BP 3: Computational Biophysics I

Time: Monday 9:30–13:00 Location: BAR 0106

BP 3.1 Mon 9:30 BAR 0106

Elucidating the Binding Process of a Disordered Protein to a Membrane Containing Ionic Lipids via Atomistic Simulations: a Case Study of LKB1 — •Azadeh Alavizargar and Andreas Heuer — Institute of Physical Chemistry, University of Muenster, Corrensstr. 28/30, 48149 Muenster, Germany

Liver kinase LKB1 is a serine/threonine kinase, which apart from from playing a significant role in many biological processes such as cell proliferation and polarity, it functions also as a downregulator in tumors. In this work, we probe the significance of phosphatidic acid (PA) lipids as well as the poly-basic region for the binding of the C-terminus of the protein to the membrane, using molecular dynamics simulations. It was revealed that PA lipids are essential for the protein-membrane binding and that the mutation of the first three lysine residues does not abolish the binding. We specifically show the details of the protein-membrane binding at the atomic resolution using various amount of PA lipids in the membrane. Importantly, it was also found that the protein-membrane binding is dynamic and gives rise to structural changes of the protein as a result of the interaction and the accumulation of PA lipids in the membrane, which is beyond the accessible resolution in the corresponding experiments. Furthermore, we quantified the significance of each polar amino acid in the poly-basic region of the protein. These results provide important insights into the understanding and mechanism of the interaction of disordered proteins with membranes including ionic lipids.

BP 3.2 Mon 9:45 BAR 0106

Migration of oxygen in the human bc1 complex and the behavior of QH2 and Q cofactors inside it — •Katarina Kretschmer, Malena Kottke, and Ilia Solov'yov — Insitute of Physics, University of Oldenburg, Oldenburg, Germany

The dimeric bc1-complex embedded in the inner membrane of mitochondria is a relevant part of the respiratory chain in a mitochondrial cell of eukaryotes. Through different electron transfers that include oxidation and reduction reactions of the substrate molecules at the Qo- and Qi-site in this protein complex, it contributes to the metabolic system of the cell. Specifically, the complex facilitates proton transfers across the membrane to maintain an electrostatic potential, which is in turn used to drive ATP synthesis. This molecular machinery, however, is suspected to be a source of superoxide and is believed to be one of the factors in cellular aging.

Through molecular dynamics simulations, we have investigated the migration of molecular oxygen in the bc1-complex in order to identify possible reaction sites that could lead to superoxide formation. The investigation follows an earlier study of the bc1-complex from Rhodbacter capsulatus and reveals several important differences. Specifically, we investigate further into the behavior of the cofactors Ubiquinol (QH2) and Ubiquinone (Q) in both monomers in the bc1-complex and determine the oxygen diffusion pathways that could lead to the sites where O2 could be efficiently converted to superoxide, thereby disturbing the regular functioning of the bc1-complex.

BP 3.3 Mon 10:00 BAR 0106

On the road to cellular digital twins of in vivo tumors — •Eric Behle[1], Julian Herold[2], and Alexander Schug[1] — [1]NIC Research Group Computational Structural Biology, Jülich Supercomputing Centre, Jülich Research Center, Jülich, Germany — [2]Steinbuch Centre for Computing, KIT, Karlsruhe

To this day, cancer remains an insufficiently understood disease plaguing humanity. In particular, the mechanisms driving tumor invasion still require extensive study. Current investigations address collective cellular behavior within tumors, which leads to solid or fluid tissue dynamics. Furthermore, the extracellular matrix (ECM) has come into focus as a driving force facilitating invasion. To complement the experimental studies, computational models are employed, and advances in computational power within HPC systems have enabled the simulation of macroscopic tissue arrangements. We hereby present our work using Cells in Silico (CiS), a high performance framework for large-scale tissue simulation previously developed by us. CiS is capable of simulating tissues composed of tens of millions of cells, while accurately representing many physical and biological properties. Our ultimate aim is to build a cellular digital twin of an in vivo tumor. Unfortunately, current in vivo measurement methods lack the required resolution for directly parameterizing our simulations. Therefore, we aim to parameterize CiS via a bottom-up approach, utilizing experimental data from multiple in vitro systems. We focused our first studies on tumor spheroids, a main workhorse of tumor analysis. Towards this, we developed a novel method to compare spatial features of spheroids in 3D.

