BP 3: Computational Biophysics I

Time: Monday 9:30–13:00 Location: H44

BP 3.1 Mon 9:30 H44

RNA plasticity emerges as an evolutionary response to fluctuating environments — •Paula García-Galindo[1] and Sebastian E. Ahnert[1,2] — [1]Department of Chemical Engineering and Biotechnology, University of Cambridge, Philippa Fawcett Drive, Cambridge CB3 0AS United Kingdom — [2]The Alan Turing Institute, 96 Euston Road, London NW1 2DB, UK

Phenotypic plasticity, the ability of a single genotype to produce multiple distinct phenotypes, can be studied effectively using RNA. RNA is a dynamic macromolecule that probabilistically shifts its structure due to thermal fluctuations at the molecular scale. To model the evolution of RNA plasticity, we use the RNA sequence-to-structure non-deterministic mapping, a computationally tractable genotype-phenotype (GP) map where probabilistic phenotypes are derived from the Boltzmann distribution of structures for each RNA sequence. Through evolutionary simulations with periodic environmental switching on the GP map, we observe that RNA phenotypes adapt to these fluctuations by evolving toward optimal plasticity. These optimal phenotypes are defined by nearly equal Boltzmann probabilities for distinct structures, each representing the most advantageous configuration for alternating environments. Our findings demonstrate that phenotypic plasticity, a widespread biological phenomenon, is a fundamental evolutionary adaptation to fluctuating environments.

BP 3.2 Mon 9:45 H44

Symmetry of loop extrusion by dimeric SMC complexes is DNA-tension-dependent — Biswajit Pradhan[1], •Adrian John Pinto[2], Peter Virnau[2], and Eugene Kim[1] — [1]Max Planck Institute of Biophysics, 60438 Frankfurt am Main, Germany — [2]Institut für Physik, Staudingerweg 9, Johannes Gutenberg-Universität Mainz, 55128 Mainz, Germany

Structural maintenance of chromosome (SMC) complexes are involved in genome organization and regulation via DNA loop extrusion. During extrusion SMC proteins reel DNA from one or both sides and a loop forms and increases. At low DNA tension (< 0.1pN), Smc5/6 and Wadjet extrude DNA from both sides of the loop. At higher tension, however, they transition to a behavior akin to one-sided extruders, yet still capable of extruding from one or the other side thereby switching the direction of extrusion [1]. In order to model this process in simulations, we propose a coarse-grained model for DNA loop extrusion using a Kratky-Porod chain as a basis for DNA and a handcuff for SMC proteins. By matching stalling forces, we are able to simulate loop extrusion on experimental time and length scales. We find that the observed switching from two- to one-sided behavior does not require a change in motor activity, but can be explained as a complex interplay of extrusion, stalling and thermal fluctuations.

[1] Pradhan, B., Pinto, A., Kanno, T., et al. (2024). Symmetry of loop extrusion by dimeric SMC complexes is DNA-tension-dependent. bioRxiv. https://doi.org/10.1101/2024.09.12.612694

BP 3.3 Mon 10:00 H44

NucleoSeeker - Precision filtering of RNA databases to curate high-quality datasets — •Utkarsh Upadhyay[1], Fabrizio Pucci[2], Julian Herold[3], and Alexander Schug[1,4] — [1]Jülich Supercomputing Centre, Germany — [2]Universite Libre de Bruxelles, Belgium — [3]Karlsruhe Institute for Technology, Germany — [4]University of Duisburg- Essen, Germany

The structural prediction of biomolecules via computational methods complements the often involved wet-lab experiments. Unlike protein structure prediction, RNA structure prediction remains a significant challenge in bioinformatics, primarily due to the scarcity of RNA structure data and its varying quality. Many methods have used this limited data to train deep learning models but redundancy, data leakage and bad data quality hampers their performance. In this work, we present NucleoSeeker, a tool designed to curate high-quality, tailored datasets from the Protein Data Bank (PDB) database. It is a unified framework that combines multiple tools and streamlines an otherwise complicated process of data curation. It offers multiple filters at structure, sequence and annotation levels, giving researchers full control over data curation. Further, we present several use cases. In particular, we demonstrate how NucleoSeeker allows the creation of a non-redundant RNA structure dataset to assess AlphaFold3's performance for RNA structure prediction. This demonstrates NucleoSeeker's effectiveness in curating valuable non-redundant tailored datasets to both train novel and judge existing methods. NucleoSeeker is very easy to use, highly flexible and can significantly increase the quality of RNA structure datasets.

