From all-atom to mesoscopic simulations of amyloid proteins

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Protein aggregation has attracted considerable attention because of its implication in neurodegenerative diseases. This process is described by a nucleation and growth mechanism, in which proteins form transient oligomeric aggregates until the formation of a nucleus, from which amyloid fibrils form rapidly with a cross-β structure. Of fundamental importance for Alzheimer's disease (AD) affecting more than 26 million people worldwide, is played by the amyloid-β (Aβ) protein of 42 amino acids, Aβ1-42, and the fact that the metastable early formed oligomers are the most neurotoxic species. Many compounds are known to reduce amyloid formation and toxicity in cells, but all of them have failed to pass successfully clinical trials.

Any effective drug design strategy against AD requires detailed knowledge on the structure of $A\beta_{1\text{-}42}$ oligomers in solution and interacting with small-molecule drugs and a full understanding of the mechanisms between random coil conformations and nucleus formation. Thus far, all standard tools of structural biology and computational methods have, however, failed to provide this information.

In this talk, I shall present recent results of state-of-the-art simulations using all-atom, coarse-grained and mesoscopic protein models aimed at understanding the dynamics of the early formed oligomers, determining nucleus formation and the structures of Aβ1-42 dimer and trimer with two inhibitors (Nqtrp and EGCG).

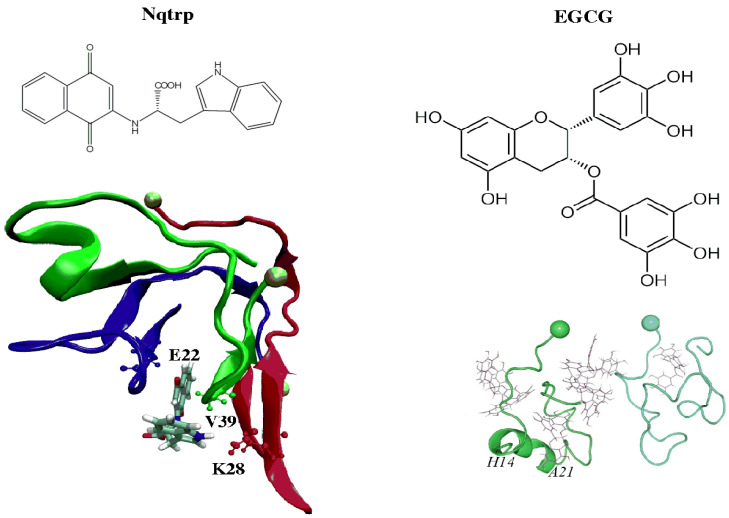

Figure. Chemical structures of Nqtrp (upper, left) and EGCG (upper, right) and 3D structures of trimer $A\beta_{17\text{-}42}$ with Nqtrp (lower, left) and $(A\beta_{1\text{-}42})_2$-EGCG complexes (lower, right) predicted by simulations.