BP 10: Computational Biophysics II

Time: Tuesday 9:30–12:45 Location: H 0112

BP 10.1 Tue 9:30 H 0112

Picosecond to Microsecond Dynamics of Aggregates of an Intrinsically Disordered Protein — •Saikat Chakraborty[1], Tatiana I. Morozova[2], and Jean-Louis Barrat[1,2] — [1]Université Grenoble Alpes, CNRS, LIPhy, 38000 Grenoble, France. — [2]Institut Laue-Langevin, 71 Avenue des Martyrs, 38042 Grenoble, France.

Aggregates of intrinsically disordered proteins (IDPs) can exhibit multiple time scales of fluctuations because of the widely different relaxation times of their components. Neutron backscattering or neutron spin-echo spectra of such systems carry useful dynamic information on self- and pair-correlations at several spatio-temporal regimes. However, The motions of the different segments can be correlated and time scales can be entangled. Therefore, we employ explicit solvent molecular dynamics (MD) simulations with explicit solvent to disentangle the time scales at atomistic resolution with β-casein as the IDP. Microseconds-long simulations starting from different initial configurations of the protein retain the effect of conformational diversity on the dynamics. A Systematic study of the fluctuations of different parts of the aggregates reveals that the protein side chains show Rouse-like internal dynamics at the scale of picoseconds. Whereas, the motion of the proteins is primarily that of its center of mass. At the longest time regime diffusion of center of mass of the aggregate dominates.

BP 10.2 Tue 9:45 H 0112

Grand Canonical Simulations of Disordered Proteins — •Rodrigo F. Dillenburg[1], Hao Ruan[2,3], Edward A. Lemke[2,3], and Martin Girard[1] — [1]Max Planck Institute for Polymer Research, Mainz, Germany — [2]Institute of Molecular Biology, Mainz, Germany — [3]Biocenter, Johannes Gutenberg University, Mainz, Germany

Investigations on Liquid-liquid phase separation (LLPS) have typically focused on intrinsically disordered proteins (IDPs), with theoretical support from polymer science. While great attention has been given to the study of large molecular condensates, little is known about non-deterministic smaller protein assemblies such as micelles. Such structures have been observed experimentally in artificially constructed sequences. We hypothesize that they could also arise in biologically relevant sequences. Coarse-grained force fields have provided an efficient framework for LLPS simulations with residue-level resolution and are remarkably accurate in reproducing phase diagrams of IDPs and the effects of residue mutations. Simulation methods designed for the study of molecular condensates must be modified to allow for simulations of microphases. The slab geometry devised to overcome slow diffusion times in highly dilute biological systems (~0.1% volume fraction), inhibits the formation of micelles. We implemented a Configurational Bias Monte Carlo algorithm based on the Rosenbluth-Rosenbluth method that allows for efficient LLPS simulations in a cubic simulation box and the investigation of microphase separation. We demonstrate the usefulness of this algorithm in the context of IDPs.

BP 10.3 Tue 10:00 H 0112

Structure of water molecules in FUS protein molecular condensate — •Daniel Chavez Rojas[1], Joseph Rudzinski[2], and Martin Girard[1] — [1]Max Planck Institute for Polymer Research, Mainz, Germany — [2]Institut für Physik, Humboldt-Universität zu Berlin, Berlin, Germany

There is evidence that molecular condensates of the FUS protein play a role in the development of some neurodegenerative diseases like ALS. For this reason, understanding the molecular mechanism by which these condensates form at an atomistic level is of therapeutic interest. However, the molecular structure and water-protein interactions of these condensates is poorly understood. In this work we investigate this structure with atomistic simulations, made possible by backmapping large condensates generated by a coarse grained model. We first use these simulations to explain the slowing of water dynamics of the protein condensate measured by 2D Infrared spectroscopy experiments, as highlighted In our recently accepted manuscript (*Liquid-liquid phase separation of the intrinsically disordered domain of the fused in sarcoma protein results in substantial slowing of hydration dynamic* J Phys Chem Lett). We then expand upon this analysis by comparing the network of protein and water contacts around individual amino acids in the condensate and in solution. Our results hint at a reduction of water tetrahedral structure in dense areas of the protein network. This analysis provides insights into the driving forces that promote the formation of these molecular condensates.

BP 10.4 Tue 10:15 H 0112

Determination of elastic moduli of lipid membranes with improved accuracy: a binning-free approach for lipid height and tilt fields. — •Jonas Paulus[1], Friederike Schmid[1], and Giovanni Settanni[1,2] — [1]Department of Physics, Johannes Gutenberg University Mainz, Germany — [2]Faculty of Physics and Astronomy, Ruhr University Bochum, Germany

Lipid membranes play a pivotal role in various research domains. This study addresses the need for an improved measurement of the elastic properties of lipid membranes, which can be extracted from the fluctuation spectra of the height of lipids and their orientations. Traditional approaches involve binning the lipids onto a discrete evenly-spaced grid, average their positions and orientation in each bin, and then calculate the spectra by Fourier transform the binned data. However, this method introduces sampling errors and aliasing, due to the uneven distribution of lipids. Here, we first calculate the amplitude of the binning-related inaccuracies and a correction term to mitigate them. Then, we consider a binning-free approach for the fluctuation spectra based on least-square fitting the positions and orientations of lipids with a superposition of wave functions. We show how to cast it into a linear algebra problem involving the computation of a pseudoinverse matrix via singular value decomposition. We show that this approach improves the accuracy of the analysis over those based on data binning and apply it to the characterization of lipid formulations for nucleic acid delivery, computing the effect of pH on their elastic properties.

