Is there a "lipid code" that regulates information flow in neural circuits?

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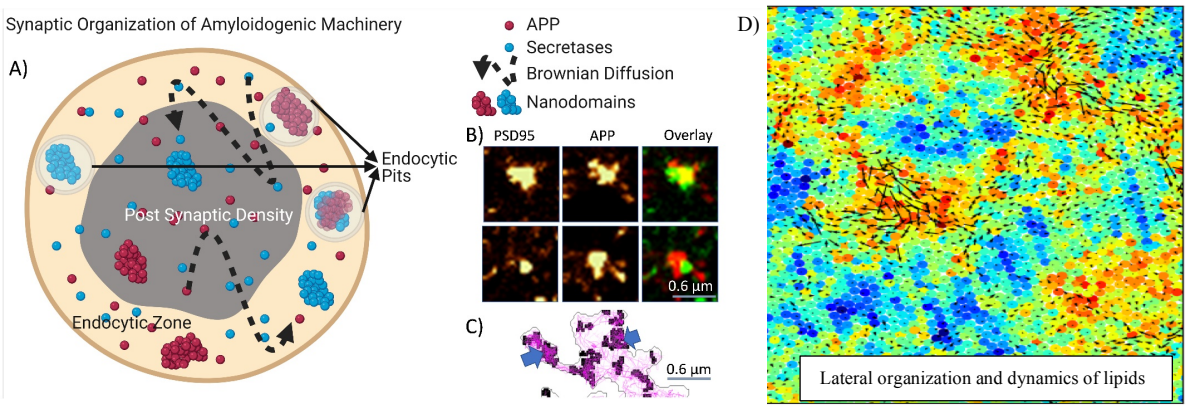
Recent lipidomics data show that there are more that 40,000 unique lipid structures in Eukaryotic cells. Neuronal plasma membrane, which is a complex self-assembly of a variety of lipids, sterols and proteins, is estimated to have more than 1000 chemically different types of lipids and hundreds of proteins. Differential molecular interactions among these extremely diverse constituents give rise to functionally important spatial and dynamic heterogeneities in the neuronal membrane lateral organization. These sub-100 nm transient structures ("molecular portraits"), which are stabilized far away from equilibrium, are believed to be functionally important in various physiological processes of the cell ranging from cell growth and movement to signal transduction, neurotransmission and intercellular transport of proteins. Anand Srivastava (MBU) and Deepak Kumaran Nair (CNS) laboratories at IISc seeks to understand the evolutionary advantage of maintaining the complex lipid diversity in neuronal membranes vis a vis factors that determine synaptic plasticity and function. Towards that end, we are building up a integrative framework that combines biochemical and super high-resolution imaging data with the state-of-the-art computational methods to rigorously characterize nanoscale domains in neuronal membrane and we are exploring the various functional implications of membrane heterogeneity in terms of processes that regulates information flow in neural circuits.

There is an immediate need to build a framework to rigorously characterize these "molecular portraits" in neuronal membrane that would allow the community to rationally explore the various functional implications of membrane heterogeneity and synaptic transmission. Our framework will be used to robustly address biologically pertinent questions such as "Why are there so many lipids?" or "Is there a lipid code??". Recent findings from several labs (including that of Srivastava and Nair labs) suggest that lipids can form functional nanodomains on membrane surface that regulate several processes in the cells. Data suggests that these lipid nanoclusters, with features of small-world network, can form interesting "structural" motifs that are degenerate and exhibit unique "fingerprints" around specific proteins. From a design principle point of view, it can be argued that each lipid acts as a Lego piece and the tremendous diversity in lipids allows for a huge design space at oligomeric nanodomain level and in turn at the functional diversity. We aim to unravel the molecular and thermodynamics underpinning of such a design principle encoded in the neuronal membrane. With these discoveries where oligomeric lipid network motifs ("molecular portraits") are reported to act as functional building blocks, neuronal membrane biophysics and synaptic plasticity field is poised to harness the emerging concepts from machine learning, network science and graph theory to understand synapses in a new "lipid centric" way.

Our project redefines the synapse as a nanoscale information-processing unit, where lipid-based molecular self-organization governs its function through thermodynamic principles. Instead of focusing solely on neurotransmission, we explore how the spatial arrangement and phase behaviour of lipids, ion channels, and scaffold proteins organized into lipid-protein nanodomains in the 10–100 nm range determine synaptic plasticity and function. Using super-resolution imaging, high-dimensional morpho-functional analysis, non-linear dimensionality reduction techniques, machine learning and molecular simulations based computational modelling, we are constructing precise maps of lipid and protein architectures within synapses. These maps highlight how nanoscale heterogeneity, referred to as "compositional degeneracy," allows multiple lipid-mediated organizational states to support both similar and distinct synaptic outcomes. We conceptualize synaptic transitions as thermodynamic phase phenomena, with lipid bilayers and associated proteins undergoing phase separation driven by local thermodynamic fluctuations that are stabilized far away from equilibrium. This process governs the shift from stochastic to deterministic neurotransmitter release, depending on the structural dynamics of lipid domains. During developmental stages and homeostatic scaling, we demonstrate how lipid nanodomains within synapses dynamically reorganize, enabling the encoding of probabilistic inference and multiplicative scaling through lipid-protein interactions. By integrating principles of statistical physics with systems neuroscience, our approach provides a quantitative framework for understanding synaptic computation as it relates to lipid-mediated molecular organization. Ultimately, we aim to define the upper and lower thermodynamic limits of synaptic strength, revealing how lipid-driven molecular logic encodes flexible, robust information flow in neural circuits. Through this work, we uncover the pivotal role of lipids in shaping synaptic transmission and plasticity, bridging molecular neurobiology with the thermodynamics of biological information processing.



An example of lateral organization on neuronal membrane (Amyloid Precursor Protein (APP) and secretases on the membrane of an excitatory synapses. A) APP or Secretases which form the machinery that process APP into proteoforms can laterally diffuse by random diffusion or be reversibly immobilized in nanodomains with varying compositionality of APP and Enzymes. Endocytic compartments can now internalize these molecules by trapping these molecules at endocytic pits, where each hot spots of internalization can have variable combination of substrate and enzymes that can process APP and secretases. Thus every synapse may have its own dynamic range of proteoforms production that can be regulated locally and at the level of single chemical reactions B) Localization of APP in diffraction limited functional zones of the synapse. PSD95 is marker for Post synaptic density and in the upper panel we have presented a synapse where the APP localization is lateral to it, in endocytic zone C) Lateral trafficking of APP molecules on the plasma membrane and the nanodomains (black) represent hotspot of immobilization as observed by shorter steps (blue arrows) resulting anomalous diffusion and trapping. D) Lipid phase (Blue to Red where Blue is highly ordered and Red highly dynamic) and single particle displacement profiles of lipids on membrane: Data obtained through molecular modelling. Both spatial and temporal heterogeneity is clearly visible from these Physics-based models.

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