# BP 15: Protein Structure and Single Molecules

Time: Wednesday 10:00–12:15 Location: H13

BP 15.1 Wed 10:00 H13

**Using physics to understand and fight viruses** — •Jan Lipfert[1], Willem Vanderlinden[1], Pauline Kolbeck[1], Sophia Gruber[2], Magnus Bauer[3], and Hermann Gaub[2] — [1]Utrecht University — [2]LMU Munich — [3]Stanford University

Viruses can cause human disease, with dramatic and global consequences. Here, I will present how we use single-molecule approaches to investigate aspects of the life cycles of SARS-CoV-2 and HIV. First, we have developed a tethered ligand assay to investigate how SARS-CoV-2 attaches to human cells. Using magnetic tweezers and AFM force spectroscopy, we obtain a comprehensive view of the force stability of the critical first interaction of the virus with our cells (Bauer, Gruber, et al. PNAS 2022) and investigate the current variants of concern. We find differences in force stability that help rationalize the epidemiology of the different variants (Gruber et al., unpublished). Second, we use magnetic tweezers and AFM imaging to investigate the interactions of retroviral integrases with DNA. We obtain a comprehensive view of the free energy landscape of retroviral integration for prototype foamy virus (Vanderlinden et al. Nature Comm. 2019) and find that, in addition to it well known catalytic role, HIV integrase can efficiently condense DNA into biomolecular condensates (Kolbeck et al., unpublished).

BP 15.2 Wed 10:15 H13

**Angle-dependent strength of a single chemical bond by stereographic force spectroscopy** — Wanhao Cai[1], •Jakob Tómas Bullerjahn[2], Max Lallemang[1,3], Klaus Kroy[4], Bizan Balzer[1,3,5], and Thorsten Hugel[1,3] — [1]Institute of Physical Chemistry, University of Freiburg, Germany — [2]Department of Theoretical Biophysics, Max Planck Institute of Biophysics, Frankfurt am Main, Germany — [3]Cluster of Excellence livMatS@FIT - Freiburg Center for Interactive Materials and Bioinspired Technologies, University of Freiburg, Germany — [4]Institute for Theoretical Physics, Leipzig University, Germany — [5]Freiburg Materials Research Center, University of Freiburg, Germany

A wealth of chemical bonds and polymers have been studied with single-molecule force spectroscopy, usually by applying a force perpendicular to the anchoring surface. However, the direction-dependence of the bond strength lacks fundamental understanding. Here we establish stereographic force spectroscopy to study the single-bond strength for various pulling angles. Surprisingly, we find that the apparent bond strength increases with increasing pulling angle relative to the anchoring surface normal, indicating a sturdy mechanical anisotropy of a chemical bond. This finding can be rationalized by a fixed pathway for the rupture of the bond, resulting in an effective projection of the applied pulling force onto a nearly fixed rupture direction. Our study is fundamental for the molecular understanding of the role of the direction of force application in molecular adhesion and friction.

BP 15.3 Wed 10:30 H13

**Rebinding kinetics from single-molecule force spectroscopy experiments close to equilibrium** — •Jakob Tómas Bullerjahn[1] and Gerhard Hummer[1,2] — [1]Department of Theoretical Biophysics, Max Planck Institute of Biophysics, 60438 Frankfurt am Main, Germany — [2]Institute of Biophysics, Goethe University Frankfurt, 60438 Frankfurt am Main, Germany

Analysis of bond rupture data from single-molecule force spectroscopy experiments commonly relies on the strong assumption that the bond dissociation process is irreversible. However, with increased spatiotemporal resolution of instruments it is now possible to observe multiple unbinding-rebinding events in a single pulling experiment. Here, we augment the theory of force-induced unbinding by explicitly taking into account rebinding kinetics, and provide approximate analytic solutions of the resulting rate equations. Furthermore, we use a short-time expansion of the exact kinetics to construct numerically efficient maximum likelihood estimators for the parameters of the force-dependent unbinding and rebinding rates, which pair well with and complement established methods, such as the analysis of rate maps. We provide an open-source implementation of the theory, evaluated for Bell-like rates, which we apply to synthetic data generated by a Gillespie stochastic simulation algorithm for time-dependent rates.

