BP 16: Single Molecule Biophysics II

Time: Tuesday 11:00–13:30 Location: BPa

BP 16.1 Tue 11:00 BPa

Comparison of continuous and discrete Markov models of biomolecular dynamics — •Benjamin Lickert and Gerhard Stock — Universität Freiburg

Motions of biomolecular systems, recorded by molecular dynamics simulations, are often modeled as Markov processes. A very popular approach is given by Markov state models where the conformational space is divided into different states [1]. To be Markovian, the intrastate dynamics need to be significantly faster than the interstate dynamics. On the other hand, the observed dynamics can be modeled as a continuous diffusive process, called Langevin dynamics, on some low-dimensional free energy landscapes $F(\vec{x})$. In this case, Markovianity is given if the system, i.e., $\vec{x}(t)$, evolves substantially slower than the neglected degrees of freedom, i.e., the bath surrounding the system. Recently, a data-driven approach was formulated to estimate such a Langevin model from a given trajectory $\vec{x}(t)$. Here, we compare the features of both modeling frameworks. While Markov state models are very appealing due to their clearly structured generation and interpretation, Langevin dynamics have the advantage that they allow for the estimation of continuously defined observables, like free energy and autocorrelations. Using molecular dynamics simulations of systems with varying complexity we have a look at these points in practice [2].
[1]: J.H.Prinz et al., J.Chem.Phys. 134, 174105 (2011)
[2]: B.Lickert and G.Stock, J.Chem.Phys. 153, 244112 (2020)

BP 16.2 Tue 11:20 BPa

Magnetic Tweezers Protein Force Spectroscopy: Applications to Von Willebrand Factor and SARS-CoV-2 Cell Adhesion — •Jan Lipfert[1], Magnus Bauer[1], Steffen Sedlak[1], Achim Löf[1], Tobias Obser[2], Maria Brehm[2], Martin Benoit[1], Adina Hausch[1], and Sophia Gruber[1] — [1]Department of Physics, LMU Munich — [2]Department of Pediatric Hematology and Oncology, University Medical Center Hamburg Eppendorf

The physiological function of proteins is often critically affected by forces acting on them. We have developed a versatile and modular approach for force measurements on proteins in magnetic tweezers [Löf et al. PNAS 2019; Gruber et al. Nanoscale 2020] that enables ultrastable (>days) and parallel measurements (>50) in a wide force range, in particular at low forces (<1 pN).

We apply our new assay to two systems critical in human pathologies: the blood protein von Willebrand Factor (VWF) and the Spike-mediated adhesion of SARS-CoV-2, the causative agent of the current pandemic. First, we probe regulatory transitions at low forces within VWF. Our results reveal fast (~250 ms) transitions in the dimeric VWF stem around 1 pN, which likely constitute the first steps in its mechano-activation. Second, we use a tethered ligand assay to quantitate how the SARS-CoV-2 spike protein binds to its cellular receptor ACE2. We find that SARS-CoV-2 has a higher force stability and lower off-rate than the previous SARS-CoV-1, which caused the 2002 pandemic, which might contribute to different infection patterns observed for the two viruses.

BP 16.3 Tue 11:40 BPa

Watching an enzyme at work: Time-Resolved Serial Crystallography reveals water mediated allosteric regulation — •Henrike Müller-Werkmeister — Uni Potsdam, Institut für Chemie, Physikalische Chemie, Karl-Liebknecht-Str. 24-25, 14476 Potsdam

We have studied the homodimeric enzyme fluoroacetate dehalogenase by time-resolved serial synchrotron crystallography (TR-SSX). Using a fixed target based sample delivery [1] with an efficient interlacing pattern allowed us to realize "hit-and-return" (HARE) TR-SSX to cover the full timescale from 30 milliseconds to 30 seconds [2]. With a photocaged substrate for reaction initiation, four catalytic turnovers could be resolved [3]. The total of 18 independent structures not only provide unprecedented insight into the reaction mechanism, showing the substrate binding, the Michaelis-Menten-complex and the covalent intermediate, but also reveal the allosteric mechanism leading to half-the-sites reactivity. In fact, a molecular water wire can be observed that together with molecular breathing is clocked to the enzymatic reaction.

