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.

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 chloroplast. Construction of this model drives pioneering advances in crystallography and electron-microscopy based structure determination techniques, namely through simulation of atomistic relaxation in a minimal MDF (Molecular Dynamics Flexible) 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 structure and efficiency of energy conversion. Leveraging a nanoscale network of bioenergetic proteins in a man-made solar device in robustness, adaptation to environmental stress, evolution into highly efficient energy-harvesting machines that surpass photosynthetic organelles have been optimized by over two billion years of evolution into highly efficient energy-harvesting machines that surpass photosynthetic organelles have been optimized by over two billion years of evolution into highly efficient energy-harvesting machines that surpass photosynthetic organelles have been optimized by over two billion years of evolution into highly efficient energy-harvesting machines that surpass photosynthetic organelles have been optimized by over two billion years of evolution into highly efficient energy-harvesting machines.

Verifying Self-Consistency of Protein Structure and Dynamics through Molecular Dynamics
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 sites 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 existing constant-pH λ-dynamics by providing a way 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 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, Paramjot S. Arora.
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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 (PPI). 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 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 Xiaohua Ma1, Maolin Lu1, Daniel S. Terry2, Jason Gorman1, Peter D. Kwong1, Scott C. Blanchard3, James B. Munro3, Walther Mothes4.
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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 pro- tomers 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, Markus Seeger1, Jingwei Weng1, Song Song1, Wenning Wang1, Yan-Wen Tan2.
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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 dicyclophosphocholine (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. Smith1, Pamela J. Focia2, Yongbo Zhang1, Julian L. Klosowiak1, Douglas M. Freyman1, Sarah E. Rice1.
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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, Mg2+, and water molecules for hydrolysis. In contrast, the cGTPase shows no large conformational changes between different nucleotide states and may be