Dynamical nanoscale organization of Amyloid precursor protein (APP) at excitatory synapses

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Bio-molecular structures dynamically assemble, perform highly orchestrated biochemical functions, and disassemble seamlessly before reassembling to continue the cycle. Since the molecular structure and the biochemical pathways in biological processes are optimized over evolutionary timescales to perform elaborate functions, the information processing in "*biological circuitry*" is extremely sophisticated. Despite being under strong thermal noise and embedded in a crowded molecular milieu, the molecular machines and motors encrypt and process complex set of information in a precise manner. This information is embedded at multiple length and time scales that range from structures at atomic resolution to molecular complexes leading to subcellular and cellular processes such as ion transport across channels and pumps, presynaptic neurotransmission, morphogenesis and metastasis to name a few.

With Alzheimer's disease (AD) related synaptic physiology as the primary system of interest, we propose to develop an experimentally guided computational/theoretical framework to dissect the dynamics and molecular localization of Amyloid precursor protein (APP) and components of amyloidogenic pathway at excitatory synapses. APP first attracted attention when one of its degradation products, the 40-amino acids long amyloid (Aβ) peptide, was found in senile brain plaques isolated from patients with AD. Several years of research has established that alteration in proteolytic processing of APP is a crucial element towards progression of AD. With the help of super high-resolution microscopy, Deepak Nair's laboratory (Nano-Organization Laboratory, CNS-IISc) study the compartmentalization of major components of amyloidogenic machinery at functional zones of the synapse. Their work indicates that the dynamic molecular organization of APP and secretases at the endocytic zone might serve as a pivotal link in amyloidogenic processing of APP. Through their sophisticated imaging and biochemical data, they also illustrate fundamental mechanisms where alterations in real-time nanoscale association of components of amyloidogenic machinery may contribute towards long term deficits like those seen in AD. In spite of such advances in experimental techniques, it is impossible to see such processes in great detail.

Understanding the detailed mechanisms of real-time spatiotemporal arrangement of APP molecules in the nanodomains is imperative for discerning AD. Computational approaches that models the realistic geometry of dendritic spines with the underlying heterogeneity in localization, the dynamical motion and the reaction kinetics of the macromolecules can fill the knowledge gap in space and time scales that are not directly resolvable experimentally. Srivastava's laboratory (MBU-IISc) aims to develop an "*in silico*" framework, which is informed by experimental data and higher-resolution simulations, to elucidate a unique data driven model on how the heterogeneity of molecular organization and millisecond scale exchange of APP molecules on the membrane can create these "*regulatory nanodomains*" that could function as a loci for APP processing. The framework will seamlessly integrate the molecular structural determinants with the exquisitely crafted network of biochemical interactions by using methods such as molecular dynamics (MD) simulations, machine learning techniques and stochastic reaction-diffusion kinetics modules such that biomolecular components appear/associate, disappear/dissociate and change their type based on reaction rules. Our paradigm of integrating nanoscale localization and real-time trafficking of APP from experiments in conjunction with biophysically realistic 3D mathematical models will allow us to predict the modulation of APP processing by amyloidogenic pathway.

For more details: https://www.dropbox.com/s/p4k0i5ipuafrbpc/Draft-APP-Summary.pdf?dl=0

Candidates with strong analytical, mathematical and programming skills will be preferred. Students with background in Physical Chemistry, mathematical modelling, engineering and Physics are encouraged to apply.