BP 3.4 Mon 10:15 BAR 0106

Resolving hierarchical interactions of proteins in phase-separated condensates by multi-scale simulations — •Lukas Stelzl[1,2,3], Kumar Gaurav[1,2,3], Xiaofei Ping[1,2,3], Arya Changiarath Sivadasan[1,2,3], René Ketting[3], and Dorothee Dormann[3,4] — [1]Institute of Physics, JGU Mainz, Germany — [2]Faculty of Biology, JGU Mainz, Germany — [3]IMB Mainz, Germany — [4]Institute of Molecular Physiology, JGU Main, Germany

Liquid-liquid phase separation and the resulting phase-separated condensates of proteins help to organize cellular processes in time and space. At same time, dysregulation of phase separation is implicated in the development of neurodegenerative diseases. Using particle-based multi-scale simulations we are elucidating how phase-separated condensates can provide for specific molecular recognition and thus cellular regulation and how this specificity is lost in diseases. With simulations we are elucidating how a hierarchy of interactions such as strong interactions of folded domains and weak and multivalent interactions between disordered regions of proteins determine phase behavior. With our multi-scale methods we can simulate condensates with atomic resolution and resolve molecular details of "sticker"-"sticker" interactions, their kinetics and how these provide for specific recognition and cellular function. We also show how mutations and biochemical modifications can shift the conformational equilibria of proteins and their interactions in phase-separated condensates and favor the formation of toxic aggregates in neurodegenerative diseases.

Invited Talk BP 3.5 Mon 10:30 BAR 0106

Resolving gating and allosteric modulation in ion channels through simulations and small-angle neutron scattering — •Erik Lindahl — Dept. Biophysics & Biochemistry, Science for Life Laboratory, Stockholm University

Pentameric ligand-gated ion channels (pLGICs) perform electrochemical signal transduction in organisms ranging from bacteria to humans. In addition to their normal gating cycle, pLGICs are highly sensitive to allosteric modulation where small compounds such as barbiturates, benzodiazepines or alcohols influence the gating kinetics by binding in separate sites, either in the transmembrane or extracellular domain. Despite a wealth of new experimental structures, it has been challenging to understand the gating kinetics, in particular since the channels rapidly undergo transitions to a desensitized nonconducting state rapidly after opening. I will present our recent combined experimental and computational work on a number of prokaryotic and eukaryotic pLGICs from the team, and how we are trying to combine low-resolution experimental techniques such as SANS (small-angle neutron scattering) with simulations to model channels under realistic conditions. In addition, I will show how we have been able to resolve structures in all separate functional states, their state-specific interactions with lipids, and not least how we are beginning to understand the properties of the desensitized state.

15 min. break

BP 3.6 Mon 11:15 BAR 0106

Clustering Molecular Dynamics Trajectories using Density and Flux — •Jayashrita Debnath[1] and Gerhard Hummer[1,2] — [1]Max Planck Institute of Biophysics, Frankfurt am Main, Germany — [2]Goethe University, Frankfurt am Main, Germany

Molecular dynamics (MD) simulations are a powerful tool for studying a wide range of molecular systems and processes, with applications ranging from materials science to biology and medicine. Analyzing these simulations often involves finding a low-dimensional representation of the trajectory data and clustering the sampled configurations into kinetically relevant metastable states. The steady growth in the time and length scales of MD simulations, and in the complexity of their molecular systems, necessitates the development of new analysis

tools that do not rely entirely on chemical or physical intuition. Here, we propose a neural network based unsupervised algorithm that can identify states using the static and dynamic information encoded in the trajectories. The network identifies metastable states by modeling a probability distribution of the data in a reduced dimensional space and learns the state boundaries by minimizing the flux between states. Furthermore, it can learn the optimal number of states from single long equilibrium trajectories or multiple short ones. After demonstrating the effectiveness of this method for a toy potential, we apply it to trypsin-benzamidine unbinding as a model of drug binding kinetics, to and folding-unfolding transitions of the villin headpiece subdomain.