BP 10.5 Tue 10:30 H 0112

Condensate Coexistence in Gene Transcription: Molecular Dynamic Insights — •Arya Changiarath Sivadasan[1,2], Jasper J. Michels[3], Sonya M. Hanson[4], Jan Padeken[2], Friederike Schmid[1], and Lukas Stelzl[1,2] — [1]Johannes Gutenberg University, Mainz — [2]Institute of Molecular Biology, Mainz — [3]Max Planck Insitute for Polymer Research, Mainz — [4]Flatiron Institute, New York, USA

The formation of distinct phase-separated condensates of biological macromolecules underpins specific regulation in cells. Here we elucidate under what conditions phase-separated condensates can regulate biochemical processes by providing distinct chemical environments with particle-based multi-scale simulations. We study the disordered C-terminal domain of RNA polymerase II (CTD), which in experiments has been found to form condensates under both unphosphorylated and phosphorylated (pCTD) states. CTD condensates have been proposed to underpin transcription initiation, while pCTD condensates may support transcription elongation. A better understanding of the molecular driving forces of CTD phase separation will provide insights into how CTD and pCTD condensates can regulate transcription initiation and elongation. It has remained unclear whether CTD and pCTD condensates would mix when coexisting or remain as distinct chemical environments. Computing surface tensions from coarse-grained molecular dynamics simulations we establish under what conditions they remain coexist either as multi-phase condensates or by forming entirely distinct condensates.

BP 10.6 Tue 10:45 H 0112

Allosteric communication in PDZ3 studied by nonequilibrium simulations and Markov State Model — •Ahmed Ali, Adnan Gulzar, Steffen Wolf, and Gerhard Stock — Institute of Physics, University of Freiburg, Germany

While allostery is of paramount importance for protein signaling and regulation, the underlying dynamical process of allosteric communication is not well understood. PDZ3 domain represents a prime example of an allosteric single-domain protein, as it features a well-established long-range coupling between the C-terminal α3-helix and ligand binding. In an intriguing experiment, Hamm and coworkers employed photoswitching of the α3-helix to initiate a conformational change of PDZ3 that propagates from the C-terminus to the bound ligand within 200 ns. Performing extensive nonequilibrium molecular dynamics simulations combined with Markov modeling, the modeling of the experiment reproduces the measured timescales and reveals a detailed picture of

the allosteric communication in PDZ3. In particular, a correlation analysis identifies a network of contacts connecting the α3-helix and the core of the protein, which move in a concerted manner. Representing a one-step process and involving direct α3-ligand contacts, this cooperative transition is considered as elementary step in the propagation of conformational change.

15 min. break

Invited Talk BP 10.7 Tue 11:15 H 0112

RNA Contact Prediction by Data Efficient Deep Learning — Oskar Taubert[1], Fabrice von der Lehr[2], Alina Bazarova[3,4], Christian Faber[3], Philipp Knechtges[2], Marie Weiel[1,4], Charlotte Debus[1,4], Daniel Coquelin[1,4], Achim Basermann[2], Achim Streit[1], Stefan Kesselheim[3,4], Markus Götz[1,4], and •Alexander Schug[3,5] — [1]Scientific Center of Computing, Karlsruhe Institute of Technology — [2]Institute for Software Technology, German Aerospace Centre — [3]Jülich Supercomputing Centre, Forschungszentrum Jülich — [4]Helmholtz AI — [5]Faculty of Biology, University of Duisburg-Essen

On the molecular level, life is orchestrated via many biomolecules. To gain detailed understanding of biomolecular function, one needs to know their structure. Yet the structural characterization of many important biomolecules and their complexes remains experimentally challenging. For proteins, the richness of labeled training data enables highly successful deep-learning approaches. Deep learning on RNA, however, is hampered by the lack of such data. The limited data, however, can still be used to predict spatial adjacencies (*contact maps*) as proxy for 3D structure. Statistical physics based approaches such as direct coupling analysis can provide such contact maps. Going beyond such approaches, our recent model BARNACLE combines using unlabeled data through self-supervised pre-training and efficient use of the sparse labeled data. We observe a considerable improvement over both the established classical baseline DCA and other neural networks.