**15 min. break**

**Invited Talk** BP 15.4 Wed 11:00 H13

**The importance of water in membrane receptor function** — •Anthony Watts — Biochemistry Department, South Parks Road, Oxford, OX1 3QU, UK

Resolving conformational changes in membrane receptors in response to a stimulus, and capturing their functionally relevant dynamics, is very challenging. Over the years we have addressed this challenge using a range of spectroscopic approaches1,2,3 on functionally competent photoreceptors, often in their natural membranes4 or Lipodisqs*5. We have complemented this work with functional studies, mass spec characterization6 and very high resolution (1.07Å) crystallography7,8, as well as photo-induced x-ray, free electron laser studies (XFELS), without the use of detergents and including natural lipids. This high-resolution information reveals waters and their importance in both receptor activation-desensitization and QM(SCC-DFTB)/MM MD trajectories give information about the activation process. The system studied is achearhodopsin-3 (AR3), a photoreceptor utilized widely in optogenetics despite the lack of structures. The arrangement of internal water networks is responsible for the faster photocycle compared to homologs. These insights have generic implications for other receptors. (1). Higman et al., (2011) Angew. Chemie 50(36):8432 (2). Dijkman et al., (2018) Nature Comms. 9:1710 (3). Dijkman et al., (2020) Science Advances, 6:33 (4). Lavington & Watts (2020) Biophys. Rev. 12:1287 (5). Juarez et al., (2019) Chem. Phys. Lipids 221:167 (6). Hoi et al., (2021) Nano Letters, 21(7):2824 (7). Axford et al., (2022) Acta Cryst D78:52 (8). Juarez et al (2021) Nature Comms. 12:629

BP 15.5 Wed 11:30 H13

**Exploring the molecular details of the role of methylation and ATP in chemotaxis signaling** — •HIMANSHU JOSHI[1] and MEHER PRAKASH[2] — [1]Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bengaluru, 560064 — [2]EPFL EssentialTech Center, Switzerland

Chemotaxis is the movement of bacteria in response to the surrounding chemical concentration gradients. Bacteria perform runs and tumbles due to the anti-clockwise and clockwise rotation of their flagella depending on the type and gradient of chemical concentration. The molecular concentration sensed by the binding of nutrients is transmitted across the membrane and over 200 Angstroms for a kinase domain actuation. The question then arises as to what is the molecular basis of this signal propagation? Performing long all atom molecular dynamics (MD) simulations on the CryoEM structures that have become recently available, we study the plausible interactions between the methylation and the ATP hydrolysis. Our study, the MD first one which includes methylation and ATP, finds several correlations with the experimental data such as the matching contacts among the dynamic domains, the intermediate state, higher gamma-phosphate coordination by the methylated protein. The results on this very important signaling mechanism are encouraging, a validation which is non-trivial when performing MD on an extended spatial or time scale or with a new class of proteins (fibrillar in this case), to perform further MD studies on this large protein complex.

BP 15.6 Wed 11:45 H13

**Identifying the Functional Dynamics in Proteins - Divide and Conquer the Feature Space** — •Daniel Nagel, Georg Diez, and Gerhard Stock — Biomolecular Dynamics, Institute of Physics, Albert-Ludwigs-Universität, 79104 Freiburg, Germany

The function of proteins is closely linked to their conformational changes. To support experiments, molecular dynamics simulations allow high spatiotemporal resolution while generating large amounts of data. To model and interpret them, it is essential to identify suitable features, such as backbone dihedral angles or interresidual distances. However, in this high-dimensional feature space—in addition to the motion of interest—one finds uncorrelated motions described by small subsets of features, which poses a difficult challenge for the subsequent dimensionality reduction and understanding of the underlying biological process.

In the following we present an effective and scalable correlation-based feature selection method (MoSAIC) that identifies functional

dynamics in the feature space and separates it from noise in order to facilitate the further analysis. To demonstrate the different application purposes, we adopt the unsupervised method to systems of various complexity.

G. Diez, D. Nagel, and G. Stock, Correlation-based feature selection to identify functional dynamics in proteins, arxiv:2204.02770, 2022

BP 15.7 Wed 12:00 H13

**Understanding friction in ligand protein systems** — •Miriam Jäger[1], Wanhao Cai[2], Jakob T. Bullerjahn[3], Thorsten Hugel[2], Steffen Wolf[1], and Bizan N. Balzer[2] — [1]Biomolecular Dynamics, Institute of Physics, University of Freiburg, Hermann-Herder-Str. 3, 79104 Freiburg, Germany — [2]Institute of Physical Chemistry, University of Freiburg, Albertstr. 21, 79104 Freiburg, Germany — [3]Department of Theoretical Biophysics, Max Planck Institute of Biophysics, 60438 Frankfurt am Main, Germany

Both experiments and simulations have shown the importance of friction in biomolecular system dynamics. To gain a deeper understanding of the connection between directional forces and friction, we study the streptavidin-biotin complex in a combination of stereographic force spectroscopy experiments and biased molecular dynamics simulations. While experiments show an increasing mean rupture force and rupture force variance with steeper pulling angles, the simulations display similar internal friction, but an anisotropy in the free energy barriers. Based on the simulation results, we propose that this anisotropy in barriers manifests itself in experiments as the increase in friction. This effect can be viewed as anisotropic friction.