BP 3.7 Mon 11:30 BAR 0106

Enhancing Traction-Force Microscopy with Machine Learning — •Felix S. Kratz, Lars Möllerherm, and Jan Kierfeld — TU Dortmund University, Germany

Traction patterns of adherent cells provide important information on their interaction with the environment, cell migration or tissue patterns and morphogenesis. Traction Force Microscopy is a method aimed at revealing these traction patterns for adherent cells on engineered substrates with known constitutive elastic properties from deformation information obtained from substrate images. Conventionally, the substrate deformation information is processed by numerical algorithms of varying complexity to give the corresponding traction field via solution of an ill-posed inverse elastic problem. We explore the capabilities of a deep convolutional neural network as a computationally more efficient and robust approach to solve this inversion problem. We develop a general purpose training process based on collections of circular force patches as synthetic training data, which can be subjected to different noise levels for additional robustness. The performance and the robustness of our approach against noise is systematically characterized for synthetic data, artificial cell models and real cell images, which are subjected to different noise levels. A comparison to state-of-the-art Bayesian Fourier transform traction cytometry reveals the precision, robustness, and speed improvements achieved by our approach, leading to an acceleration of Traction Force Microscopy methods in practical applications.

BP 3.8 Mon 11:45 BAR 0106

Finding pathways in molecular dynamics simulations using machine learning and graph methods — •Steffen Wolf[1], Miriam Jäger[1], Victor Tänzel[1], Simon Bray[1,2], Matthias Post[1], and Gerhard Stock[1] — [1]Biomolecular Dynamics, Institute of Physics, University of Freiburg, 79104 Freiburg, Germany — [2]Bioinformatics Group, Institute of Informatics, University of Freiburg, 79110 Freiburg, Germany

Understanding the mechanisms of biomolecular systems and complexes, e.g., of protein-ligand (un)binding, requires the understanding of paths such systems take between metastable states. In MD simulation data, paths are usually not observable per se, but need to be inferred from simulation trajectories. Here we present novel approaches to cluster trajectories according to similarities. These approaches include neighbor-nets allowing to correct for input data ambiguity [1] and an unsupervised learning approach employing only a single free parameter [2]. We demonstrate how such clusters of trajectories correspond to pathways, and how the approaches help in the identification of reaction coordinates for a considered process. Last, we present a theoretical framework how potentials of mean force can be calculated for individual pathways, and how these potentials and kinetics along paths can be combined into a comprehensive complete free energy profile and process kinetics.

[1] Bray, S., Tänzel, V. & Wolf, S. J. Chem. Inf. Model. 62, 4591-4604 (2022). [2] Diez, G., Nagel, D. & Stock, G. J. Chem. Theory Comput. 18, 5079-5088 (2022).

BP 3.9 Mon 12:00 BAR 0106

Artificial Intelligence for Molecular Mechanism Discovery — •Hendrik Jung[1], Roberto Covino[2], A Arjun[3], Christian Leitold[4], Peter G Bolhuis[3], Christoph Dellago[4], and Gerhard Hummer[1] — [1]Max Planck Institute of Biophysics, Frankfurt, Germany — [2]Frankfurt Institute for Advanced Studies, Frankfurt, Germany — [3]University of Amsterdam, Amsterdam, The Netherlands — [4]University of Vienna, Vienna, Austria

We present a machine learning algorithm to extract the mechanism of collective molecular phenomena from computer simulations. The algorithm combines transition path sampling (TPS), deep learning (DL), and statistical inference to simultaneously enhance the sampling and understanding of complex molecular reorganizations without human intervention. TPS is a Markov Chain Monte Carlo method in trajectory space that samples the rare transition trajectories connecting meta-stable states. In our algorithm a DL model is selecting the configurations from which the new trial trajectories are generated using shooting moves, i.e., the trajectories are propagated according to the physical model of the simulated system. By iteratively training on the outcomes of the shooting moves, the model simultaneously increases the efficiency of the rare-event sampling and gradually reveals the underlying mechanism of the transition. In a second step we distill the knowledge about the transition encoded in the DL model into a simplified mathematical expression. With this algorithm we study a diverse set of molecular systems ranging from the association of ions in solution to the oligomerization of a transmembrane alpha helix dimer.

