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
Hao Zhou[1], Hugo Guterres[2], Carla Mattos[2], Lee Makowski[3].
[1]EECE, Northeastern University, Boston, MA, USA, [2]Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA, USA, [3]Bioengineering Department, Northeastern University, Boston, MA, USA.
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
Abhishek Singharoy, Klaus Schulten.
Physics, University of Illinois, Urbana-Champaign, IL, USA.
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
Mona Habibi[1], Joerg Rottler[1], Steven S. Plotkin[1,2].
[1]Department of Physics & Astronomy, University of British Columbia, Vancouver, BC, Canada, [2]Genome Sciences and Technology Program, Vancouver, BC, Canada.
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
Hanif Muhammad Khan[1,2], Cédric Grauffel[3], Ria Broer[4], Alexander D. MacKerell Jr[5], Remco W.A. Havenith[4,6], Nathalie Reuter[1,2].
[1]Department of Molecular Biology, University of Bergen, Bergen, Norway, [2]Computational Biology Unit, Department of Informatics, University of Bergen, Bergen, Norway, [3]Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, [4]Zernike Institute for Advanced Materials, University of Groningen, Groningen, Netherlands, [5]Department of Pharmaceutical Sciences, University of Maryland, School of Pharmacy, Baltimore, MD, USA, [6]Stratingh Institute for Chemistry, University of Groningen, Groningen, Netherlands.
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
R. Thomas Ullmann[1], Carsten Kutzner[1], Andreas Beckmann[2], Bartosz Kohnke[1], David Haensel[3], Ivo Kabadshow[2], Holger Dachsel[2], Berk Hess[4], Helmut Grubmüller[1].
[1]Theoretical and Computational Biophysics, Max Planck Institute for Biophysical Chemistry, Göttingen, Germany, [2]Mathematics Division, Jülich Supercomputing Centre, Institute for Advanced Simulation, Jülich, Germany, [3]Mathematics Division, Jülich Supercomputing Centre, Institute for Advanced Simulation, Göttingen, Germany, [4]Theoretical Physics, School of Engineering Sciences, RIT, Stockholm, Sweden.
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

variability of the charge distribution as physical detail missing in standard MD. The FMM ideally complements by enabling efficient, non-redundant computation of the electrostatic forces needed also in standard MD and of the additional electrostatic interaction energies required to compute the forces that drive the interconversion between the different site forms. In addition, the FMM allows us to take full advantage of highly parallel supercomputers beyond 10,000s of CPU cores, as predicted for the upcoming exascale machines, by avoiding time consuming communication between compute nodes.
Our λ-dynamics method extends existing constant-pH λ-dynamics beyond protonation by allowing for titratable sites with any number of forms of potentially entirely different chemical structure, including binding of different ligand types. Allowing for many different site forms, and thus λ-variables, increases the size of the configuration space that needs be sampled. While interconversion between the site forms via continuous λ-variables increases sampling efficiency, it also leads to the occurrence of unphysical intermediate states. A new bias potential that explicitly controls the occurrence of unphysical intermediate states avoids their overrepresentation and ensures sampling of physically relevant configurations.

872-Plat
A Hybrid All-Atom/Coarse-Grained Approach to Problems in Chemistry and Biology
Samuel Genheden.
Chemistry and molecular biology, University of Gothenburg, Gothenburg, Sweden.
Molecular dynamics simulations offer a unique tool to study chemical and biological processes at the microscopic level. Usually one has to make a choice between an all-atom (AA) model that is accurate but limited in the spatial and temporal scales that can be affordably simulated, and a coarse-grained (CG) model that is less accurate but can be used to simulate large systems for longer times. Unfortunately, this dichotomy renders some problems currently intractable. Therefore, we developed a hybrid approach where an AA solute is coupled with a CG solvent model. This novel method is a unique and complementary biophysical technique and can be used to study important chemical and biological problems. The hybrid AA/CG model is straightforward to use and was benchmarked on the membrane transfer of amino acid analogs, membrane partition coefficients of small molecules and the stability of transmembrane helices. Here, we present the latest work with the AA/CG model on partition coefficient of small molecules and protein dynamics. We also present our results in the SAMPL5 blind challenge and outline future directions.

Platform: Protein Structure and Conformation II

873-Plat
Using Hydrogen Bond Surrogate Technology to Stabilize Beta-Hairpins
Nicholas Sawyer, Paramjit S. Arora.
Chemistry, New York University, New York, NY, USA.
Beta-hairpins are comprised of two β-strands connected by a short hairpin loop. The β-hairpin motif is critical in many protein folds and diverse protein-protein interactions (PPIs). Extensive studies on the forces governing β-hairpin folding and stability have led to the development of many strategies for β-hairpin stabilization, including side-chain cross-linking, rigid loop mimics, and macrocyclization. While these strategies have provided valuable insight into β-hairpin behavior, sacrifice of side chains may limit their application in the design and evaluation of β-hairpin PPI inhibitors. To overcome these challenges, we investigated the hydrogen bond surrogate (HBS) strategy as a method for β-hairpin stabilization. Previous studies have demonstrated the effectiveness of the HBS strategy in nucleation and stabilization of peptides in the α-helical conformation. Alpha-helix nucleation is accomplished by replacing the N-terminal backbone hydrogen bond with a covalent bond using ring-closing olefin metathesis on alkene substrates positioned at the i and i+4 peptide positions. Importantly, mimicry of a backbone hydrogen bond yields peptides with a full complement of side-chain functional groups. Our model system is a well-characterized β-hairpin derived from the B1 domain of protein G (GB1). The HBS macrocycle was formed on solid support by joining alkenes that mimic a hydrogen bond between the peptide's N- and C-termini. Conformational stabilities of unconstrained and HBS peptides were evaluated by circular dichroism (CD) and nuclear magnetic resonance (NMR) spectroscopy. Consistent with previous results, we find that the unconstrained peptides show weak propensity for the β-hairpin conformation while HBS macrocyclization significantly increases β-hairpin propensity. We envision that the HBS strategy will be generally effective in stabilizing diverse β-hairpin sequences.

