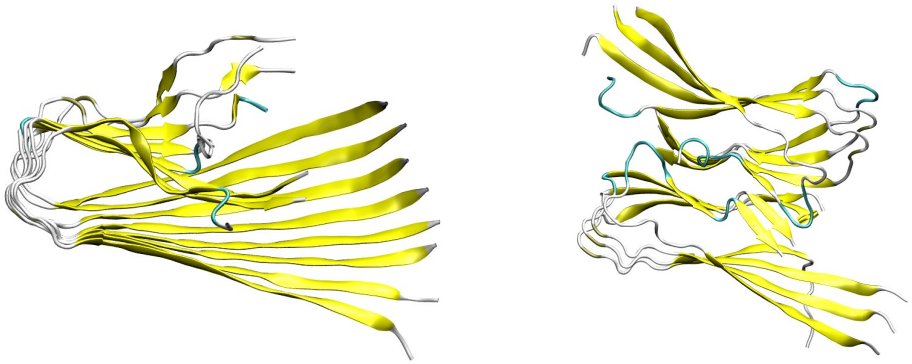
# How Quartenary Structure Influences the Conformation of Fibrillar Aβ-Oligomers

Anna Kahler, Anselm H.C. Horn, Heinrich Sticht

*Bioinformatik, Institut für Biochemie,*
*Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany*

For quite some time it is known that amyloid-β oligomers play a crucial role in Alzheimer's disease due to their neurotoxic properties but they can also act as seeds for fibril formation[1]. Due to the plasticity of Aβ it is difficult to experimentally characterize oligomeric structures so there exists a dynamically equilibrium of structurally different oligomers and even macroscopic fibrils. It is decisive to know how fibrillar conformation is affected by oligomeric size and formation of single- and double-layered structures.

Thus, all-atom molecular dynamics (MD) simulations in explicit solvent were performed on single- and double-layered oligomers of different size ranging from the tetramer up to the 48-mer; the following figure shows the final MD structure of an Aβ octamer in single-layered (left) and double-layered (right) conformation.



Our simulations indicate that the initial U-shaped topology of each oligomer with its two β-sheets and the connecting turn per monomer is maintained over time in accord with our previous study[2]. However, analyses show that deviations from the starting structure increase significantly with size caused by the twisting of the in-register parallel β-sheets which leads to an overall torsion of the oligomers along the longitudinal growth axis. The twist angle per Aβ monomer is similar for single- and double-layered oligomers (tetramer to hexamer), leading to a better shape compatibility for smaller oligomers suggesting that they can form double-layered fibril structures. In contrast to the double-layered oligomers which generally remain rather stable, large single-layered oligomers show a large twist and global instabilities.

The shape complementarity of the hydrophobic interface in double-layered systems is increasing from octamer to decamer but is not further changed for higher oligomers.

Additionally, we performed binding free energy calculations with MM/GBSA as available with the Amber program suite. The MM/GBSA results are in agreement with the structural findings and show that large single-layered oligomers are rather unstable while the association of a double layer stabilizes large oligomers.

Our results suggest, that fibrillar Aβ oligomers are stable in both single- and double-layered conformation for small oligomers while large single-layered oligomers exhibit structural instabilities. This suggests that the formation of these species is unfavoured as supported by experiment[3]. Double-layered oligomers on the other hand are expected to represent potent seeds for fibril formation because they possess the necessary structural characteristics of fibrils.

[1] C. Haass, D. Selkoe, *Nature Rev Mol Cell Biol,* **2007**, 8, 101-112.

[2] A. H. C. Horn, H. Sticht, *J. Phys. Chem. B.*, **2010**, 114, 2219-2226.

[3] M. E. Larson, S. E. Lesné, *J. Neurochem.*, **2012**, 120 (Suppl. 1), 125-139.