2368-Pos Board B505
Introducing Molecular Flexibility in Efficient Simulations of Many-Protein Systems
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A novel multiple conformations Monte Carlo (mcMC) computational method is presented that allows the modeling of protein-protein interaction and aggregation. Such processes are relevant in realistic biological environments, such as the cytoplasm and the extracellular matrix, which are characterized by high concentrations of biomolecular solutes, e.g. of 300-400 mg/mL for proteins and RNA in the cytoplasm of E. coli. Simulation of such environments necessitates the inclusion of a large number of protein molecules and therefore computationally inexpensive methods, such as rigid-body Brownian dynamics (BD) and Monte Carlo (MC) methods, must be used. However, the rigid-body representation typically employed in simulations of many-protein systems give rise to certain artifacts in protein-protein interactions. We present a methodology that allows us to incorporate molecular flexibility in MC simulations at low computational cost, and thereby eliminate ambiguities based on the structure selection in rigid molecule simulations. We benchmark and validate the methodology on solutions of hen egg white lysozyme (HEWL), an extraordinarily well-studied system for which extensive experimental data, including osmotic virial coefficients, solution structure factors, and multiple structures determined by x-ray and neutron crystallography and solution NMR, as well as previous BD simulation results, are available.

2369-Pos Board B506
Docking and Design of Oligosaccharides, Glycoproteins, and Glycolipids
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Carbohydrates are infamously challenging to model, yet they affect protein structure, stability, and activity. We are developing accurate and fast methods of modeling and designing carbohydrates for applications in glycobiology. We have built a framework within the Rosetta structure and design suite for modeling saccharide ligands and complex glycoconjugates. Our intuitive and efficient data structures allow access to all torsion angles (φ, ψ, ω, and χ) and Cremer–Pople parameters for sampling ring forms and capture the high degree of flexibility, stereochemistry, and branching in carbohydrates. Rosetta's flexibility and speed enable modeling of any glycan-containing molecule in docking and refinement protocols through exploration of this vast torsional and ring-conformational diversity.
Rosetta's residue-centric approach, coupled with combinatorial "patching" of standard residues with specific functional groups, allows for design algorithms that sample alternative saccharide units, enabling high-throughput screening of thousands of protein variants and glycoforms in a search for stable or functional molecules.
Here, we will report three studies benchmarking monosaccharide ring conformations, oligosaccharide structure prediction, and bound–bound protein–oligosaccharide docking. We explore the relative energy surfaces of the ring forms of all D-aldohexopyranoses; we examine predicted structures of two Lewis^X oligosaccharides; and we compare the docking predictions of eleven antibody–glycoantigen pairs with known structures. These studies will allow us to rigorously test the Rosetta scoring (energy) function, to adapt it to the unique chemical effects of sugars.
We will also present preliminary real-world applications in antibody accessibility for glycosylation enzymes, x-ray crystal refinement of an extensively glycosylated HIV-1 envelope protein trimer, and the activity of glycosylated carboxylesterases.
These new approaches will provide glycobiologists and glycoengineers a new computational toolbox, further the understanding of the biomolecular mechanisms of disease, and create opportunities for a wide range of previously intractable studies.

Computational Methods and Bioinformatics

2370-Pos Board B507
Simulating Metabolism with Statistical Thermodynamics
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The development and application of fluctuation theories over the past 20 years are promising ways to model the time-dependence of coupled reactions across large time scales with the same rigor as mass action-based kinetic simulations. Here, we report the progress that has been made in modeling metabolism with fluctuation theory. The basic concept that is that, instead of setting rate constants and sampling for steady-state concentrations and fluxes, we set chemical potentials and sample for rates, fluxes and concentrations. The assumption inherent in the use of the standard chemical potential for modeling reactions is that each change of state occurs with a probability proportional to the thermodynamic driving force for the respective reaction. In regions of state space where the linear free energy relationships exist, this is an excellent assumption. Applications to the central metabolism of microbes are discussed, including the niche-specific thermodynamics of the TCA cycles of the heterotroph E. coli, the cyanobacterium Synechococcus sp. PCC 7002, and the green sulfur bacterium Chlorobium tepidum. The TCA cycle of *E. coli* functions in an environment in which the breakdown of saccharides is used to provide energy for cellular growth and maintenance. The cyanobacterial TCA cycle, in contrast, functions in an environment in which photosynthesis provides a significant amount of NADPH and ATP necessary for growth, yet despite high ATP and NADPH concentrations the TCA cycle in cyanobacteria must be able to produce three carbon precursors for anapleuritic reactions necessary for synthesis of biopolymers. The reductive TCA cycle of *C. tepidum* functions in a low oxygen environment and uses sulfide and thiosulfate as electron donors and CO_2 as a carbon source. Green sulfur bacteria such as *C. tepidum* only contain photosystem I, which produces large amounts of ATP and reduced ferredoxins.