BP 10.8 Tue 11:45 H 0112

Next-Gen Protein Sequencing with Nanopores Empowered by Machine Learning — •Julian Hossbach and Christian Holm — Institute for Computational Physics, University of Stuttgart, D-70569 Stuttgart, Germany

In the last decade, the rise of DNA sequencing using nanopores has garnered significant attention within the scientific community, however, protein sequencing continues to pose substantial challenges. Recent investigations using the aerolysin nanopore have demonstrated that the discrimination of oligopeptides on a single amino acid basis is possible (Ouldali et. al, Nat. Biotechnol. 2020). Building on these advancements, our study showcases the use of machine learning to identify peptides that have thus far been undistinguishable. Our approach marks a pivotal step towards overcoming the complexities associated with protein sequencing, offering a pathway to more accurate and efficient analyses in the realm of molecular biology.

BP 10.9 Tue 12:00 H 0112

Enhancing protein-ligand binding affinity via optimal selection of water molecules — •Miljan Dašić, Jindřich Fanfrlík, and Jan Řezáč — Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Flemingovo náměstí 2, 166 10, Prague, Czech Republic

Accurate and fast determination of protein-ligand (P-L) binding affinity represents a foundational problem of computational biophysics. A promising solution is an universal physics-based scoring function **SQM2.20** based on semi-empirical quantum-mechanical computational methods. Its performance has been rigorously verified over a benchmark dataset **PL-REX** consisting of high-resolution crystal structures and trustworthy experimentally determined P-L affinities (10 diverse protein targets; 164 QM-optimized P-L complexes). Presence of water molecules has a significant impact on P-L binding affinity, via formation of hydrogen bond bridges. We have developed a computational tool which optimally selects waters enhancing the P-L binding affinity. Each of the ten protein targets comprises different crystals. Waters present in all of them represent the input for selection procedure. Such procedure includes clustering and comparison of waters contained in clusters with waters present in one selected reference crystal. Presence of optimally selected waters improves the correlation with experimental data. We investigated the sensitivity of scoring on the geometry of crystals. For each protein target, we determined the best reference crystal which maximizes the scoring results.

BP 10.10 Tue 12:15 H 0112

Transition intensities decomposition for $\pi-\pi$ interaction of X-ray absorption for proteins — •Carlos Ortiz-Mahecha[1], Lucas Schwob[2], Sadia Bari[2], and Robert Meissner[1,3] — [1]Technische Universität Hamburg — [2]Deutsches Elektronen-Synchrotron (DESY) — [3]Helmholtz-Zentrum Hereon

π-π stacking between aromatic side chains leads to structure stabilization in proteins, which could be studied by X-ray absorption spectroscopy (XAS) and quantum mechanical (QM) calculations. Access to such excited state calculations for proteins is quite challenging due to their computational cost. In order to decompose the XAS spectra of proteins into a sum of smaller constituents, we propose that the inner-shell transition intensities of aromatic amino acids can be correlated with the charge transfer occurring in the π-π^* interactions. We therefore propose a theoretical analysis to decompose the XAS spectra transition intensities into their atomistic contributions in order to derive distance thresholds for the core-to-valence transition between aromatic amino acid pairs in proteins.

We found that the intertransition intensities and the charge transfer energy can be correlated, enabling intermolecular properties to be associated with core-electron excited-state properties. We suggest that, for XAS in proteins, the electronic neighbourhood influence of the high conjugated electronic density of the aromatic amino acid interactions can be inferred by evaluating the charge transfer between them. This can be used as a criterion to define smaller constituents in a proteins by the charge transfer of the aromatic amino acid interactions.

BP 10.11 Tue 12:30 H 0112

Understanding the redshift of the absorption spectrum in ClCry4 protein — •Katarina Kretschmer, Anders Frederiksen, and Ilia A. Solov'yov — Universität Oldenburg, Germany

It is still a puzzle how some migratory birds utilize the Earth's magnetic field for biannual migration. The most consistent explanation so far roots on modulation of the biological function of the Cryptochrome 4 (Cry4) protein by external magnetic field. This phenomenon is closely linked with the FAD cofactor that is bound in the protein. The Cry4 protein with the bound FAD cofactor is activated by blue light, absorbed by the FAD cofactor. Through several transfers that trigger radical pair formation in Cry4, the protein can become sensitive to the geomagnetic field. An important redox state of the FAD cofactor is the signaling state, which is present after completion of the different electron transfers inside the protein. Recently it has been possible to crystallize the Cry4 protein from Columbia Livia (ClCry4) with the associated important residues needed for photoreduction. It is the most promising crystallization of the Cry4 protein so far, which also has great similarity with the Cry4 proteins of night migratory birds. The absorption spectrum of the FAD cofactor inside the ClCry4 protein was investigated experimentally in its different redox states during protein's activation. The absorption spectrum of the signaling state demonstrated a redshift if compared to the photoabsorption properties of the FAD cofactor in its signaling state in other Cry proteins. The aim of this study is to understand this redshift by employing the tools of computational microscopy, and in particular the QM/MM approach.