CPP 55: Focus Session: Theoretical Modeling and Simulation of Biomolecular Condensates III (joint session CPP/BP)

Time: Friday 9:30–11:15 Location: ZEU/0260

Topical Talk CPP 55.1 Fri 9:30 ZEU/0260

Data-driven modelling of phase-separating intrinsically disordered regions — •Giulio Tesei[1,2], Fatima Kamal Zaidi[3], Shanlong Li[4], Julian O. Streit[1], Jianhan Chen[4], Tanja Mittag[3], and Kresten Lindorff-Larsen[1] — [1]Department of Biology, University of Copenhagen, Copenhagen, Denmark — [2]Department of Biomedical Science, Malmö University, Malmö, Sweden — [3]Department of Structural Biology, St. Jude Children's Research Hospital, Memphis, U.S.A. — [4]Department of Chemistry, University of Massachusetts, Amherst, U.S.A.

Intrinsically disordered regions (IDRs) constitute about one third of the human proteome and play important roles in biological processes. While lacking well-defined 3D structures, IDRs adopt heterogeneous ensembles influenced by multivalent interactions; these same interactions can promote phase separation and contribute to the formation of biomolecular condensates. I will first present CALVADOS, an efficient one-bead-per-residue model optimized on experimental data reporting on IDR conformational properties and extensively validated on both single-chain and phase behavior across diverse sequences. I will then describe how we used large sets of CALVADOS simulations to train machine-learning models that accurately predict single-chain compaction and homotypic phase-separation propensity directly from sequence. Finally, I will introduce a hybrid-resolution model with an atomistic backbone representation that matches the accuracy of CALVADOS for global dimensions and phase separation while also capturing local structure and backbone hydrogen bonding.

CPP 55.2 Fri 10:00 ZEU/0260

Born to Condense: Polysomes Drive Co-Translational Condensation of Biomolecular Condensate Proteins — •Zhouyi He, Jens-Uwe Sommer, and Tyler Harmon — Leibniz Institute of Polymer Research, 01069, Dresden, Germany

Biomolecular condensates formed by protein LLPS are ubiquitous and crucial in cells. While the physics and functions of LLPS are well studied, its interplay with protein synthesis, translation, remains largely unexplored. Here we propose Co-Translational Condensation (CTC), a mechanism in which nascent protein chains of polysomes, multiple ribosomes on one mRNA, interact with condensates, localizing translation to condensate surfaces. Using coarse-grained simulations, we show that protein domain architecture dictates the extend of CTC, consistent with a Langmuir adsorption model. Bioinformatic analysis reveals that most condensate-associated proteins have architectures favoring CTC, with strong interaction regions of nascent chains exposed on polysomes. Dynamically, simulation and reaction-diffusion modeling reveal that CTC is kinetically feasible within typical polysome lifetimes, either through large polysomes nucleating new condensates or via diffusion to pre-existing condensates. As a case study, we demonstrate that CTC enhances post-translational modifications by minimizing unmodified intermediates. More broadly, we anticipate CTC may also influence protein folding, misfolding, and signal-integration latency. Together, our results establish CTC as a general mechanism coupling translation with phase separation, with broad implications for protein evolution, cellular organization, and synthetic biology.

CPP 55.3 Fri 10:15 ZEU/0260

Local RNA/protein stoichiometry tunes the electrostatic microenvironment inside reconstituted multicomponent condensates — •Patrick M. McCall — Leibniz Institute for Polymer Research Dresden, Dresden, DE

Biomolecular condensates are demixed phases of biopolymers and, in living cells, commonly form through the associative phase separation of strongly-charged nucleic acids together with protein polyampholytes carrying a weak net charge. While condensates are proposed to offer distinct aqueous environments for the organization of cellular biochemistry, it remains unclear which physical aspects of the microenvironment are relevant and how widely they can vary between condensates. Motivated by the large asymmetry in structural charge between typical condensate components such as RNAs and RNA-binding proteins, we explore here the implications of electroneutrality on the electrostatic environment within model multicomponent condensates. Combining classical Donnan theory with recent measurements of the macromolecular composition of condensates reconstituted from full-length FUS protein and a homopolymeric RNA [McCall et al Nat Chem 2025], we compute the partitioning of salt ions as well as the Donnan potential across the phase boundary. We find that RNA/FUS stoichiometry tunes both co-ion exclusions over a wide range and is coupled to a pH jump across droplet interface. We also find that co-ion exclusion is suppressed by counter-ion condensation and enhanced by non-ideality of un-bound ions. These results provide insight into the range of ionic conditions accessible to a prominent class of biomolecular condensate.

