INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Programme of Study	:	**Ph.D.**

Thesis Title: **Mechanistic Insight Into the Aggregation Pathways of the hLL-37$_{17-29}$ Peptide and the Effect of These Aggregates on Model Membranes**

Name of Thesis Supervisor(s)	:	**SANDIP PAUL**
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SHORT ABSTRACT

This thesis addresses the growing challenge of antimicrobial resistance and explores how antimicrobial peptides can be leveraged to tackle this threat. We focus on the hLL-37$_{17–29}$ peptide, which exhibits antimicrobial activity and can aggregate into α-amyloid fibrils, a novel self-assembly motif recently reported. To investigate this system, we performed molecular dynamics simulations of hLL-37$_{17–29}$ and its mutants in solution and in the presence of model membranes, and used the resulting simulation data to train unsupervised models within the Markov state modeling framework. We study the pathways by which hLL-37$_{17–29}$ peptides form encounter complexes starting from a fully dispersed state using semi-empirical Markov state models and transition path theory. We further construct Markov state models with finer molecular descriptors to resolve how encounter complexes evolve from disordered to ordered states, identify key interactions that drive this organization, and propose a comprehensive model for α-amyloid self-assembly. We then explore how pre-formed hLL-37$_{17–29}$ fibrils interact with model membranes ranging from bacterial to mammalian, aiming to explain their selectivity. Finally, we examine how point mutations at Ile24 influence the aggregation behavior of hLL-37$_{17–29}$ and why these mutations may diminish its antimicrobial activity.