874-Plat
Single-Molecule FRET Delineates Asymmetric Trimer Conformations during HIV-1 Entry
Xiaochu Ma[1], **Maolin Lu**[1], Daniel S. Terry[2], Jason Gorman[3], Peter D. Kwong[3], Scott C. Blanchard[2], James B. Munro[4], Walther Mothes[1].
[1]Department of Microbial Pathogenesis, Yale University School of Medicine, New Haven, CT, USA, [2]Department of Physiology and Biophysics, Weill Cornell Medical College of Cornell University, New York, NY, USA, [3]Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA, [4]Department of Molecular Biology and Microbiology, Tufts University School of Medicine, Boston, MD, USA.
HIV-1 entry into cells requires binding of the viral envelope glycoprotein (Env) to receptor CD4 and coreceptor. Imaging of individual Env molecules on native virions revealed that Env trimers are dynamic, spontaneously transitioning between three distinct conformations. Binding of CD4 and coreceptor surrogate antibody 17b promotes opening of the closed Env (State 1) to stabilize an activated conformation (State 3) by way of at least one structural intermediate (State 2). Here, using single-molecule Fluorescence Resonance Energy Transfer (smFRET), we identify this intermediate as an asymmetric conformation where only a single CD4 molecule engages the Env trimer and individual protomers adopt distinct conformations. Binding of a second CD4 molecule is needed to completely open the trimer. Thus, our work reveals a novel asymmetric structural intermediate and gives insights into cooperativity during the opening of the HIV-1 Env trimer.

875-Plat
Lipid Regulated Intramolecular Conformational Dynamics of SNARE-Protein Ykt6
Yawei Dai[1], Markus Seeger[2], Jingwei Weng[3], Song Song[1], Wenning Wang[3], **Yan-Wen Tan**[1].
[1]Department of Physics, and State Key Laboratory of Surface Physics, Fudan University, Shanghai, China, [2]Institute of Biophysics, Goethe-University Frankfurt, Frankfurt, Germany, [3]Department of Chemistry and Institutes of Biomedical Sciences, Fudan University, Shanghai, China.
Cellular informational and metabolic processes are propagated with specific membrane fusions governed by soluble N-ethylmaleimide sensitive factor attachment protein receptors (SNAREs). SNARE protein Ykt6 is highly expressed in brain neurons and plays a critical role in the membrane-trafficking process. Studies suggested that Ykt6 undergoes a conformational change at the interface between its longin domain and the SNARE core. In this work, we study the conformational state distributions and dynamics of rat Ykt6 by means of single-molecule Förster Resonance Energy Transfer (smFRET) and Fluorescence Cross-Correlation Spectroscopy (FCCS). We observed that intramolecular conformational dynamics between longin domain and SNARE core occurred on a timescale around 200 μs. Furthermore, this dynamics can be regulated and even eliminated by the presence of lipid dodecylphoshpocholine (DPC). Our molecular dynamics simulations have shown that, the SNARE core exhibits a flexible structure while the longin domain retains relatively stable in apo state. Combining kinetic rates of the dynamics process extracted from single molecule experiments, we are the first to explain this functional conformational change from a quantitative point of view.

876-Plat
The Two GTPase Domains of the Outer Mitochondrial Membrane Protein Miro have Novel Active Site Conformations and Distinct Biochemical Properties
Kyle P. Smith[1], Pamela J. Focia[2], Yongbo Zhang[3], Julian L. Klosowiak[1], Douglas M. Freymann[2], Sarah E. Rice[1].
[1]Cell & Molecular Biology, Northwestern University, Chicago, IL, USA, [2]Biochemistry & Molecular Genetics, Northwestern University, Chicago, IL, USA, [3]Chemistry, Northwestern University, Evanston, IL, USA.
Mitochondria motility and dynamics are tightly linked. Dysfunction in mitochondrial dynamics cause a host of neurological disorders. The outer mitochondrial membrane protein Miro contains two GTPase domains that control mitochondrial dynamics. While it is known that each of Miro's GTPases are responsible for different mitochondrial morphology and localization phenotypes, the biochemical and structural mechanisms are unknown. We have determined the crystal structure of the entire human Miro1 protein in two separate fragments. Using SAXS and MD, we have investigated how the full-length protein assembles. Our structures reveal significant differences between the n-terminal and c-terminal GTPases (nGTPase and cGTPase). In the nGTPase, unique Switch 1 and Switch 2 residues coordinate the bound GTP, Mg^{2+}, and water molecules for hydrolysis. In contrast, the cGTPase shows no large conformational changes between different nucleotide states and may be