Biophysical perspectives of amyloid-β and amylin induced modulations in its optical and electrical properties

Thesis Abstract

Amyloid-β (Aβ), a 42 residue peptide, is derived from a transmembrane protein named Amyloid precursor protein. Its misfolding leads to amyloid deposition which associates it with Alzheimer's disease (AD). Amyloid formation kinetics depends on many intrinsic and extrinsic factors. Amylin, a peptide from the pancreatic β-cell, has potential therapeutic relevance in AD; hence, deciphering the amylin-induced modulations in Aβ aggregation may help elucidate the implications of Aβ-amylin interactions in the proteinopathy.

In this thesis, we studied the folding/unfolding transitions of Aβ under the standard geometry model to determine the density of states using Wang-Landau simulations, elucidating the calorimetric and geometric details of Aβ transition states and the associated thermodynamic properties. Next, non-equilibrium MD simulation in explicit solvent showed the competitive effects of temperature and 20 mV/nm static electric field in stabilizing/destabilizing helical conformation of Aβ. The propensity of α-helix to β-sheet conversion was related to the electric field orientation, end-to-end distance, RMS fluctuations, and changes in secondary structures. Further, we observed that the as-prepared solution of Aβ under diffusion-limited conditions formed oligomers capable of self-assembling into fractals. We present a generic model, predictions of which were correlated with patchy diffusion-limited aggregation, to understand the pH-sensitive morphological transitions in the fractal self-assemblies in terms of electrostatic and hydrophobic patches.

Photoluminescence emission spectra acquire tyrosine, oligomer interactions, and β-sheet originated structure-specific intrinsic fluorescence, which we employed as a label-free quantitative assay to monitor Aβ aggregation. The modulations in the emission bands were used to sense different structures, the influence of amylin on Aβ aggregation, and promotion/inhibition of Aβ fibrillation by 40-200 V/cm electric field. Further, the influence and association of activation energy of proton transfer to the dynamics of secondary structure and its heterogeneity were estimated by measuring impedance spectra during Aβ and amylin aggregation. The electrical properties revealed that Aβ aggregations are μm-scale and amylin aggregations are sub-nm scale proton hopping-dominated systems.

This thesis provides a simulation tool to pinpoint the stable intermediates for nucleation of the fibril growth that may help design efficient drugs to slow down or inhibit the fibrillation process. These peptides' optical and electrical properties may be used in biosensing, optoelectronic, and nanotechnological applications.

Keywords: Amyloid-β, Amylin, Alzheimer's, Transition state, Conformational heterogeneity, Fractal self-assembly, Aggregation, Intrinsic fluorescence, Proton transfer