INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title: Binding and Destabilization of Amyloid-β Protofibrils by β-sheet Breaker Molecules: A Molecular Dynamics Simulation Study

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SHORT ABSTRACT

Alzheimer's disease is a fatal neurodegenerative disease which affects the elderly population leading to the loss of memory and the ability to perform activities, and eventually death. There is no cure for Alzheimer's disease at present. One of the hallmark characteristics of this disease is the presence of plaques in the brains of patients, formed mainly by the amyloid-beta peptide in the form of beta-sheets. One of the therapeutic strategies is the use of small molecules as drugs to destabilize these fibrils. In the present thesis, we employ all atom molecular dynamics simulations in order to study the destabilization of amyloid-beta protofibrils by small molecules. The extent of destabilization and the binding affinities were characterized, and the dominant interactions which influenced the binding process were identified. The first major finding of the thesis was that oligoproline chains of various lengths could break the beta-sheet structure of the protofibrils and induce the formation of random coils. The second major finding was that a peptide $KLVFFP_5$ which was designed to exploit the properties of the self-recognition sequence of the amyloid-beta peptide KLVFF and the beta-sheet breaker amino acid proline could destabilize the amyloid protofibrils to a greater extent than the KLVFF peptide. The third major finding was that for a model of the protofibrils which is known to be a particularly difficult target for drugs, the increased presence of aromatic amino acids can enhance the binding of a known beta-sheet breaker peptide LPFFD, when it was modified by these aromatic amino acids. The fourth important finding was that THC molecules could destabilize the amyloid-beta protofibrils. We obtained insights into the destabilization of the protofibril structure by the THC molecules.