CPP 55.4 Fri 10:30 ZEU/0260

Coarse-grained model to study the effects of electric fields on protein interactions — •Agaya Johnson[1], Debes Ray[2,4], Mahnoush Madani[3], Jan Dhont[2,3], Florian Platten[2,3], Kyongok Kang[2], and Sofia Kantorovich[1] — [1]University of Vienna, Kolingasse 14-16, 1090, Vienna, Austria. — [2]nstitute of Biological Information Processing IBI-4, Forschungszentrum Jülich, 52428 Jülich, Germany. — [3]Faculty of Mathematics and Natural Sciences, Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany. — [4]Solid State Physics Division, Bhabha Atomic Research Centre, Trombay, Mumbai 400085, India.

Proteins can undergo transition between a wide range of organisational states, from soluble monomers to disordered phases and ordered structures. Experiments have shown that lysozyme in sodium thiocyanate solution can form homogeneous, crystalline, or liquid phases depending on the salt and protein concentrations, and that these phase boundaries can be shifted by applying an electric field. We present a coarse-grained model of lysozyme in sodium thiocyanate solution, representing the protein as an ellipsoid decorated with charged and adhesive surface patches. Counterions and monovalent salt are treated explicitly via excluded-volume repulsion and Coulombic interactions. We investigate (i) how patch size and salt*patch interactions influence ion distributions around a single protein, with and without an external electric field, and (ii) the resulting effective interactions between two proteins as functions of patch properties, salt concentration, and applied electric field.

CPP 55.5 Fri 10:45 ZEU/0260

Entropic Clustering of Stickers Induces Aging in Biocondensates — •Hugo Le Roy[1] and Paolo De Los Rios[2] — [1]Department of Civil, Chemical and Environmental Engineering, University of Genoa, Genoa, Italy — [2]Institute of Physics, Ecole Polytechnique Fédérale de Lausanne

Neurodegenerative conditions, such as Parkinson's disease, results from the aggregation of synaptic proteins such as alpha-synuclein. In a healthy presynaptic neuron, effective neurotransmission relies on the spatial organization of synaptic vesicles within phase-separated droplets. These vesicles release neurotransmitters into the synaptic cleft to activate ion-gated channels on the postsynaptic neuron.

In this work, we investigate how this transmission process is impaired during neurodegeneration. Specifically, we focus on the solidification of these phase-separated droplets, a phenomenon described as aging, leading to protein aggregation and associated with the emergence of pathology. We explore the connection between the mechanical properties of the condensates and their microscopic structure using a minimal physical model that treats complex molecules as stickers and spacers. We show that entropy maximization of spacers leads to an effective attractive force between stickers. As a result, our system displays a surprisingly slow relaxation toward equilibrium, reminiscent of glassy systems and consistent with the liquid-to-solid transition observed in aging droplets. By analyzing the clustering dynamics of stickers, we successfully explain the microscopic origin of this glassy relaxation.

CPP 55.6 Fri 11:00 ZEU/0260

Biomolecular condensates with a Twist: From Assembly to Arrest — •Mahesh Yadav[1,2] and Lukas Stelzl[2] — [1]Institute of Physics, Johannes Gutenberg University, Mainz — [2]Institute of Molecular Physiology, Johannes Gutenberg University, Mainz

In this work, we investigate the phase behavior of RNA-binding protein Fused in Sarcoma (FUS), whose multivalent and intrinsically disordered regions drive the formation of biomolecular condensates through

liquid-liquid phase separation. FUS is a multi-domain protein with arginine-glycine-rich segments (RG-rich domains) that participate in essential cellular proceses. We examine how characteristic sequence motifs such as RGG.. mediate homotypic and nucleic acid binding, and how targeted point mutations (e.g., RtoK, RtoA) disrupt these motifs and impair condensate formation. Using the thermodynamics phase diagram as a benchmark we highlighted the shift in phase separation propensity of the FUS and its variants. Furthermore, we identify the role of key interactions such as electrostatics, π-π and cation-π in nucleic acid binding at atomistic scale. We further characterized the emergent viscoelastic behavior of FUS condensates at multiple scales. We observe that upon mutations the overall dynamics slows down which reflects the gel-like state. Within the condensate interior, protein chains exhibit sub-diffusive dynamics arising from intermittent binding and viscoelastic resistance, mobility at the interface is further suppressed due to anisotropic interactions and interfacial confinement. To quantify these behaviors across relevant scales, we employ multi-resolution simulation models.