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Alzheimer's Disease Amyloid Beta(25-35): An Oligomeric Aggregation Simulation From Monomers to Ordered Filaments

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Amyloid Beta (Aβ) plaques have long been correlated with Alzheimer's disease; however, efforts made to link the plaques to pathogenic effects or utilize them for diagnostic purposes have not been very fruitful. Modern investigations point to peptide intermediate structures or their oligomers as likely candidates for the toxic agents, yet much remains unknown about the aggregation life cycle from monomers to aggregated ordered filament structure. From a simulation standpoint, this is generally difficult due to the high residue count and long time frames involved in such investigations. Fortunately, in the case of Alzheimer's disease, there is a fragment of the Aβ peptide, Aβ_{25-35} which has a short residue length, aggregates rapidly, and is highly pathogenic[1], making it particularly well suited for biophysical simulation.

Our work investigates Aβ_{25-35} utilizing a molecular dynamics simulation and course-grained *Cα model based on that presented by Yap et al. in [2] which includes hydrogen bond pairing to stabilize the secondary structure. The entire aggregation process is explored from random-coil monomers, through formation of unordered intermediate oligomeric states, and into ordered filament structure. Utilizing standard cluster criterion, the nucleation free-energy landscape for Aβ*25 − 35 as a function of the number of peptides and hydrogen bond count between peptides is mapped and nucleation barriers are determined as in [3]. Also thermodynamic and kinetic measures are determined. The determination of these factors is the necessary first step to conducting future investigations involving solvents and in the presence of surfaces.

[1] J. Biosci. 34(2), pp. 293–303, 2009
[2] Proteins 70, pp. 626-638, 2008
[3] PRL 101 (25), 258101, 2008

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