BP 3.4 Mon 10:15 H44

Uncovering the Non-Canonical RNA Binding site on the Immune Sensor OAS2 by combining AI, MD simulations and experiments. — •Adrian F. Schnell[1], Veronika Merold[2], Indra Bekere[2], Carina C. de Oliveira Mann[2], and Nadine Schwierz[1] — [1]Institute of Physics, University of Augsburg — [2]Department of Bioscience, Technical University of Munich

Molecular dynamics (MD) simulations and machine learning provide powerful tools to predict protein-RNA interactions, but their predictions require experimental verification. In this talk, we showcase an advancement in understanding the immune sensor 2'-5'-oligoadenylate synthetase 2 (OAS2) by combining AlphaFold 3, MD simulations, cryo-electron microscopy (cryo-EM), and cellular assays. Although the structure of the OAS2 has been resolved through cryo-EM, the precise mechanisms underlying its activation and the RNA binding site remained elusive.

To fill this gap, we combined all-atom MD simulations based on cryo-EM structures and AlphaFold 3 predictions to identify non-canonical RNA binding interfaces on the catalytically deficient OAS2 domain. By integrating mutagenesis studies and contact data from MD simulations, we uncovered critical structural details of RNA binding and OAS2 activation. Importantly, our findings reveal how OAS2 domains discriminate RNA length, providing new insights into its function and regulatory mechanisms. These results enhance our understanding of OAS2's antiviral immune role and offer a foundation for developing antiviral strategies targeting the OAS-RNase L pathway.

BP 3.5 Mon 10:30 H44

Computational bridging between sequence design and network-level behaviour of programmable DNA-nanomotifs — •Aaron Gadzekpo[1] and Lennart Hilbert[1,2] — [1]Karlsruhe Institute of Technology, Institute of Biological and Chemical Systems — [2]Karlsruhe Institute of Technology, Zoological Institute

DNA can serve as a programmable material, by using the DNA sequence to control the 3D-structure of building blocks at the nanometre-scale. In our work, we construct X-shaped particles, or "nanomotifs", from four single-stranded DNA-oligomers, each 46 nucleotides in length. The X-motifs' four arms selectively and transiently hybridize, linking into large, dynamic networks guided by DNA sequence complementarity. We present our scale-bridging computational methods to predict how DNA-oligomer sequences translate into physical properties of X-motifs and the emergent behaviour of networks. In particular, we leverage machine learning to transition from base-pair resolution simulations of single X-motifs and linked pairs to coarse-grained molecular dynamics simulations of networks at increased time and length scales. These simulations are used to explore how nanomotif design at nucleotide level influences emergent behaviour, including liquid-liquid phase separation and condensation on target DNA strands with complementary binding motifs. We connect our observation to corresponding experiments, showcasing model-aided design of DNA-based materials.

BP 3.6 Mon 10:45 H44

Ionizable cationic lipids and helper lipids synergistically contribute to RNA packing and protection in lipid-based nanomaterials — •David Noel Zimmer[1,2], Friederike Schmid[1], and Giovanni Settanni[1,2] — [1]Physics Department Johannes Gutenberg University Mainz — [2]Faculty of Physics and Astronomy Ruhr University Bochum

