Ph.D. Open Seminar
Department of Chemistry, IISER Bhopal

Title: "Understanding the molecular mechanism of allostery in proteins and conformational plasticity of natively disordered human CD4 peptide using molecular dynamics simulations and network models"

Speaker: Mr. Navjeet Ahalawat (Supervisor: Dr. Rajesh K. Murarka) **Roll No.:** 1010208
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Abstract

Proteins are vital parts of living organisms and involved in almost every single biological process. We tried to address two open questions of protein structural biology: characterization of structural ensemble of intrinsically disordered proteins/peptides (IDPs) and protein allostery. To this end, my thesis work is based on four studies: nucleotide dependent allosteric regulation of AMP-activated protein kinase (AMPK)[1], activation mechanism of corticotropin-releasing factor 1 (CRF1) G-protein coupled receptor[2], understanding the extraordinary ligand-binding ability of human serum albumin (HSA)[3], and characterization of structural ensemble of cytoplasmic tail of human cluster determinant 4 (CD4)[4].

Allostery is a form of signaling within biomolecules in which ligand binding to a site in protein affects the function or activity of a distant site. The aim of my thesis work was to investigate allosteric mechanisms in different biomolecular systems such as protein kinase (AMPK), membrane receptor (CRF1R) and transport protein (HSA). We analyzed how the change in protein conformational states on ligand binding helped to propagate signals to a distant site. Towards this goal, a number of theoretical approaches are used, including advanced molecular dynamics (MD) simulations, elastic network model (ENM), principal component analysis (PCA), statistical coupling analysis (SCA), and graph theory. Our results are in good agreement with experiments and provide detail explanation of allosteric communications in the studied systems.

Experimental characterization of IDPs is challenging due to their structural heterogeneity. MD simulation is a powerful tool in providing information on both structure and dynamics at atomic-resolution and becoming popular to study IDPs. The cytoplasmic tail of CD4 (residues 402-419) is known to be involved in direct interaction with the HIV-1 proteins Vpu and Nef. We carried out extensive replica exchange MD simulations in explicit water to characterize the equilibrium conformational ensemble of CD4-tail. Markov state model (MSM) and clustering analysis show that this peptide adapts multiple, rapidly interconverting distinct conformations with varying degree of residual secondary structures. Our results could help to understand the key molecular mechanisms of T-cell activation and HIV-mediated receptor interference.

References:

1. **Ahalawat, N.**; Murarka, R. K. (Manuscript communicated).
2. Singh, R.; **Ahalawat, N.**; Murarka, R. K. *J. Phys. Chem. B* **2015**, *119*, 2806.
3. **Ahalawat, N.**; Murarka, R. K. *J. Biomol. Struct. Dyn.* **2015**, *33*, 2192.
4. **Ahalawat, N.**; Arora, S.; Murarka, R. K. *J. Phys. Chem. B* **2015**, *119*, 11229.