamics. In examples presented here, we show that the correspondence between observed and calculated intensities are often excellent, providing direct experimental validation of the MD results. In other examples, we demonstrate how the approach can identify over or under-estimates of large scale motions in MD simulations that may arise from under-sampling of the structural ensemble or inappropriate choice of simulation parameters.

868-Plat
Atom-Resolved View of a Cell Organelle on a Computational Microscope
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Photosynthetic organelles have been optimized by over two billion years of evolution into highly efficient energy-harvesting machines that surpass man-made solar devices in robustness, adaptation to environmental stress, and efficiency of energy conversion. Leveraging a nanoscale network of bioenergetic proteins, these fascinating properties emerge from the confluence of hundreds of biochemical reactions across the entire organelle. I present the first all-atom model of an entire cell organelle, namely that of a bacterial chromatophore. Construction of this model drives pioneering advances in crystallography and electron-microscopy based structure determination techniques, namely through the innovation of molecular dynamics flexible fitting (MDFF) methodologies in xMDFF and ReMDFF (eLife 2016, 5, e16105; JACS 2015, 137, 8810; Acta. Cryst. D 2014, 70, 2344). Multiscale computations starting with this 100 million-atom model deliver novel insights on the organelle's membrane curvature and charge transport properties, mechanisms of light adaptation, and impact on cellular aging. The results have been confirmed employing atomic force microscopy and biochemical assays. Preliminary results are reported in JACS 2016, 138, 12077 and eLife 2016, 5, e09541.

869-Plat
As Simple as Possible but not Simpler: On the Reliability of Protein Coarse-Grained Models
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Mechanical unfolding of a single domain of loop-truncated superoxide dismutase protein has been simulated via force spectroscopy techniques with both all-atom (AA) models and several coarse-grained models having different levels of resolution: A Gō model containing all heavy atoms in the protein (HA-Gō), the associative memory, water mediated, structure and energy model (AWSEM) which has 3 interaction sites per amino acid, and a Gō model containing only one interaction site per amino acid at the Cα position (Cα-Gō). To systematically compare results across models, the scales of time, energy, and force were suitably renormalized in each model. TM alignment, native contact, and clustering analysis show that all models consistently predict a similar single pathway unfolding mechanism for early force- induced unfolding events, but these models diverge in their predictions for late stage unfolding events when the protein is more significantly disordered. When the protein is about half-unfolded, the unfolding pathways of the AA, HA-Gō, Cα-Gō models bifurcate repeatedly to multiple branches. The AWSEM model has a single dominant unfolding pathway over the whole range of unfolding, in contrast to all other models. However, the AWSEM pathway has the most structural similarity to the AA model at high nativeness, but the least structural similarity to the AA model at low nativeness. In comparison to the AA model, the sequence of native contact breakage is best predicted by the HA-Gō model.

870-Plat
Improved CHARMM Additive Force Field Parameters to Accurately Model Tyrosine-Choline Cation-π Interactions
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Cation-π interactions between methylated ammonium groups and tyrosine amino acids have been shown to be important for epigenetic recognition motifs, choline-binding proteins, and for protein-lipid interactions. Accurately modeling cation-π interactions in biomolecular simulations remains a challenge due to the lack of explicit polarization or charge transfer effects. In this work, we investigate the nature of tyrosine-choline cation-π interactions by performing high-level Quantum Mechanical (QM) calculations and building Potential Energy Surfaces (PES). We benchmark QM levels of theory and find that SAPT2+/aug-cc-pVDZ level of theory performs well compared to large basis set CCSD(T). Further, we compared QM PES (using SAPT2+/aug-cc-pVDZ) to both additive CHARMM36 and Drude polarizable force field. With CHARMM36, the equilibrium distances are well captured while the interaction energies are underestimated for various approach angles of TMA with respect to phenol. While using the Drude polarizable force field, the interaction energies deviate less compared to target QM data. However, the obtained equilibrium geometries are slightly underestimated. The best agreement between force field and QM PES is obtained by modifying the Lennard-Jones potentials for selected atom pairs involved in phenol-TMA cation-π interactions. We performed MD simulations of a bilayer-bound bacterial phospholipase and calculate the occupancies of tyrosine-choline cation-π interactions. The cation-π occupancies obtained with the modified set correlate better with experimental data than those obtained with the CHARMM force field.

871-Plat
Gromex: Electrostatics with Chemical Variability for Realistic Molecular Simulations on the Exascale
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Molecular electrostatics, notably in proteins and other macromolecules, is complicated by the presence of titratable sites which occur in different forms whose charge distribution differs, e.g., due to protonation or reduction in response to changes in their environment. This variability is often crucial for molecular function and interaction properties and thus has to be included for a realistic description of electrostatics. The computation of electrostatic interactions is also the computationally most demanding part of a molecular dynamics (MD) simulation. To address these issues, we combine a fast multipole method (FMM) with λ-dynamics for the open source molecular dynamics package GROMACS.
λ-dynamics bridges discrete, physical site forms via continuous λ-variables to allow the variable sites to interconvert between their forms, thus adding the