BP 20: Protein Structure and Dynamics

Time: Wednesday 15:00–17:45 Location: BAR/0106

BP 20.1 Wed 15:00 BAR/0106

Enhanced Conformational Dynamics of Biomolecules with Quantum-Accurate Machine Learning Force Fields — •Naziha Tarannam — University of Luxembourg, Luxembourg

Machine Learning Force Fields (MLFFs) address a long-standing challenge in computational biophysics: lifting quantum accuracy in the treatment of biomolecules to the large scales, above nanometres and nanoseconds, normally available only to classical-like molecular mechanics force fields (MMFFs). Our recently developed SO3LR model was trained on a diverse set of over four million configurations and achieves ab initio-level accuracy while remaining computationally efficient for large systems in explicit solvent. We explore the dynamics of several globular proteins in aqueous systems comprising up to 35,000 atoms using SO3LR, and compare its performance against a set of widely used MMFFs. While SO3LR faithfully reproduces the static structural properties of proteins, it exhibits enhanced exploration of conformational space during molecular dynamics simulations compared to MMFFs, showing qualitatively different properties of sampling and convergence. This stems from its relatively accurate treatment of quantum many-body forces. Notably, SO3LR enables proteins to explore a broader spectrum of dihedral angles (ψ/ϕ distributions) that are inaccessible to conventional force fields, leading to higher configurational entropy over comparable simulation timescales. These results imply that classical treatments of biomolecules, even if they reach an adequate thermodynamic accuracy, may often do so for the wrong reasons.

BP 20.2 Wed 15:15 BAR/0106

Molecular dynamics simulations of native state collagen fibrils — Konstantinos Steiakakis[1], Alan Pichard[2], and •Maxime Vassaux[2] — [1]Processing and Performance of Materials, Department of Mechanical Engineering, Eindhoven University of Technology, Eindhoven, 5600 MB, The Netherlands — [2]Univ. Rennes, CNRS, IPR - UMR 6251, Rennes, 35000, France

Collagen fibrils are the building block of many biological tissues, which viability depend on the fibrils properties. Altered properties of collagen fibrils are central to the appearance of many diseases, and physiological or native properties must be reproduced for tissue engineering. Yet, the self-assembly, the structure, and therefore the properties of collagen fibrils remain elusive. One main reason is the extreme sensitivity of the fibrils to their environmental conditions, and in particular hydration which is only loosely bound by experimental measurements. Furthermore, mechanics are an integral part of the self-assembly process and may result in internal stresses in collagen fibrils in native conditions. Here, we investigate hydradtion, structure and internal stresses in collagen fibrils by means of molecular dynamics simulations of the collagen microfibril model. Overall, our findings provide insights into the native properties of collagen fibrils such as longitudinal prestrain and water content. More than ever, collagen fibrils appear to be assembled via an out-of-equilibrium process key for the synthesis of viable tissues.

BP 20.3 Wed 15:30 BAR/0106

Atomic-Level Insights into Amyloid Resistance Gained from Molecular Dynamics Simulations — •Adrian Felix Schnell[1], Tim Moderer[2], Marcus Fändrich[2], and Nadine Schwierz[1] — [1]Institute of Physics, Computational Biology, University of Augsburg, Universitätsstraße 1b, 86159 Augsburg, Germany — [2]Institute of Protein Biochemistry, Ulm University, 89081 Ulm, Germany

Systemic AA amyloidosis arises from the misfolding and aggregation of normally soluble serum amyloid A1 (SAA1) protein into pathogenic fibrils. Despite extensive experimental efforts, the molecular driving forces that govern fibril formation and resistance remain only partly understood.

Using atomistic molecular dynamics (MD) simulations of experimentally resolved structures in both the fibrillar and native states, we investigated sequence-specific features that modulate amyloid stability and resistance. Simulations of wild-type SAA1 and two naturally occurring variants known to display amyloid resistance reveal how single-point mutations can markedly influence fibril stability and impede fibril growth. Specifically, the atomistic MD trajectories show that the resistant variants fail to stably adopt the pathogenic fibril conformation, pointing to distinct structural and dynamical mechanisms underlying their protective effect.

