INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Programme of Study	:	Ph.D.

Thesis Title: Mechanism of Antimicrobial Peptide Binding to Membrane-mimetic Systems: Insight from Molecular Dynamics Simulations

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SHORT ABSTRACT

The focus of the Ph.D. thesis was to understand the mechanism of cationic antimicrobial peptide (7 and 14 amino acid residue long) binding to membrane-mimetic systems (micelle and bilayer) using classical molecular dynamics free energy simulations. The peptides were modeled and subjected to conventional classical MD simulations in the presence and absence of micelle/bilayer [micelles: SDS/DPC and bilayers: (DOPE:DOPG and POPE:POPG)/POPC as bacterial/mammalian membrane-mimic]. The structures of the free peptides in water and in complex with the membrane-mimetic systems were predicted from the conventional MD simulations and verified by our experimental collaborators. The MD structures were used as a template for estimating the energetics of peptide: micelle/bilayer binding (ΔG_{bind}; absolute binding affinity and $\Delta\Delta G$; Binding free energy difference between two peptides to the membrane-mimetic system) by employing various popular methods: Molecular mechanics Poisson-Boltzmann surface area (MM-PBSA), Steered Molecular Dynamics (SMD), Umbrella Sampling (US), and Alchemical free energy simulations (FEP, TI, BAR). The simulations of peptide binding to the simplest membrane-mimetic systems provide insight into the kinetics and establish a direct link between the calculated energetics and molecular structures.

The thesis consists of 6 chapters. Chapter 1, describes the relevant literature, adopted methodology, and objectives of this thesis. Chapter 2 discusses the binding of cationic, non-toxic, non-hemolytic, and salt-tolerant heptapeptide (P4: $NH3^{+}$-LKWLKKL-CONH2, Charge +4 and analogs P5: Lysine's → Arginine's; P6: Lysine's→ Uncharged-Histidine's; P7: Tryptophan→ Leucine) to bacterial-membrane-mimetic models (SDS micelle and DOPE:DOPG

bilayer). Chapter 3 discusses the salt-sensitivity of 14 residue-long antimicrobial peptides (LL-14) obtained by doubling the peptide P4 (LL-14: NH_3^+-LKWLKKLLKWLKKL-$CONH_2$, Charge = +7). In Chapter 4, the effect of Leu/Val Mutation on the Energetics of peptide:SDS binding has been discussed. In Chapter 5, the effect of unnatural amino-acid substitution on the stability of the LL-14:bilayer (POPE:POPG or POPC) complex has been discussed. The overall conclusion of the thesis and the future scope of this work is discussed in Chapter 6.

The thesis has shown that it is possible to bridge the microscopic structures of biomolecules and free energy differences by combining classical molecular dynamics and statistical mechanics. The methodology adopted in this thesis is general and could be useful for studying peptide: membrane recognition in general.