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Abeta peptides and beta-sheet breakers. A coarse grained molecular dynamics approach

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The problem of protein misfolding is of the utmost biological and medical interest, since it is at the basis of a class of pathologies known as protein conformational disorders or amyloidosis. These diseases are characterised by the mis-folding of proteins that, becoming insoluble, accumulate in aggregates of fibrillar shape. It is remarkable that all the known neuro-degenerative diseases belong to the class of amyloidosis pathologies. Among them, the Alzheimer Disease (AD) is one of the most studied for its enormous impact.

The brain of AD patients is known to display accumulation of Abeta peptides amyloid plaques. The Abeta peptides originate from the proteolytic cleavage of a membrane protein called APP (Abeta Precursor Protein). The process that leads to the misfolding, aggregation and amyloid plaques formation is not yet fully elucidated. It seems, however, that the "starting point" of the process is an abnormal switch of the peptide secondary structure that leads to beta-sheet formation, a peculiar structure able to promote the formation of "stackable" sheets with intermolecular bonding. Unfortunately, nowadays, an effective treatment for AD is still missing.

Several effectors have been studied in order to interfere with the Abeta aggregation process. Recently, the observation that short synthetic peptides, called beta-sheet breaker (BSB's), are able to directly interact with soluble oligomers or amyloid aggregates precluding amyloid polymerisation, was at the origin of a significant scientific effort aimed at trying to modulate and prevent Abeta aggregation and fibrillation processes. In this general framework and admittedly with the ultimate ambitious goal of providing structural information for the possible development of a really effective pharmaceutical strategy, it appears to be of the greatest bio-medical relevance to try to elucidate the way Abeta peptides interact with such compounds.

In the work I am going to present here, we have studied the aggregation process of Abeta_1-40 peptides in the presence or in the absence of the BSB's with the help of Coarse Grained Classical Molecular Dynamic simulations. Our investigation shows that among the various BSBs proposed in the literature, the Ac-LPFFN-NH_2 peptide, designed and first studied by the Tor Vergata Biophysics group, is the most effective in reducing the Abeta_1-40 residues mobility and thus delaying fibril formation.

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