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# Stability of single and double layer fibrillar amyloid- $\beta$ oligomers

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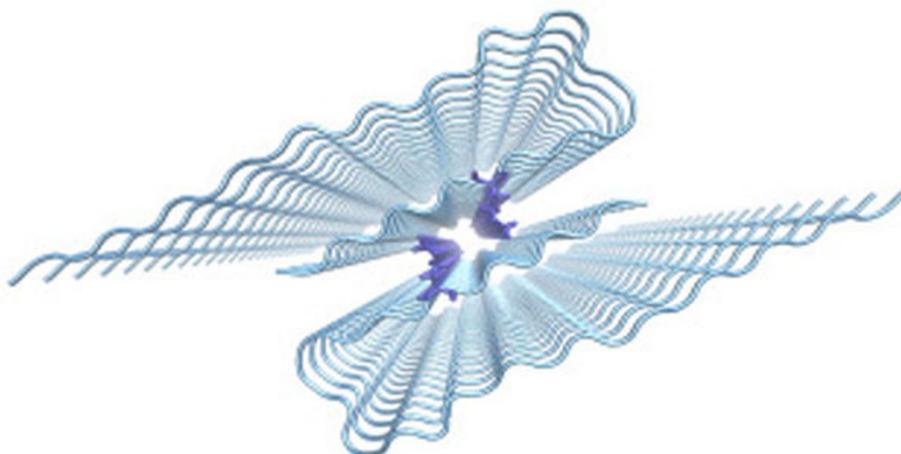
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Alzheimer's disease (AD) is the most common form of dementia world-wide. The causative agent in this protein misfolding disease is the 39 to 42-residues long amyloid- $\beta$  ( $A\beta$ ) peptide, that aggregates into oligomers, filaments, and fibrils found in plaque deposits in the brain of AD patients [1].

Up to now a viable cure for this disease is still not available. One reason for this is  $A\beta$ 's conformational flexibility and structural heterogeneity in solution paired with its aggregation tendency. This renders the determination and isolation of distinct  $A\beta$  structures experimentally challenging. Especially the soluble oligomers, that are thought to be the neurotoxic species in AD, may adopt a plethora of conformations in vivo [1].

It is known from experiment, that there exist toxic fibrillar oligomers, but the details of their topology are not yet known [2]. Thus, we used molecular dynamics simulations to investigate the structural stability of fibrillar single and double layer  $A\beta$ 42 oligomers of different size (4-mer to 48-mer), that we constructed from the experimental structure [3] (cf Figure 1).

We found that there is a clear correlation between oligomer size and preference for double layer structure: Large oligomers display an enhanced stability in double layer conformation, whereas small oligomers prefer the single layer structure. On the other hand, large single layer oligomers dissociate into smaller oligomers, while small double layer oligomers collapse or are energetically unfavorable. From



**Figure 1** Double layer  $A\beta$  48-mer (Met35 in the interface in sticks representation).

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our simulations we deduce that the critical number of oligomers to construct a stable A $\beta$  double layer is in the range of 10 to 12.

In a more general picture, longitudinal growth along a single layer is limited by the increasing structural instability. Lateral growth, i.e. forming a double layer, creates stable mini-fibrils. These may act as seeds for further stable fibril growth.

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