BP 3.10 Mon 12:15 BAR 0106

MD simulations of *n*-alkanes in a phospholipid bilayer: CHARMM36 vs. Slipids — •Anika Wurl and Tiago Ferreira — Institute of Physics, Martin-Luther Universität Halle-Wittenberg

The incorporation of *n*-alkanes into phospholipid bilayers is a convenient starting point for studying the molecular behavior of linear, (purely) hydrophobic molecules in lipid membranes. Here, we perform atomistic molecular dynamics simulations using two state-of-the-art lipid force fields, CHARMM36 [1] and Slipids [2], to systematically investigate how the miscibility of n-alkanes in dipalmitoylphosphatidylcholine (DPPC) bilayers depends on alkane chain length. The two force fields show a distinct behavior: Slipids simulations predict an effect of chain length on miscibility, while for CHARMM36 simulations this is not the case for the alkanes studied. A comparison with ^{2}H NMR spectra shows that the accuracy of the two force fields is dependent on alkane length. CHARMM36 performs well for the shorter chains, while Slipids models the longer alkanes better. Slipids chains are more flexible, due to reduced electrostatic 1-4 interactions compared to CHARMM36. By scaling these 1-4 interactions, CHARMM36 can be adapted to model longer alkanes and lipid acyl tails better. The presented results are of general interest for future studies of other long and flexible hydrophobic molecules inside lipid membrane environments, and show that *n*-alkane/lipid mixtures should be taken into account for optimization of force fields designed to model lipid membranes. [1] Jämbeck et al.; *J Phys Chem B* 2012, 116, 3164-3179 [2] Klauda et al.; *J Phys Chem B* 2010, 114, 7830-7843

BP 3.11 Mon 12:30 BAR 0106

Scission criteria upon proteins X-ray absorption — •Carlos Ortiz-Mahecha[1], Lucas Schwob[2], Sadia Bari[2], and Robert Meissner[1,3] — [1]Technische Universität Hamburg, Hamburg, Germany — [2]Deutsches Elektronen-Synchrotron, Hamburg, Germany — [3]Helmholtz-Zentrum Hereon, Geesthacht, Germany

Dynamic protonation in a protein lead to conformational changes which could be studied by challenging near-edge X-ray absorption mass spectrometry (NEXAMS) experiments and computationally expensive quantum mechanical (QM) calculations. Less demanding assessment is essential for interpreting the underlying electronic density changes in proteins. Those density changes in the amino-acid (AA) non-covalent environment are evaluated by *in-silico* X-ray spectra and their chemical-physical properties by the pair interaction energy decomposition analysis (PIEDA) method. In order to represent a protein X-ray absorption spectra as a summation of their smaller protein fragments X-ray spectra, we first assess its electronic neighboring influence to establish a scission criteria. For that, we propose a pattern involving the change of excited-state transition energy probability in a two-body AA localized density population and the charge transfer energy change from PIEDA as a function of the non-covalent interaction distance. In this way using this criteria, the X-ray absorption spectra of proteins could potentially be represented as a composition of X-ray spectra of their smaller fragments, which would be computationally more efficient.

BP 3.12 Mon 12:45 BAR 0106

Fluid defomable surfaces, the influence of surface viscosity in fluid membranes — Veit Krause and •Axel Voigt — Institute of Scientific Computing, Technische Universität Dresden, Germany

We consider a fluid-solid duality of membranes, with in-plane fluid properties and out-of-plane solid (bending) properties. In such systems any tangential flow induces shape deformationas and any change in morphology induces tangential flow. This numerically challanging surface problem is solved by surface finite elements and we explore

the dynamics towards equilibrium states in various settings, ranging from transitions from biconcave to dumbell shapes, coarsening of two-component surface fluids under the influence of curvature and wrinkling in fluid membranes.