Title: Conformational Plasticity and Disorder-to-Order Transition of Intrinsically Disordered α-synuclein: Interactions with Lipid Membranes, Tau and Chaperones

Abstract: The conventional sequence-structure-function paradigm states that proteins adopt a well-defined 3-dimensional structure that is encoded by the amino acid sequence. However, an emerging class of proteins, known as intrinsically disordered proteins (IDPs), confronts this traditional paradigm. IDPs being conformationaly plastic can adopt different structures depending upon their binding partners. This property of IDPs might be an evolutionary conserved strategy that makes them more useful in a wide range of physiological functions involving cell signaling, transcription, etc. Under certain stress conditions, in the cellular milieu, both folded proteins and IDPs can adopt a thermodynamically more stable state known as amyloid state. These amyloids represent exquisite protein nano-aggregates that are constituted by characteristic highly ordered cross-β structures and are known to be implicated in a large number of debilitating neurodegenerative diseases, such as Parkinson's disease (PD) and Alzheimer's diseases (AD). α-Synuclein is an IDP, mainly found in the presynaptic terminals of neurons in the brain and the central nervous system. The precise function of α-synuclein is poorly understood, though, there are few proposed functions known such as synaptic transmission, synaptic vesicle localization, maintenance of neuronal plasticity, etc. α-Synuclein adopts a helical structure in the membrane-bound form. The membrane-bound state plays a crucial role in the biological function of α-synuclein and in the etiology of Parkinson's disease. α-Synuclein being a cytosolic protein and is also known to interact with other cytosolic proteins, namely, tau, which is also an IDP that stabilizes microtubules and its amyloid formation is implicated in AD. Recent evidences suggest that tau and α-synuclein interact to form pathological co-amyloids that are localized in different regions of the brain and are associated with several neurological diseases such as PD, AD, Down syndrome, multiple system atrophy, etc. Furthermore, protein folding and amyloid dissociation are tightly regulated at multiple levels with the help of molecular chaperones. α-Synuclein is known to associate with the mitochondria and interact with heat shock proteins (Hsps) under several stress conditions, including PD. In my talk, I will discuss the structural and dynamical aspects of interaction of α-synuclein with membranes, tau protein and molecular chaperones using a variety of biophysical tools.