Structure Determination of Amyloid-β Oligomers (40-, 42-residues) with AlphaFold2

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Alzheimer's disease (AD) afflicts millions worldwide and its impact will only worsen as the population ages. One of the most important aspects of AD's pathogenesis is the aggregation of amyloid-β peptides into complexes of amyloid-β oligomers (AβOs). However, relatively little is known about AβOs as their instability makes them resistant to traditional imaging techniques.

To elucidate AβOs, we used Alphafold-2.3.2's complex prediction algorithm for structure determination of 2- through 15-peptide AβOs using the most common pathogenic amyloid-β peptides (40-, and 42-residues). To determine the viability of these generated structures we firstly relied on AlphaFold's built-in confidence metric to rank them. The highest-ranked structures were then run through molecular dynamics simulations to assess stability. Finally, we assessed their similarity to the experimentally available Aβ fibril structures using a novel metric to compare the secondary structure of the AlphaFold-generated AβO against the aggregate of Aβ secondary structures. To validate AlphaFold's ability to accurately place Aβ monomers, we generated all experimentally-derived Aβ-containing protein complexes in PDB. We found a high correspondence between the experimental and AlphaFold-generated placement of Aβ monomers within the complexes, suggesting that AlphaFold was capable of accurately predicting their position.

Using AlphaFold, we discovered several viable Aβ structures and motifs: among smaller AβOs (3-4-monomers), the most stable structures consisted of 2 antiparallel β-sheets oriented parallel to one another. In AβOs consisting of 5+ monomers, AlphaFold consistently formed a channel composed of either parallel or antiparallel twisted β-hairpins around a hydrophobic center, forming a closed β-barrel. We also observed several structures resembling Aβ-fibrils consisting of stacked, parallel β-strands. The majority of our high-ranking structures contained mostly β-topology and very little (if any) α-topology. Our results shed light on structural features of AβOs that have the potential to impair synaptic function.