2371-Pos Board B508
Bayesian cryo-EM Refinement
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In light of recent high-resolution cryo-electron-microscopy (cryo-EM) structures of large complexes, modeling atom coordinates into cryo-EM densities faces new challenges. Though high-resolution structures provide more data, finding the best-fitting structure with current refinement methods is more difficult with increased resolution, because the used refinement potentials become more rugged the higher the resolution. Currently used refinement potentials are defined by empirically chosen measures of similarity between a calculated cryo-EM density and the given experimental map, e.g. cross-correlation or absolute distance.
Here, we present a new refinement potential that is based on a statistical physics model of the cryo-EM measuring and reconstruction process using Bayesian statistics. Our method contains previously previously developed algorithms as limiting cases.
The minima of the refinement potential and its shape both influence the efficiency of the refinement algorithm; a smoother energy landscape allows a more efficient exploration of the minima, i.e. fitting structures, in this landscape. Compared to earlier methods, our refinement energy landscape is smoother, allowing more efficient sampling of the energy landscape. Further, our refinement protocol provides an appropriate refinement force constant and takes into account the thermal fluctuation of the atoms. Additionally, our algorithm allows us to generate molecular dynamics ensembles that represent the simultaneous input from multiple cryo-EM maps.

2372-Pos Board B509
Applying Derivative-Free Optimization to Fit Kinetic Parameters of Viral Capsid Self-Assembly Models from Multi-Source Bulk in vitro Data
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Virus capsid assembly has been a powerful model system for biological self-assembly in general due to the combination of experimental tractability but complicated pathway space. Detailed experimental resolution of viral assembly processes, however, has so far proven impossible. Computational approaches have provided a solution, allowing us to learn models of assembly consistent with indirect experimental measures of bulk in vitro assembly and thus fill the gaps between coarse-grained experimental measurements and detailed theoretical models. Nonetheless, accurate simulation predictions rely on building accurate models, which has proven to be a challenging data-fitting problem due to the high computational cost of simulating capsid assembly trajectories, high stochastic noise inherent to the system, and limited and generally noisy experimental data available. Here, we describe progress in learning accurate kinetic models of capsid assembly systems by computationally fitting assembly simulations to experimental data. We previously developed a heuristic optimization approach to learn rate parameters of coat-coat interactions by minimizing the deviation between real and simulated static light scattering measurements. We now show that one can substantially improve fitting to light scattering data using an alternative class of methods called derivative-free

optimization, designed to deal with challenges of costly, noisy computations. Simultaneously, simulated exploration of potential alternative sources of experimental data for monitoring bulk assembly (e.g, non-covalent mass spectrometry) suggest that other feasible technologies providing richer data on assembly progress can more precisely pin down true parameters and assembly pathways. Advancing such simulation-based data fitting methods provides a general technology for greatly enhancing our ability to learn fine-scale details of complex assembly processes from experimental data, a strategy with potential application to developing accurate quantitative models of numerous other assembly systems found through biology.

2373-Pos Board B510

A Computational Model of Cell-Generated Traction Forces and Fibronectin Assembly

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The extracellular matrix (ECM) is an assembly of proteins that surround cells, and serves as the cell substrate in vivo. A primary component of newly synthesized ECM is the fibronectin (FN). Despite many years of research, the mechanism of FN assembly is still not completely understood. While it is recognized that FN assembly requires application of traction force to expose a buried FN-FN binding site, such a site has never been elucidated. We hypothesize that assembly of fibronectin (FN) fibrils is a complex event: each of the 15 Type III domains in FN is made up of a sandwich of 7 beta strands; when relaxed, the Type III domains are folded such that the beta strands are twisted, blocking the non-specific binding of other proteins. Application of force straightens these beta-strands, allowing for binding of other FNs via a beta-strand addition mechanism. This suggests that all 15 domains are capable of binding FN molecules in a growing fibril. To investigate this hypothesis, we present a mechanistic computational model of cell/FN/substrate biomechanical interactions, which accounts for the unique, nonlinear mechanical properties of each domain and the stochastic binding between molecular clutches and the moving actin bundle. Monte Carlo simulations predict that increasing substrate stiffness leads to longer and thicker fibrils. Additionally, the model demonstrates complex time-dependent dynamics governing the size of the growing fibril, the domains' stiffness, and traction forces; that is, at low force, a small subset of domains open, allowing for minimal fibril assembly, while large forces unfold a considerable fraction of domains and create large, thick fibrils. Simulation outputs are compared to experimental data in which traction force, FN assembly, and domain opening are quantified using microfabricated pillar arrays and cysteine-labeling of recombinant FNs with introduced buried cysteines.

