National Institute of Technology Rourkela

Synopsis Seminar

Seminar Title	: Protein-Protein Association in a Crowded Environment: A study on GB1 Protein Dimerization
Speaker	: Sweta Pradhan (Rollno : 519ph1010)
Supervisor	: Mithun Biswas
Venue	: MC 126 (Physics Seminar Room)
Date and Time	: 14 May 2025 (4 PM)
Abstract	: Protein association reaction is key to biological functions of cells. Most of the *in vitro* studies of protein association are done in dilute solutions, whereas the intracellular medium is a dense mixture of macromolecules. To understand the physiological relevance of the dense environment, several experimental and computational studies have been performed recently. It has been found that the macromolecules constituting the environment, named as crowders, tend to significantly induce the formation of protein-protein complexes which further leads to the formation of either the dimers, trimers or higher-order oligomers. Protein associated state plays a crucial role in regulating proteins in ion channels, DNA binding, signal transduction, enzymatic actions, immune response. However, any redundancy in the association mechanism of proteins may also trigger the formation of pathogenic structures. To estimate the mechanism leading to the protein associated state, conformational dynamics of the proteins has been determined through several experimental and computational studies. The crowder molecules exclude the *in-cell* reactant molecules from occupying certain regions of the cell, resulting in changes in the reaction thermodynamics and kinetics. Recent studies, both experiment and simulations, revealed that the nature of interaction between crowder and protein species, in particular the soft interactions, plays an important role in crowder induced effects on protein association. To this end, with a computer simulation approach, we investigate dimerization of model system GB1 protein in presence of lysozyme crowders. From the simulations, it is found that GB1 dimer formation is destabilized in presence of lysozyme crowders and the destabilization is more for the domain-swapped dimer compared to the side-by-side dimer, that is in qualitative agreement with experimental findings. However, the SPT calculation predicts stabilization of dimer in presence of lysozyme crowder. A detailed understanding of the crowding influence on protein association requires characterization of transient intermediates on a free energy landscape. In this work, we explore the free energy landscape of dimerization of protein GB1 in a dilute and crowded medium by employing advanced sampling techniques, such as metadynamics and parallel tempering. Dimerization proceeds via a single dominant pathway encountering few minima in dilute solutions. However, in presence of lysozyme crowders, the free energy landscape exhibits multiple minima and multiple barriers, providing alternative pathways for dimerization. The minimum free energy pathway indicates that dimerization starts by destabilizing the N-termini of monomers in both the cases. The population of the on-pathway intermediate states in dilute medium reveals the structural modulations in GB1 conformation that eventually leads to a final dimer-like state. The presence of lysozyme crowders stabilizes new intermediates although no stable dimer is formed. The study highlights modification of dimerization pathway by attractive protein-crowder interactions.