At certain conditions natural proteins can undergo structural transition, leading to quite regular structures that are completely different from their functional native folds. Many of these misfolded proteins may undergo aggregation to insoluble large fibril structures. Such molecular aggregates may cause a wide variety of effects within living cells, in some cases causing severe diseases, including neurodegenerative and metabolic diseases.

The molecular mechanisms of fibril self-assembly and protein aggregation are not fully understood. Structural data are difficult to collect experimentally, and obtained data usually lack accuracy and are incomplete. On the other hand, theoretical methods, including classical molecular modeling techniques, have thus far been unable to model the exceptionally long time of fibril assembly and the large sizes of molecular systems that need to be simulated. In this context, it is necessary to develop a new modeling strategy capable of simulating the entire fibril assembly process and allowing a better interpretation of experimental data. The importance of new, more efficient modeling techniques cannot be underestimated.

In this project we will develop a new multi-scale modeling protocol enabling fast computer simulations of the fibril assembly process, predicting not only structures of the mature fibrils but also providing a detailed overview of intermediate structures. The preliminary studies indicated that the task is fully feasible and the expected results should significantly contribute to a deeper understanding of the structures and biological functions of these huge molecular complexes formed by misfolded proteins or peptides.

The new simulation protocol will start from very fast coarse-grained simulations of molecular docking of peptide chains leading to formations of protofilament structures. The coarse-grained modeling approach allows computational studies of much larger molecular objects than is accessible for classical molecular dynamics methods. The resulting plethora of coarse-grained multimeric structures will be properly clustered and the best clusters representatives will be converted into the all-atom representations and refined employing molecular dynamics simulations. Obtained protofilament models will be used for the assembly of fibril final structures.

The new modeling method developed within this project will be based on an efficient multi-scale approach, allowing a rapid prediction of amyloid fibril structures. The designed bioinformatics tool will be made freely available for the scientific community throughout a web-server on homepage of our laboratory. A user will need to provide only the amino acid sequence of amyloidogenic polypeptides to obtain a detailed description of the expected three-dimensional structures of fibrils and structural characteristics of possible intermediates of the fibril assembly process.

The results of this project will have a significant impact on the amyloid fibril field of research. It will accelerate structural studies of those complicated systems, including a better understanding of the aggregation process, fibril structure (including the impact of selected point mutations on the fibril structure), their dynamical properties, polymorphisms, and identification of possible therapeutic targets. A deeper understanding of these processes is crucial not only for structural studies of molecular biology but also for medicine, especially for the rational design of new therapeutics. Also, it has several significant implications for biotechnology. The predicted fibril models and their structural characteristics will be also helpful in planning new experiments and in interpreting collected data.