[1] I. Martiel, H. M. Müller-Werkmeister, A. E. Cohen, Acta Cryst. D, 2019, D75, 160*177 [2] E. C. Schulz*, P. Mehrabi*, H. M. Müller-Werkmeister*, F. Tellkamp, A. Jha, W. Stuart, E. Persch, R. De Gasparo, F. Diederich, E. F. Pai, R. J. D. Miller, Nature Methods, 2018, 15 (11), 901-904 [3] P. Mehrabi*, E. C. Schulz*, R. Dsouza, H. M. Müller-Werkmeister, F. Tellkamp, R. J. D. Miller, E. F. Pai, Science, 2019, 365 (6458), 1167-1170

BP 16.4 Tue 12:00 BPa

Hybrid Kinetic Monte Carlo / Molecular Dynamics Simulations of Bond Scissions in Proteins — •Benedikt Rennekamp[1,2] and Frauke Gräter[1,2] — [1]Heidelberg Institute for Theoretical Studies, Schloss-Wolfsbrunnenweg 35, 69118 Heidelberg, Germany — [2]Interdisciplinary Center for Scientific Computing, Heidelberg University, INF 205, 69120 Heidelberg, Germany

Proteins are exposed to various mechanical loads that can lead to covalent bond scissions even before macroscopic failure occurs. In regular Molecular Dynamics (MD) simulations covalent bonds are, however, predefined and reactions cannot occur. Furthermore, such events rarely take place on MD time scales.

We have developed a hybrid Kinetic Monte Carlo / Molecular Dynamics (KIMMDY) scheme that overcomes the separation of time scales of these processes and drastically increases the accessible time scales for reactive MD simulations. Here, bond rupture rates are calculated in the spirit of a transition state model based on the interatomic distances in the MD simulation and then serve as an input for a Kinetic Monte Carlo step.

With this new technique we investigated bond ruptures in a multi-million atom system of tensed collagen, a structural protein found in skin, bones and tendons. Our simulations show a clear concentration of homolytic bond scissions near chemical crosslinks in collagen. We suggest that these created mechanoradicals are a yet unknown connection converting mechanical into oxidative stress. This application also demonstrates the scalability of our hybrid computational approach.

BP 16.5 Tue 12:20 BPa

van der Waals Forces in Biomolecular Systems: from Solvation to Long-range Interaction Mechanisms — •Martin Stöhr and Alexandre Tkatchenko — Department of Physics and Materials Science, University of Luxembourg

A decisive characteristic of the biomolecular machinery is the access to a rich set of coordinated processes within a small energy window. Most of these processes involve collective conformational changes and occur in an aqueous environment. Conformational changes of (bio)molecules as well as their interaction with water are thereby largely governed by non-covalent van der Waals (vdW) dispersion interactions. By virtue of their intrinsically collective nature, vdW forces also represent a key influence on collective nuclear behavior. Our understanding of vdW interactions in large-scale (bio)molecular systems, however, is still rather limited. Here, we employ the Many-Body Dispersion framework to investigate the vdW interaction in biomolecular systems and its spatial and spectral aspects. In particular, we show the role of beyond-pairwise vdW forces for protein stability and highlight the delocalized character of the protein-water vdW interaction. We further examine intrinsic electronic behaviors and reveal a coexistence of strong delocalization with spatially-separated, yet correlated, local domains. This, ultimately, forms the basis for a potential, efficient long-range interaction mechanism for coordinated processes in biomolecular systems such as enzymatic action, regulation and allostery.

BP 16.6 Tue 12:40 BPa

Q band mixing in chlorophyll a - spectral decomposition of Qx and Qy absorption bands — •Clark Zahn[1], Till Stensitzki[1], Angelica Zacarias[2], and Karsten Heyne[1] — [1]Institutfür Experimentalphysik, Freie Universität Berlin, Arnimallee 14, 14195 Berlin, Germany — [2]Max Planck Institute of Microstructure Physics, Weinberg 2, D06120 Halle, Germany and ETSF

Chlorophyll a (Chl a) is one of the most abundant pigments on earth. Despite extensive research, the composition of its absorption spectrum is yet not well understood. Here, we apply polarization resolved femtosecond Vis pump - IR probe spectroscopy, providing a detailed insight into Q band mixing of Chl a. The excitation was tuned to various wavelengths covering the Q band absorption. We show, that

the dichroic ratio of the keto-C=O stretching vibration at 1698 cm-1 strongly depends on the excitation wavelength. Hence, the angle between the excited electronic transition dipole moment (tdm) and the vibrational keto-C=O tdm changes significantly across the Q band. By tracing this angle Θ for different excitation wavelengths, we are able to determine the Qx contribution along the Q band region. We find that Qx contributes 42-71% to the absorption of the lower energetic peak at 618 nm and to 59-100% to the absorption of the high energy flank at around 580 nm. Complementary measurements on the C=C stretching vibration at 1608 cm-1 provide corroborating evidence for our findings. Our results provide a direct spectral disentanglement of the Q band, without any previous assumptions. Thus, making them a reliable benchmark for quantum chemical calculations.

30 min. Meet the Speaker