Lipid-based nanomaterials are used as a common delivery vehicle for RNA therapeutics. They typically include a formulation containing ionizable cationic lipids, cholesterol, phospholipids, and a small molar fraction of PEGylated lipids. The ionizable cationic lipids are considered a crucial element of the formulation for the way they mediate interactions with the anionic RNA as a function of pH. Here[1], we show, by means of molecular dynamics simulation of lipid formulations containing two different ionizable cationic lipids (DLinDMA

and DLinDAP), that the direct interactions of those lipids with RNA, taken alone, may not be sufficient to determine the level of protection and packaging of mRNA. Our simulations help and highlight how the collective behavior of the lipids in the formulation, which determines the ability to envelop the RNA, and the level of hydration of the lipid-RNA interface may also play a significant role. This allows the drawing of a hypothesis about the experimentally observed differences in the transfection efficiency of the two ionizable cationic lipids.

[1] Zimmer, D. N., Schmid, F., & Settanni, G. (2024). J. Phys. Chem. B 2024, 128, 41, 10165-10177.

15 min. break

Invited Talk BP 3.7 Mon 11:15 H44

Killing to survive - how protein-lipid interactions drive programmed cell death — •Kristyna Pluhackova — University of Stuttgart, Stuttgart, Germany

Programmed cell death is an essential process of eukaryotic life, enabling e.g., embryonic development, regeneration, or fighting pathogens. Depending on the needs of an organism, diverse molecular mechanisms of cell death exist, determining among others the speed of cell death, its extent and the impact on surrounding cells. Not surprisingly, dysregulation of cell death culminates in diverse diseases, the most prominent of all being cancer.

Here, I reveal molecular details of protein-lipid interactions in programmed cell death by multiscaling molecular dynamics simulations. First, I unveil how lipids unplug medium-sized membrane pores formed by a pyroptotic agent gasdermin and reveal astonishing adaptability of the pore shape. Next, I demonstrate how the gasdermin species and the lipid composition determine the process of gasdermin pore formation. At last, I resolve the mechanism through which ninjurin-1 disrupts membranes during plasma membrane rupture, the terminal event of many cell-death processes.

BP 3.8 Mon 11:45 H44

Integrative Modeling of Cellular Dynamics: Applications to Viruses and Neurotransmission — •Mohsen Sadeghi — Freie Universität Berlin, Berlin, Germany

A comprehensive understanding of cellular processes requires a quantitative analysis of biomembrane dynamics in interaction with protein populations, within a model that integrates kinetics and protein structural information. This is crucial for deciphering and potentially manipulating complex biological pathways. In this work, we introduce a dynamic framework for modeling membranes and proteins [1-5], showcasing its large-scale applications. These include the first computational model of the human cytomegalovirus [6] and the simulation of synaptic vesicle docking. We highlight how large-scale mesoscopic simulations provide unprecedented insights into complex cellular dynamics, capturing spatiotemporal scales that are directly relevant to cell biology.

1 Sadeghi and Noé, Nat. Commun. (2020) 11:2951.

2 Sadeghi, Weikl and Noé, J. Chem. Phys. (2018) 148:044901.

3 Sadeghi and Noé, J. Chem. Phys. (2021) 155:114108.

4 Sadeghi and Noé, J. Phys. Chem. Lett. (2021) 12:10497-10504.

5 Sadeghi, Soft Matter (2022) 18:3917-3927.

6 Bogdanow, et al. Nat. Microbiol. (2023) 8:1732.

BP 3.9 Mon 12:00 H44

Hepatitis C Virus Infection Alters NK Cell Receptor Expression: A High-Dimensional Analysis — •Andrea Schneider — Heirich-Heine Universität Düsseldorf

Hepatitis C virus (HCV) infection influences the expression of receptors on natural killer (NK) cells, a crucial component of the innate immune system. Using fluorescent markers for flow cytometry measurements, receptor expression can be analyzed to identify differences between healthy individuals, recovered patients, and those with chronic infections. Due to the possibility of using many markers simultaneously in one measurement, algorithms for dimension reduction are necessary for the evaluation of flow cytometry data. These findings could provide a potential starting point for novel therapeutic approaches. A key focus of the talk is the application of t-SNE, a dimensionality reduction algorithm that visualizes high-dimensional data in two-dimensional scatterplots while preserving high-dimensional clustering. The analysis offers valuable insights into the cellular differences among the three patient groups and opens new perspectives for immunological research.

