SynGAP and PSD-95 Phase Separation

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https://gregconradismith.github.io/

The computational biology laboratory is currently funded to study how molecular interactions organize the postsynaptic density (PSD), the protein-rich assembly that regulates signalling and plasticity at excitatory synapses. With Jennifer Bestman and graduate student Sarah Sakly, I am developing mathematical and experimental approaches to connect SynGAP–PSD-95 binding and phase separation with synaptic organization and dendritic development. Our NSF-supported project asks how protein variants, dosage and activity-dependent regulation alter the stability and remodelling of these assemblies.

Mathematical modelling of synaptic condensates

With Sarah Sakly, I have developed a multicomponent framework coupling Flory–Huggins equilibrium theory to Cahn–Hilliard–reaction dynamics. The model explicitly represents free SynGAP, free PSD-95, their reversible complex and solvent. Phase diagrams characterize coexistence regions and the compositions of coexisting phases; spatial simulations examine the redistribution of individual species. This combination distinguishes stoichiometric association from additional effective molecular interactions and connects equilibrium organization with finite-rate dynamics. It builds on evidence that SynGAP–PSD-95 condensation involves interactions beyond those stabilizing discrete complexes.[1,2]

In illustrative simulations, weakening association together with selected interaction changes redistributes SynGAP while preserving a PSD-95-rich phase. In a separate equilibrium comparison, reducing total SynGAP by 50% changes predicted phase compositions while retaining coexistence for the illustrative parameter sets. These results suggest testable mechanisms for remodelling and dosage sensitivity; they are not calibrated predictions of phosphorylation or intact synapses.[1]

Connecting molecular organization to development

Our NSF project combines three directions: measuring isoform- and variant-dependent phase behaviour; relating condensate organization to dendritic maturation and synaptic function; and developing theory for finite, membrane-associated condensates. Planned experiments include purified-protein phase-separation assays, fluorescence recovery after photobleaching, and live imaging and electrophysiology in the Xenopus retinotectal system. Mathematical extensions will address multivalent network formation, finite-size effects, membrane geometry and exchange with the surrounding cytosol. These studies aim to connect molecular organization with measurable cellular phenotypes relevant to SYNGAP1-associated neurodevelopmental disorders, while providing reusable computational tools and interdisciplinary training.

Selected references

1. Sakly S, Conradi Smith G (2026). Modeling phase separation dynamics of SynGAP and PSD-95 in postsynaptic densities. bioRxiv preprint; under revision at Physical Biology. doi:10.64898/2026.07.23.740312.

2. Lin YH, Wu H, Jia B, Zhang M, Chan HS (2022). Assembly of model postsynaptic densities involves interactions auxiliary to stoichiometric binding. Biophysical Journal 121:157–171. doi:10.1016/j.bpj.2021.10.008.

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