Role of N-Terminal Residues for Structural Stability of Triangular Aβ_{40} Fibrillar Oligomers

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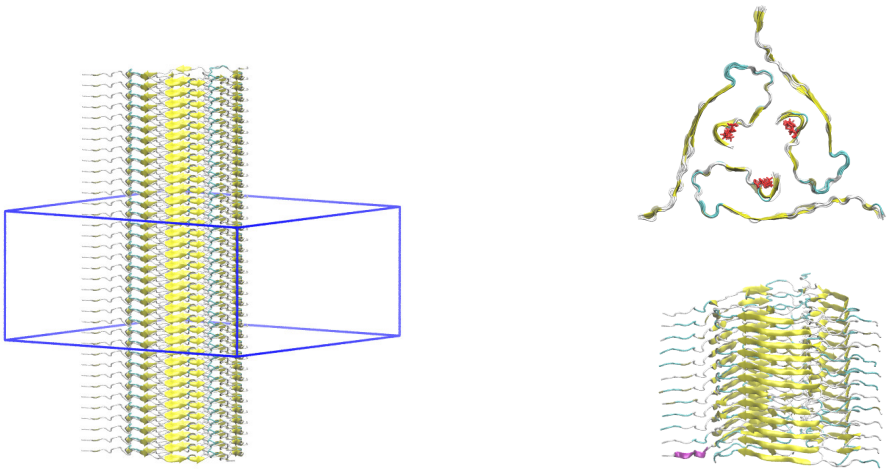
Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder and the main cause for dementia in industrial nations. One hallmark of AD is the development of senile plaque deposits in the brain that consist primarily of fibrillar amyloid β (Aβ) peptides. Aβ is a short peptide comprising 40 to 42 residues, but nevertheless exhibits a vast conformational variability and a plethora of oligomeric states, which makes experimental studies about its structure and aggregation rather challenging.

Recently, Lu et al. published a solid state NMR structure of an Aβ_{1-40} fibril isolated from an AD patient (PDB code `2M4J`)[1]. The structure shows three-fold symmetry around the fibril axis with a central water channel and is thus markedly different from Aβ_{1-42} fibril structures. Previously, we have investigated the stability of fibrillar Aβ_{42} oligomers of different size by means of molecular dynamics (MD) simulations leading to a model for longitudinal and lateral fibril growth [2, 3].

Here, we present all-atom MD simulations in explicit water based on the patient-derived Aβ_{40} fibril to elucidate how its conformational stability depends on the oligomer size. An infinite Aβ fibril was investigated as well to study the boundary effects of the finite oligomers.

Moreover, it is known from experiment that several Aβ species of different N-terminal length exist in vivo affecting the peptide's aggregation behaviour. We thus investigated the influence of the first eight Aβ residues upon the structure and dynamics of the fibrillar oligomers and the infinite fibril of Aβ_{40}.



References

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