BP 3.10 Mon 12:15 H44

Activity enhanced shear-thinning of flexible linear polar polymers — •Arindam Panda[1], Roland G. Winkler[2], and Sunil P Singh[1] — [1]Indian Institute Of Science Education and Research, Bhopal, Madhya Pradesh, India — [2]Institute for Advanced Simulation, Forschungszentrum Jülich, Jülich, Germany

The rheological behavior of tangentially propelled flexible polymers in linear shear flow is investigated through computer simulations and compared with analytical predictions. Our study reveals a significant interplay between nonequilibrium active forces and shear-induced effects on the polymer's structural and dynamical properties. Polar activity enhances the shear-induced stretching along the flow direction while inducing compression in the transverse direction. This coupling leads to a pronounced shear-thinning response, where the viscosity decreases with increasing shear rate. In the high activity and shear limit, the polymer's behavior becomes largely independent of the active forces, with the shear flow predominantly driving the system's response. At asymptotically high shear rates, the system transitions to a regime where the polymer exhibits characteristics akin to passive polymers, with shear forces entirely overshadowing the influence of activity.

BP 3.11 Mon 12:30 H44

Patchy Particle Model for Biomolecular Condensates — •Devika Magan[1,2,3], Alena Taskina[1,4], Simon Dannenberg[1], and Stefan Klumpp[1,4] — [1]Institute for the Dynamics of Complex Systems, University of Goettingen, Friedrich-Hund-Platz 1, 37077 Goettingen, Germany — [2]Indian Institute of Science Education and Research Mohali, India — [3]Institute for Theoretical Physics, Heidelberg University, 69120 Heidelberg, Germany — [4]Max Planck School Matter to Life

Biomolecular condensates are formed via liquid-liquid phase separation (LLPS) of proteins and nucleic acids, driven by interactions between low-affinity binding sites. Computational studies of biomolecular condensates often use coarse-grained patchy particle models, representing proteins with a repulsive core and directional attractive patches. However, these simulations are typically limited by slow dynamics and struggle to capture the full range of material properties of fluid-like condensates. We present an enhanced patchy particle model to study the formation and dynamics of biomolecular condensates. By incorporating flexible patches and weak isotropic attractions between cores, our model preserves key equilibrium characteristics, including phase behavior and local structure, while significantly accelerating system dynamics. These modifications enable the simulation of larger, more complex systems previously inaccessible due to prohibitive relaxation times and provide a versatile tool for studying condensate dynamics.

BP 3.12 Mon 12:45 H44

Co-translational (polysome-protein) condensation — •Zhouyi He, Jens-Uwe Sommer, and Tyler Harmon — Leibniz Institute of Polymer Research , 01069, Dresden, Germany

Biomolecular condensates are ubiquitous in cells and play crucial roles in cellular regulation. These condensates typically form via liquid-liquid phase separation, where protein-protein interactions are crucial. However, how condensates interact with protein translation machinery is poorly studied. During translation, multiple ribosomes are simultaneously translating each mRNA forming a poly-ribosome structure (polysome), which resembles beads packed on a string. On one end of the mRNA, the ribosomes have only extruded the start of the nascent protein, and on the other end the ribosomes have a nearly finished protein. Nascent proteins from translating polysomes can interact with the finished proteins that make up the condensate (co-translational condensation). Using coarse-grained simulations, we show that the architecture of encoded proteins determines whether the polysome is adsorbed to the condensate surface or remains in the cytoplasm. Furthermore, we employ a reaction-diffusion model to analyze the time scales relevant to this process. Additionally, we model the potential cellular advantages of this phenomenon, including enhanced cellular response times, reduced noise in protein concentration, and facilitation of post-translational modifications. This work establishes a theoretical framework for co-translational condensation and highlights new functions for condensates in cells and offers promising directions for experimental validation.