Protein aggregation may cause many neurodegenerative diseases. Recent experimental evidences support the so called amyloid cascade hypothesis that the Alzheimer's disease (AD) is associated with accumulation of amyloid beta (Aβ) peptides, produced by cutting amyloid precursor protein by β- and γ-secretase, in human brain. The cytotoxicity may depend on self-assembly rates and morphology of Aβ aggregates. For instance, Aβ42 containing 42 amino acids is more toxic than Aβ40 as it forms fiber faster. Also, insoluble oligomers are more toxic than monomers and mature fibrils. Therefore, understanding key factors that control aggregation rates and polymorphism of Aβ complexes is of great interest. Within this project we will focus on two factors including copper ion Cu(II) and lipid membrane.

Experiments have shown that upon Cu(II) binding the aggregation of Aβ becomes faster and the morphology of aggregates depends on stoichiometric ratios between copper and peptide. At high Cu(II) concentrations amorphous aggregates occur while fibril-like structures were observed at low concentrations. This interesting problem cannot be solved by quantum simulations because of limited time scales. The classical molecular dynamics simulation is a suitable tool but its success depends on force fields (FF) describing the Aβ-Cu(II) complexes. In all existing FFs the torsional interaction has been omitted although the validity of this approximation remains largely ambiguous. Thus, one of our goals is to develop FFs taking into account the torsional term and apply them to study the impact of Cu(II) on the kinetics and thermodynamics of Aβ aggregation.

Another interesting question is that in the presence of copper ions Aβ becomes more toxic. Because balance in calcium homeostasis is pivotal for cell vitality we propose to explain this phenomenon by studying the impact of Aβ-Cu(II) on penetration of calcium ions Ca(II) through lipid bilayers. If binding of Cu(II) to Aβ promotes the Ca(II) permeation then the presence of Cu(II) would enhance cell death.

Because of limitation of computer speeds the estimation of protein aggregation rates in the presence of membrane is impossible using existing all-atom as well as off-lattice coarse grained models, we will develop simple on-lattice models. Such models would allow one to study the dependence of kinetics and polymorphism of aggregates on sequences and interactions with lipid bilayers.

Development of FFs for Aβ-Cu(II) and lattice models for protein-membrane systems is our main contribution to the enrichment of biophysical and biochemical tools for studying bio-molecular systems. Presently atomic structures of Aβ mature fibrils are available but structures of oligomers have not been resolved yet. Therefore structures of oligomers obtained in this projects would be valuable for drug design for AD. From this prospect, our research is not only of academic interest but it may help to enhance the quality of human life.