Posters: Molecular Dynamics I

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BPS2025 - Decoding the insulin receptor: Mechanisms of binding and structural stability

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Insulin binding to the insulin receptor (IR) initiates a series of conformational changes that lead to receptor activation. While numerous cryo-EM structures of IR in various conformations and states of insulin saturation have been resolved, they do not capture the dynamic process or the sequence of molecular events leading to activation. In this study, we utilized molecular dynamics (MD) simulations to investigate the behavior of IR-insulin complexes under physiological insulin concentrations, using experimentally resolved structures as starting points. Our simulations revealed that insulin binding at the hybrid sites triggers the opening of site 1. Further, insulin bound at site 1 promotes the extension of the α-helix in the αCT region and enhances inter-domain stabilization. These findings support a novel ''ladder-climbing'' model of IR activation, where insulin sequentially transitions from site 2 to site 1, orchestrating a stepwise conformational change in the receptor. This mechanism provides critical insights into the dynamic activation process of IR, offering a more comprehensive understanding of how insulin modulates receptor activity. This knowledge is crucial for the rational design of improved therapeutic strategies targeting IR, potentially leading to more effective treatments for metabolic disorders such as diabetes. By elucidating the finer details of IR activation, this study paves the way for developing drugs that more precisely modulate receptor function.

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BPS2025 - Predicting interacting domains in the nucleosome from kinetic correlations

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The nucleosome core particle, the fundamental component of chromatin, is composed of a positively charged histone octamer that is wrapped by an approximately 147 bp DNA strand. The DNA is dynamic and can unwrap and rewrap at ms timescales. The formation of twist defects, DNA sliding, and breathing of the DNA have been observed using atomistic molecular dynamics. How the DNA communicates with the histone and how this information propagates through the histone is suggested to be a cooperative process. Allosteric mechanisms in the nucleosome have been characterized, suggesting that small changes in the histone can shift contacts with the DNA through specific loops. Here, we characterize the kinetic correlation in histone domains using the conditional activity (CONDACT). We find correlated domains in the histone and the neighboring nucleic acid strand. We use the side chain dihedral angle of the histone and the sugar-base dihedral angle of the double-stranded DNA as our degrees of freedom. Specific domains at the histone-DNA interface are kinetically correlated with high dynamical memory. We find domains in the histone that are kinetically correlated up to 7.5 nm apart. How these domains are modified when external binding factors such as chromatin remodelers and transcription factors bind may provide critical insight into how the nucleosome regulates genomic processes.

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BPS2025 - Improving the force field for lipid interactions with calcium and beryllium

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Beryllium (Be^{2+}) is a highly polar divalent cation with a specific and high affinity for phosphates. It has been shown to bind strongly to lipids and is capable of outcompeting Ca^{2+} in its physiological complexes with lipids and proteins. The toxic effects of inhaled Be dust manifest as berylliosis, a chronic non-resolving inflammation in the lungs in predisposed individuals employed in the mining industry. To characterize Be^{2+} as a Ca^{2+} competitor, we are using experimental free energy data obtained from isothermal titration calorimetry (ITC) to fit the all-atom CHARMM36m forcefield parameters for use in molecular dynamics simulations. From ITC, we now know that the free energy of Be^{2+} and phosphatidic acid (PA)-mimic and PA liposome is about -7 kCal/mol, with favorable both enthalpic and entropic components. Similar data obtained for Ca^{2+} indicate -4 kCal/mol. Our simulation data for Be^{2+} and Ca^{2+} ions and small lipid-mimic molecules shows that the current force field overestimates the strength of the lipid interaction for both metals. Adjusting the force field parameter will allow us to simulate the correct strength of the interactions and give us insight into how the metal ion binding affects cell membranes, both the lipid component and phospholipid-recognizing proteins. This work will also be extended to the DRUDE polarizable force field to account for the highly polar nature of the metal ion and its variation with a changing electrostatic environment.

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BPS2025 - Assessing water model impact on protein-glycan dynamics: A study combining alchemical free energy and molecular dynamics approaches

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Understanding the dynamics of protein-glycan interactions is crucial for comprehending biological mechanisms, including host-pathogen interactions, intercellular communication, and immune responses. To simulate these interactions accurately, it is essential to select precise parameters, particularly the water model, due to extensive hydrogen bonding between glycans and hydroxyl groups. In this study, we utilized full atomistic molecular dynamics simulations and alchemical absolute binding free energy calculations to assess the performance of five water models across six protein-glycan complex systems. By simulating 4.8 μs per system, we evaluated the impact of different water models on binding affinity and structural dynamics. Our results indicate the choice of water model significantly influences the stability of the binding motif's and the glycan's bound-state conformation. The OPC water model demonstrated superior consistency with experimental binding data, emphasizing the importance of water model selection in accurately predicting protein-glycan interactions. Our study highlights the critical role of water models in affecting protein-glycan interactions and the accuracy of binding affinity calculations, which is pivotal in developing therapeutic strategies targeting these interactions.

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BPS2025 - Free energy calculations using generative models trained based on molecular dynamics trajectories: A diffusion model approach

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Molecular dynamics (MD) is used to predict and study the behavior of biomolecular systems on the nanosecond to microsecond timescale with high temporal and spatial resolution. Despite its great success, MD has its own drawbacks. Slow sampling, for instance, is a fundamental limitation of MD simulations. As the system size increases, MD simulations become increasingly more expensive computationally because they need to solve Newton's equations of motion for all atoms at each timestep. There is a recent interest in exploring utilization of machine learning and deep learning algorithms within the MD field whether in force field development, simulation analysis, or sampling. However, an unrealized area has been effective synthetic trajectory generation, where MD simulations can be used as a training data set to generate larger data sets. In this study, we utilize the diffusion model, a generative model, to generate synthetic trajectories in a low-dimensional space that can be used for free energy calculations. This model aims to produce the free energy surfaces based on generated synthetic MD trajectories by a diffusion model trained based on MD trajectories. This method significantly reduces the computational cost associated with large-scale MD simulations. We have examined a number of diffusion model based approaches to achieve efficient protocols. A key feature of the successful methodology used is to combine two neural networks one for estimating the noise in each step of the trajectory and one for the diffusion model itself. We first used a 2D toy model based on overdamped Langevin equation to examine the methodology and then applied it to MD simulations of a small peptide as well as a membrane transporter. Our novel method shows great potential for accurate free energy calculations with limited MD data.