Posters

Posters: Protein Structure and Conformation IV

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Conformational Dynamics of Alanine in Water and Water/Ethanol Mixtures: Experimentally Driven Evaluation of Molecular Dynamics Force Fields

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The reliability of molecular dynamics (MD) predictions depends on the accuracy of the employed force field. We examine the ability of six MD force fields (Amber ff14SB, Amber ff99SBnmr1, Amber ff03ws, OPLS-AA/L, OPLS-AA/M, and CHARMM36) to reproduce conformational ensembles of the central alanine residue in GAG and AAA obtained from an earlier analysis of φ and ψ dependent J coupling constants and amide I' profiles. To this end, MD-derived Ramachandran distributions are used to calculate five (GAG) or six (AAA) J coupling constants and amide I' profiles of respective Raman, IR, and vibrational circular dichroism (VCD) spectra. An empirical Gaussian model of the Ramachandran distribution, constructed to best fit these experimental data, is used as a benchmark. Overall, MD-derived Ramachandran plots differ from the Gaussian model predictions by producing an overly constricted polyproline II (pPII) basin, an overpopulated antiparallel β (aβ) basin, and an underpopulated transitional β (βt) basin. Amber ff14SB outperforms the other five MD force fields in the ability to reproduce the J coupling constants and yields the highest pPII populations of the central alanine residue in GAG (55%) and AAA (63%), in a good agreement with the results obtained in the Gaussian model (59% and 76%). We extended the study of GAG in water to different water/ethanol mixtures and used MD-derived Ramachandran distributions for a comparison to experimental data in order to evaluate Amber ff14SB, CHARMM36, and OPLS-AA/M. Results obtained for all three force fields suggest that the populations of pPII and right-handed helical conformations are anti-correlated. The comparison of MD-derived J coupling constants and amide I' profiles to experimental data demonstrates that Amber ff14SB again outperforms CHARMM36 and OPLS-AA/M in capturing conformational ensembles of alanine.

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Nanomechanical Differences between Inactive and Active States of Rhodopsin from Molecular-Scale Simulation

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Several membrane proteins, including G protein-coupled receptors (GPCRs), present a challenge in studying their structural and dynamical properties under physiological conditions. Moreover, to better understand the activity of proteins requires examination of single molecule behaviors rather than ensemble averaged behaviors. In this work we report the Force-distance curve-based AFM (FD-AFM) which was utilized to directly probe and localize the conformational states of a GPCR within an artificial membrane at nanoscale resolution. We have further validated the experimental results by molecular scale coarse-grained (CG) simulations of rhodopsin biomolecules. In the past, our CG model has been applied successfully for the study of the mechanical properties of large biological assemblies such as β-amyloid and α-synuclein fibrils. Both FD-AFM experimental results and the computational force profiles revealed that the active state of the receptor has a higher Young's modulus compared to the inactive state of the receptor. We show how the deformation of the hydrogen bond network triggers this difference and by the statistical analysis of the native contacts we highlight the underlying mechanism. Hence, the inactive and active states of rhodopsin could be differentiated based on the stiffness of the receptor. Our work paves the route towards the molecular characterization of protein states based on the Young's modulus, which is clear indication of the mechanochemical interplay of proteins within the cell membrane.

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Proteins on the Water/Air Interfaces: Insights from Simulations using Polarizable Force Fields

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Biomacromolecules exhibit unique conformational and self-assembly dynamics on the water/air interface. While water is highly polar, air can be considered as the ultimate hydrophobic environment with a dielectric constant of one. Polarizable force fields provide more accurate modeling of charge distribution response to external electric field, and thus assume better transferability in describing molecules in significantly different electrostatics environments.

In this presentation, we study the structure and dynamics of several model systems on the water/air interfaces using our recently developed Drude polarizable protein force fields. We first investigate the dynamics of methylguanidinium ions, the model compound for Arginine side-chain, on the water/air interfaces with molecular dynamics (MD) simulations and illustrated how they accumulate on the interface with a certain tilt angle. Our results resolve the discrepancy between previous MD studies and a recent heterodyne-detected vibrational sum-frequency generation measurement.

Furthermore, our simulations of LK peptides suggest enhanced hydrophobicity of Leu on the water/air interface with polarizable force fields. Different self-assembly processes of intrinsic disordered protein (IDP) fragments on the interfaces were also observed with the additive CHARMM36m and the polarizable Drude force fields. Overall, our results demonstrate the importance of induction effects in modeling the protein dynamics on interfaces.

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A Computational Perspective on the Gating Mechanism of β-Ketoacyl-ACP Synthases

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Elongating β-Ketoacyl-ACP synthases or ketosynthases (KSs) catalyze the formation of carbon-carbon bonds, elaborating ketide units into mature fatty acids. These fatty acid synthases (FASs) catalyze a decarboxylative Claisen-like condensation, using a ping-pong mechanism. This process requires the KS to interact with multiple acyl carrier proteins (ACPs), small globular proteins, responsible the delivery of pathway substrates and intermediates to FASs. *E. coli* fatty acid biosynthesis (FAB) involves two KSs, FabB and FabF, each possessing distinct substrate preferences and catalytic activities. This study employed chemical, structural, and computational biology methods to better characterize the molecular mechanisms utilized by FabB and FabF to control substrate selectivity, reaction order, and product fidelity. Although this work is interdisciplinary in nature, this paper will emphasize the discussion of the computational biology (i.e., molecular dynamics simulations) used to interrogate these mechanisms.

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Local Unfolding Relates to Proteolytic Susceptibility of the Major Birch Pollen Allergen Bet v 1

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Proteolytic susceptibility during endolysosomal degradation is decisive for allergic sensitization. However, in the major birch pollen allergen Bet v 1 most protease cleavage sites are located within its secondary structure elements, which are inherently inaccessible to proteases. The allergen thus has to unfold locally, exposing the cleavage site in an extended conformation to become susceptible to proteolysis. Hence, allergen cleavage rates are presumed to be linked to their fold stability, i.e., unfolding probability. Yet, these local unfolding events have neither been captured in experiment nor simulation due to limitations in resolution and sampling time, respectively. Here, we perform classic and enhanced molecular dynamics simulations to quantify fold dynamics up to the millisecond timescale of Bet v 1 A and two variants with higher and lower cleavage rates. Already at the nanosecond-timescale we observe a significantly higher flexibility for the destabilized variant compared to Bet v 1 A and the proteolytically stabilized mutant. Estimating the thermodynamics and kinetics of local unfolding around an initial cleavage site, we find that the Bet v 1 variant with the highest cleavage rate also shows the highest probability for local unfolding. For the stabilized mutant on the other hand we only find minimal unfolding probability. These results strengthen the link between the conformational dynamics of allergen proteins and their stability during endolysosomal degradation. The presented approach further allows atomistic insights into the conformational ensemble of allergen proteins and provides probability estimates below experimental detection limits.