INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Programme of Study	:	Ph.D.

Thesis Title: **Investigation of structural dynamics and allosteric mechanisms of SAMHD1 protein complex via Molecular Dynamics studies**

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SHORT ABSTRACT

SAMHD1 is a human cellular enzyme that blocks HIV-1 infection in myeloid cells and non-cycling CD4+T cells. The enzyme is an allosterically regulated triphosphohydrolase that modulates the level of cellular dNTP. Retroviral restriction is attributed to the lowering of the pool of dNTPs in the cell to a point where reverse transcription is impaired. A mechanistic understanding of the allosteric activation of the enzyme is still elusive. The catalytically active form of the protein is an allosterically triggered tetramer of the HD domain, which is considered to be the necessary and sufficient structural unit for dNTPase activity as well as restriction of HIV-1. The tetrameric form of the protein complex is assembled by the GTP-dNTP combination. In study we have used both classical MD techniques along with the correlation network analysis to study the dynamics and allosteric information flow across the active complex in the protein system. We have revealed the evidence of reciprocal allosteric "Handshakes" between adjacent monomers through correlation network analysis. We have also uncovered the allosteric links in SAMHD1 to demonstrate flow of information across the assembled SAMHD1 tetramer. In the last sections, we have studied the putative redox switching mechanisms by the probable cysteine residues present in the monomeric forms of the protein complex. We have carried out a series of MD simulations of the monomeric forms of the protein, with mutations at these sites to examine how the dynamics of the protein in the monomeric form differ from that in the tetrameric form and to illuminate the role of the cysteine residues.