SOUTENANCE de THESE

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« Lattice model for amyloid peptides : OPEP force field parametrization and applications to the nucleus size of Alzheimer's peptides »

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BIBLIOTHEQUE

Abstract :

The neurodegenerative Alzheimer's disease (AD) is affecting more than 40 million people worldwide and is linked to the aggregation of the amyloid-β proteins of 40/42 amino acids. Despite many experimental and theoretical studies, the mechnism by which amyloid fibrils form and the 3D structures of the early toxic species in aqueous solution remain to be determined. In this thesis, I studied the structures of the eraly formed oligomers of the amyloid-β peptide and the critical nucleus size of two amyloid-β peptide fragments using either coarse-grained or all-atom simulations. First, at the coarse-grained level, I developed a lattice model for amyloid protein, which allows us to study the nucleus sizes of two experimentally well-characterized peptide fragments $(A\beta)_{16\text{-}22}$ and $(A\beta)_{37\text{-}42}$ of the Alzheimer's peptide $(A\beta)_{1\text{-}42}$. After presenting a comprehensive OPEP force-field parameterization using an on-lattice protein model with Monte Carlo simulations and atomistic simulations, I determined the nucleus sizes of the two fragments. My results show that the nucleation number is 10 chains for $(A\beta)_{16\text{-}22}$ and larger than 20 chains for $(A\beta)_{37\text{-}42}$. This knowledge is important to help design more effective drugs against AD. Second, I investigated the structures of the dimer $(A\beta)_{1\text{-}40}$ using extensive atomistic REMD simulations. This study provides insights into the equilibrium structure of the $(A\beta)_{1\text{-}40}$ dimer in aqueous solution, opening a new avenue for a comprehensive understanding of the impact of pathogenic and protective mutations in early-stage Alzheimer's disease on a molecular level.