2374-Pos Board B511

Numerical Modeling of Lipid Biosynthesis in Microalgae

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A worldwide effort to find renewable alternatives to fossil fuels is underway. Potential sources of renewable fuel include microalgae. Under certain conditions, these organisms produce large amounts of triacylglycerides (TAGs), lipids that can be converted to biodiesel. However, the lipid biosynthetic pathway of microalgae is not fully understood. To better understand the conditions that govern lipid production in microalgae, we employ theoretical and computational methods to understand the topology, flux and regulatory properties of the metabolic pathway involved in TAG biosynthesis in microalgae. In particular, we seek to understand the differences that lead to altered TAG production in different microalgal species. We compare a species that naturally generates large amounts of TAG under stress conditions with a species that produces comparatively much less TAG under similar conditions. Predictions from the model will be validated by comparison with in vitro and in vivo experiments. By understanding more about lipid production in microalgae we hope to guide rational genetic engineering approaches to increase oil production in these organisms. We anticipate that these studies will ultimately provide insights into lipid biosynthesis for a wide range of other organisms.

2375-Pos Board B512

Robust Elastic Network Model: Precise Prediction of Atomic Fluctuations in Protein Crystal Structures

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Elastic network model (ENM) based normal mode analysis has become popular as its capability and suitability for the study of protein dynamics. However, the existing ENMs often fail to reproduce the experimentally observed B-factor (i.e., atomic fluctuation) because of oversimplification of their force-fields. In this work, we have proposed a robust ENM (RENM) in which, for reflecting inter-connections accused from surrounding molecules in a unit cell, symmetric constraints based on crystal space group are applied to the representative single molecule as well as its intra-connections are also represented by using lumped masses and specific spring constants depending on the types of amino acids and chemical bonds, respectively. More than 500 protein structures are tested by RENM. Their results show better agreement with experimental B-factor without additional computation burden compared to those of traditional ENM. Moreover, the global spring constant is quantitatively determined as a function of temperature at 100K and 290K, which enables us to compute directly atomic fluctuations and vibrational density of state without any fitting process. Thus, RENM is expected to play an important role in understanding protein dynamics based on its crystal structure information.

2376-Pos Board B513

Protein Translocation through an Electrically Tunable Membrane

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Understanding protein dynamics through an artificial nanopore has implications in many areas such as sensing and filtering. Collecting statistical information while tracking the movement of a full atomic protein model is computationally expensive since number of atoms ranges in the thousands. The need to represent protein with a computationally cost effective model is imperative, along with understanding its dynamics through the nanopore. In this work we studied the dynamics of the protein insulin placed near a nanopore of an electrically tunable semiconductor membrane. Using Brownian dynamics method we calculated the trajectory of the modeled protein in the electrolyte-membrane electrostatic potential. The time spent by the protein before a successful translocation and the translocation times were both analyzed. Our results indicate that the localized electric field within the nanopore affects the movement of the protein. Also, by comparing the results of the full atomic protein model with a coarse grained model and a single bead model, we evaluate which model best approximates the full atomic protein model.

2377-Pos Board B514

Traveling Wave Solutions to Reaction-Diffusion Equations based on the Lambert W Function

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Non-linear partial differential equations of the ''reaction-diffusion'' arise in many areas of biological, chemical and physical science, including the Burgers-Huxley equation associated with nerve pulses. Solutions to these types of equations are often found in the form of traveling waves, which in one dimension propagate over the entire real axis between stable limits for non-negative time. The generalization of known non-linear model equations continues to remain of interest.

It is shown here that it is possible to find traveling wave solutions to a generalized group of reaction-diffusion equations of this type, based on a traveling wave which can be represented in terms of the Lambert W function. This approach begins by considering the first order differential equation exactly solved by the traveling wave, and then using an operator approach to construct a second order differential equation solvable in terms of this traveling wave. The second-order differential equation can then be compared to the original partial differential equation after a transformation of the variables.

2378-Pos Board B515

Quantitative Theory of Active Diffusion Trajectories by Instantaneous Diffusion Coefficient

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Owing to the development of single-particle tracking techniques, it is able to observe real-time diffusive motions of labelled tiny particles in living cells. To quantify the diffusion trajectories, the mean-squared displacement (MSD) analysis is common and conventional. The diffusion coefficient quantified by the analysis is a good barometer of the mobility. But, in terms of statistical physics, equilibrium and stationarity are assumed in the MSD analysis. Accordingly, the analysis depends on the statistical ensemble. When diffusive motions are driven by non-equilibrium and non-stationary fluctuations as the outcome of biological activity, such fluctuations are averaged and neglected in the MSD analysis. Such enhanced diffusive motion is called active diffusion. To understand the interaction among diffusive motion, biological activity, and environment in detail, we should develop a new diffusion analysis theory beyond the MSD analysis.

Hence, our subject is not an ensemble of diffusion trajectories, only individual ones. The MSD analysis is based on the hypothesis of a stationary stochastic