Invited Talk BP 20.4 Wed 15:45 BAR/0106

Solution scattering and MD simulation as quantitative probes of protein-specific and temperature-dependent hydration — •Jochen S Hub — Saarland University, Saarbrücken, Germany

The hydration shell is an integral part of proteins since it plays key roles for confor- mational transitions, molecular recognition, and enzymatic activity. While the dynam- ics of the hydration shell have been described in detail by spectroscopic techniques, the structure of the hydration shell remain less understood due to the lack of hydration shell-sensitive structural probes with high spatial resolution. Whether MD simulations correctly reproduce the hydration shell structure is not known. Small-angle scattering (SAS) with X-rays or neutrons (SAXS/SANS) is sensitive to the hydration shell; however, the hydration shell effects on SAS data has traditionally been considered as a problem, which had to be absorbed into free fitting parameters, rather than a chance to learn the hydration shell structure. We combine SAS data with MD simulations and explicit-solvent SAS predictions to reveal how factors such as surface properties, temperature, and force fields influence protein hydration. We find that (i) MD simulations with certain (but not all) force fields yield excellent agreement with the SAS data; (ii) chemical characteristics of surface-exposed moieties strongly modulate the hydration shell contrast and structure; (iii) temprature-ramp SAXS and MD show consistently that the protein hydration shell is remarkably temperature-sensitive. Our studies demonstrate the combination of SAS and explicit-solvent MD simulations as quantitative structural probes of protein hydation.

15 min. break

BP 20.5 Wed 16:30 BAR/0106

Microscopic Insights into the Solvation of Stapled Peptides A Case Study of p53-MDM2 — Vikram Gaikwad, •Asha Rani Choudhury, and Rajarshi Chakrabarti — Indian Institute of Technology Bombay, Mumbai, India

Water often termed the universal solvent, plays a vital role in numerous biomolecular processes, including protein-protein interactions. One such critical complex is p53-MDM2, which is central to cellular regulation. Inhibiting the p53-MDM2 interaction remains a therapeutic challenge, and stapled peptides have emerged as promising candidates in this context.The stapled peptides are peptidomimetics in which the side chains of two suitably positioned amino acids are covalently linked using an appropriate chemical moiety. In this study, we investigate the role of water in the binding of stapled p53 peptides to MDM2 using molecular dynamics simulations. Our aim is to understand how variations in the chemical nature and stapling position of the hydrocarbon cross-linker influence the behavior of water molecules surrounding the p53 peptide. Using rigorous entropy calculations, we rationalize the enhanced binding affinity of stapled p53 peptides compared to that of their unstapled counterparts from a solvent-centric perspective. Specifically, the entropy gain of water molecules around the stapled peptides, combined with the conformational entropy loss of the peptide, contributes favorably to binding. These findings offer valuable insights into the rational design of stapled peptides and support the development of improved therapeutic inhibitors targeting the p53-MDM2 interaction.

BP 20.6 Wed 16:45 BAR/0106

What is the structure of biomolecular condensates? — •Charlotta Lorenz[1,2], Nathaniel Hess[3], Sully Bailey-Darland[1], Teagan Bate[1], Takumi Matsuzawa[1], Tong Wang[1], Kaarthik Varma[1], Dana Matthias[1], Harsha Koganti[1], Lois Pollack[1], Benjamin Schuler[2], Jerelle Joseph[3], and Eric Dufresne[1] — [1]Cornell University, Ithaca, NY, USA — [2]University of Zurich, Zurich, Switzerland — [3]Princeton University, Princeton, NJ, USA

Biomolecular condensates are important for a variety of cellular functions, such as biochemical regulation, structural organization, and RNA metabolism. While the properties and physiology of these con-

densates depend on their structure, this important aspect has received little experimental consideration. We expect a structure-function relationship determined by protein-protein interactions. Recent simulations of disordered proteins with interactions based on the sticker-and-spacer suggest fascinating structures in the bulk and surface of condensates. We reveal the structure of biomolecular condensates using small-angle X-ray scattering. We show that condensates made from a simple model system of bovine serum albumin (BSA) and polyethylene glycol (PEG) behave like a classical liquid. We extend our approach to the structure of condensates made of disordered proteins such as fused in sarcoma (FUS) and we find that FUS inside condensates structurally behaves like a gas. Our approach is applicable to a variety of different condensates and shows that diverse condensates have diverse structures.

