BP 4: Computational Biophysics II

Time: Monday 15:00–16:30 Location: BAR/SCHÖ

Invited Talk BP 4.1 Mon 15:00 BAR/SCHÖ

The Multi-faceted Role of Cholesterol in Cellular Membranes and Lipid Nanoparticles — •Rainer Böckmann — Computational Biology - Theoretical & Computational Membrane Biophysics, Friedrich-Alexander-Universität Erlangen-Nürnberg

Cellular membranes serve as dynamic interfaces regulating numerous biological processes, with cholesterol playing a central role in shaping their structure, dynamics, and function. Likewise, cholesterol is crucial for stabilizing lipid nanoparticles (LNPs) in pharmaceutical applications and for enhancing their therapeutic efficacy. Here, we elucidate the multifaceted functions of cholesterol in both biological membranes and LNPs using atomistic molecular dynamics simulations, including constant-pH approaches.

Our findings challenge conventional views of membrane organization by revealing that thermal membrane bending and local cholesterol distribution can collaborate to soften membranes [1], even though cholesterol is widely associated with membrane thickening and reduced permeability. Turning to lipid nanoparticles, we demonstrate that cholesterol is significantly enriched in the LNP shell [2], resulting in shifts of the pK_a of aminolipids by 2-4 units, contingent on the specific lipid composition [3]. This insight underscores the importance of cholesterol-lipid interactions in modulating the physicochemical properties of LNPs, with direct implications for the design and optimization of cholesterol-containing nanocarriers in drug delivery. [1] Pöhnl et al. Nat.Commun. 14, 8038 (2023) [2] Trollmann, Böckmann. Biophys.J. 121, 3927 (2022) [3] Trollmann, Böckmann. Small (2026)

BP 4.2 Mon 15:30 BAR/SCHÖ

Transient interactions between cationic ionizable lipids and anionic lipids foster lamellar to hexagonal phase transition — •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

RNA-based therapeutics have demonstrated remarkable efficacy and hold great promise for future applications. The most common delivery systems for these drugs are lipid-based nanoparticles (LNPs), which incorporate ionizable cationic lipids (ICLs) as key components. ICLs are believed to facilitate endosomal escape of the cargo by interacting with anionic lipids in the endosomal membrane, although the underlying molecular mechanism remains unclear. One proposed model suggests that the membrane is destabilized by cone-shaped complexes formed between ICLs and endosomal anionic lipids; clear evidence of stable complexes is still missing. Here[1], we re-examine the problem through equilibrium and nonequilibrium simulations of model membrane systems containing DODMA (ICL), DOPS (anionic lipid) and DOPE (helper lipid). Our results confirm absence of co-localization at equilibrium, but reveal a transient formation of cone-shaped complexes during lamellar-to-inverted-hexagonal phase transitions, which considerably accelerates the transition process. These findings may open new ways for controlling endosomal escape through the rational design of ICLs optimized to interact with cell- or stage-specific endosomal anionic lipids. [1] Zimmer DN, Schmid F, Settanni G. ChemRxiv. 2025; doi:10.26434/chemrxiv-2025-rwb18

BP 4.3 Mon 15:45 BAR/SCHÖ

Osmolyte Effects on Protein Stability: Charge-Regulation is Essential — •Julia Keil and Nico F. A. van der Vegt — Technische Universität Darmstadt, Germany

Osmolytes such as glycine modulate protein stability through differences in their preferential interactions with folded and unfolded states. In this work, we revisit glycine's influence on protein stability by explicitly incorporating charge-regulation effects - protonation and deprotonation of titratable groups - into our study of glycine-protein interactions. Using constant-pH molecular dynamics simulations[1], we develop a titratable glycine model. This pH-dependent model predicts that at pH 7 glycine is depleted from nonpolar elastin-like polypeptides (ELPs) but enriched near acidic and basic ELP residues. It also shows a pH-dependent accumulation of glycine around ELPs and the miniproteins Trp-cage and GB1, both consistent with prior experimental and computational observations[2-4]. Notably, charge regulation produces systematically stronger preferential binding of glycine to ELPs and mini-proteins at neutral pH than predicted by fixed-charge models. Although glycine is zwitterionic in bulk solution at pH 7, acid-base interactions with NH_3^+ and COO^- protein groups alter its protonation state within biomolecular hydration shells. The corresponding shifts in apparent pKa values promote electrostatically favorable combinations of protonation states, providing a mechanistic explanation for the enhanced preferential binding. [1] J. Chem. Theory Comput. 2022, 18, 10,6148-6160 [2] PNAS 2017, 114, 10, 2479-2484 [3] J. Phys. Chem. B 2020, 124, 30, 6565-6574 [4] Biochem. 1987, 26, 16, 5147-5153

BP 4.4 Mon 16:00 BAR/SCHÖ

Is helicity cooperative? Mechanistic insights from IM30 folding-unfolding dynamics — •Tika Ram Bhandari[1,2], Kurt Kremer[1], Friederike Schmid[2], and Martin Girard[1] — [1]Polymer Theory, Max Planck Institute for Polymer Research, Mainz, Germany — [2]Institute of Physics, Johannes Gutenberg University, Mainz, Germany

Helical transitions help regulate protein behavior, but how different chain segments influence each other's helicity is not well understood. Using coarse-grained molecular dynamics with Hamiltonian Replica Exchange, we examine the disordered-to-helical transition of IM30, the bacterial homolog of ESCRT-III. By tuning hydrogen-bond strengths, we show that the coiled-coil region is more helical than other domains, while overall helicity stays stable due to secondary-structure interactions. Fragments behave differently inside the full chain, revealing cooperative coupling without changing total helicity. Analysis shows both positive and negative links between helicity and chain extension, and identifies four main conformational states. These results clarify how segment interactions control helical transitions and maintain global helicity stability.

BP 4.5 Mon 16:15 BAR/SCHÖ

Grand canonical simulations of micellization in intrinsically disordered proteins — •Rodrigo F. Dillenburg[1,2], Martin Girard[1,5], Friederike Schmid[2], and Edward A. Lemke[3,4] — [1]Max Planck Institute for Polymer Research, Mainz, Germany — [2]Institute of Physics, Johannes Gutenberg University, Mainz, Germany — [3]Biocenter, Johannes Gutenberg University, Mainz, Germany — [4]Institute of Molecular Biology, Mainz, Germany — [5]Institute for quantitative and computational biosciences, Mainz, Germany

Molecular dynamics (MD) simulations with coarse-grained force fields have been the gold standard in the computational modeling of liquid-liquid phase separation (LLPS) and biomolecular condensates. While much attention has been focused on large droplets, very little is known about the formation of microphases, such as micelles, in such systems. There is evidence that such assemblies arise from intrinsically disordered proteins (IDPs) with a block co-polymer architecture. However, due to their finite size they are highly sensitive to the periodic boundary conditions of the simulation box. The commonly implemented slab geometry is thus unfit to tackle such systems. To overcome this we have implemented a semi-grand canonical monte carlo (SGCMC) algorithm that significantly speeds-up MD simulations. Our implementation is compatible with implicit solvent 1-bead-per-amino acid force fields such as Calvados and HPS. We show that such approach allows one to run simulations efficiently in a cubic box, at very low densities typical of biological systems. We also highlight the advantages of SGCMC in simulating micelles compared to regular MD.