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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.

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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.

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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.

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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