BP 20.7 Wed 17:00 BAR/0106

Dynamics and (self-)interactions of the endocytic protein Eps15 — •Andromachi Papagiannoula, Ida M Vedel, Arbesa Saiti, Kathrin Motzny, and Sigrid Milles — Leibniz-Forschungsinstitut für Molekulare Pharmakologie im Forschungsverbund, Berlin

Eps15 is one of the earliest initiators of clathrin-mediated endocytosis (CME). The dimeric protein carries three EH domains per monomer, which are known to recognize Asn-Pro-Phe (NPF) motifs in intrinsically disordered regions (IDRs). Using nuclear magnetic resonance (NMR) spectroscopy, we examined interactions between EH domains and the IDR of the endocytic partner Dab2. In addition to canonical NPF recognition, we detect a high level of binding promiscuity leading to interaction with other phenylalanine-rich regions. This behavior enables EH domains to also engage with Eps15's own IDR, creating partial competition with Dab2. Nevertheless, Dab2 and the Eps15 IDR can bind EH domains simultaneously, leading to recruitment of Dab2 into Eps15 condensates. When EH domains are expressed in row, as they naturally occur in the wild type full length protein, EH2 and EH3 tumble together as one entity, while EH1 moves independently. Using single molecule Forster resonance energy transfer (smFRET), we assess the three dimensional organization of the three EH domains with respect to each other and assess binding with both Dab2 and Eps15 IDRs.

BP 20.8 Wed 17:15 BAR/0106

ASAXS Based Absolute Intra-Molecular Distance Measurements for Proteins — •Samuel Stubhan[1], Anna Baptist[1], Caroline Köröšy[1], Alessandra Narducci[2], Gustavo Gabriel Moya Munoz[2], Nicolas Wendler[2], Aidin Lak[1], Michael Sztucki[3], Thorben Cordes[2], and Jan Lipfert[1] — [1]Department of Physics and Center for NanoScience, LMU Munich, Amalienstr. 54, 80799 Munich, Germany — [2]Physical and Synthetic Biology, Faculty of Biology, LMU Munich, Großhadernerstr. 2-4, 82152 Planegg-Martinsried, Germany — [3]ESRF, 71 Avenue des Martyrs, 38043 Grenoble, France

Intramolecular distance measurements are key to understanding macromolecular structure and dynamics. Anomalous Small-Angle X-ray Scattering (ASAXS) interferometry enables such measurements by attaching small (~1 nm) gold nanoparticles to target molecules and using X-ray scattering to extract distance distributions. ASAXS provides absolute distances over >10 nm, full ensemble distributions, and minimal sensitivity to label orientation, offering advantages over FRET and NMR.

We demonstrate ASAXS on proteins for the first time using two cysteine variants of maltose binding protein in apo and holo states, directly revealing ligand-induced conformational changes. The resulting distance distributions agree with single-molecule FRET measurements. Requiring only a double-labeled sample and accommodating diverse solution conditions, ASAXS offers a robust, broadly applicable tool for probing protein conformational ensembles.

BP 20.9 Wed 17:30 BAR/0106

Probing membrane protein dynamics on lipid-functionalized graphene transistors through low-frequency noise — •Florian Steinbach[1], Mykola Fomin[1], Eduard Haar[2], Svetlana Vitusevich[3], Mykhaylo Petrychuk[3], Christian Ungermann[2], and Carola Meyer[1] — [1]Institute of Physics, University of Osnabrück — [2]Department of Biology/Chemistry and Center for Cellular Nanoanalytics, University of Osnabrück — [3]Institute of Biological Information Processing (IBI-3), Forschungszentrum Jülich

Graphene field-effect transistors (GFETs) functionalized with lipid monolayers provide a controlled and label-free platform for studying membrane-associated proteins [1]. Here, we present electronic transport experiments where the Rab7-like GTPase Ypt7 is immobilized within a lipid monolayer. While there is not electrostatic gating effect observed, the addition of the protein causes a pronounced increase in low-frequency 1/f noise. This noise signal is diminished upon binding of the membrane tethering HOPS complex [2]. The persistence of distinct noise signatures despite strong screening indicates a transduction mechanism that may circumvent the screening within the Debye length.

[1] M. Fomin, L. Jorde, F. Steinbach, C. You, C. Meyer, Phys. Status Solidi B 2300324 (2023).

[2] M. Fomin et al, accepted for publication in Fluctuation and Noise Letters (2025).