BP 36: Molecular Dynamics (Focus Session)

Focus session organized by Bert de Groot, Max Planck Institute for Biophysical Chemistry, Göttingen

Time: Wednesday 9:30–11:00 Location: H43

Invited Talk BP 36.1 Wed 9:30 H43

Molecular simulation of protein dynamics and function — •Gerhard Hummer — Max Planck Institute of Biophysics, Frankfurt am Main, Germany

We use molecular simulations to study functional protein dynamics over a broad range of temporal and spatial scales. A hybrid quantum-mechanics/molecular-mechanics (QM/MM) description allows us to follow fast, photoexcitation-driven protein motions. The resulting simulation trajectories are compared directly to femtosecond time-resolved protein crystallography experiments at X-ray free electron lasers. By contrast, to study large-amplitude functional motions in molecular motors on slower timescales, we use equilibrium and nonequilibrium classical simulations. The simulations help us elucidate the mechanisms underlying the efficient operation of biomolecular machines.

BP 36.2 Wed 10:00 H43

In Silico Reduction of Conformational Variance in Cryo-EM Imaging — •Gunnar Schröder — Forschungszentrum Jülich, Jülich, Germany

One of the biggest challenges in the analysis of cryo-EM images is the heterogeneity and flexibility of the molecules, which on the one hand severely limits the achievable resolution but on the other hand reports on conformational dynamics. A computational approach will be presented to reduce the conformational variance of a set of single-particle images with the goal of increasing the resolution. First the conformational variance of a molecule is reconstructed from the variance of the density. The information on conformational variance is then used to extensively classify the images into a number of different classes. In a next step, the individual 3D density reconstructions from all classes are recombined into one single (higher resolution) reconstruction by a novel flexible averaging procedure. In the flexible averaging the density grids of two maps are elastically deformed to account for large scale conformational differences thereby reducing the conformational variance of a data set. The goal is to improve the resolution and at the same time to gain a complete picture of the conformational variance of a macromolecule.

BP 36.3 Wed 10:15 H43

Robust Density-Based Clustering to Identify Metastable Conformational States of Proteins — •Florian Sittel and Gerhard Stock — Biomolekulare Dynamik, Physik, Uni Freiburg

Molecular dynamics (MD) simulations of proteins nowadays deliver an extensive amount of data describing dynamics up to millisecond timescales. Recently, Markov state models (MSM) have been recognized as a concise yet valid manner, to describe the relevant dynamics of proteins.

Here, we provide a novel, self-consistent and robust workflow to construct MSMs from the raw data of MD trajectories. This workflow involves (I) the reduction of dimensionality with suitable methods like Dihedral angle Principal Component Analysis, (II) the construction of geometrically defined microstates by a newly developed density-based clustering algorithm, (III) and the construction of the final MSM employing a dynamic clustering algorithm.

Additionally, we introduce a novel type of diagram to easily compare metastable protein states by their respective dihedral angle content.

BP 36.4 Wed 10:30 H43

Force probe MD simulations of peptidic foldamers — Lalita Uribe, Jürgen Gauss, and •Gregor Diezemann — Institut für Physikalische Chemie, Universität Mainz, Duesbergweg 10-14, 55128 Mainz, Germany

Foldamers are small oligomers of molecular entities that fold into ordered structures. In the recent past, interest has particularly grown in the thermal and mechanical properties of peptidic foldamers due to their possible peptide-mimetic applications. Here, we present a simulation study of the mechanical unfolding pathway of different natural and artificial peptidic foldamers presenting different folded motifs. Using force probe molecular dynamics we show the importance of the rigidity of the backbone and the strength of the intra-molecular hydrogen bonds in the stabilization of the folded conformations. We analyze the statistical behavior of the unfolding pathway of the peptidic foldamers and identify the main structural properties that shape the free energy profile.

BP 36.5 Wed 10:45 H43

High-throughput thermodynamics of drug-membrane interactions from multiscale simulations — •Tristan Bereau and Kurt Kremer — Max Planck Institute for Polymer Research, Mainz

The number of small organic molecules is overwhelmingly large–so large, that most of it remains unexplored. Computer simulations offer an appealing framework to probe many of these compounds without the need to synthesize them in the laboratory. The main hurdles preventing a high-throughput characterization of many small molecules relies on the time investment to parametrize the force field—a process that typically requires significant human intervention—and extensive sampling requirements. We address these issues by first sampling from the coarse-grained Martini model, for which we developed an automated parametrization protocol for small molecules. The resulting potential-of-mean-force (PMF) curves for the insertion of small molecules in lipid membranes show excellent agreement for a number of benchmark cases. We further use the coarse-grained trajectory as an enhanced-sampling strategy to efficiently estimate the corresponding atomistic PMF. To illustrate the method, we rationalize experimental observations of lipid-domain formation in bacterial membranes after the insertion of a small alcohol compound. This framework enables a fast and efficient strategy to gain insight in the thermodynamic properties of drug-membrane interactions.