MOLECULAR MECAHISM OF FORMATION OF EARLY AMYLOID-B OLIGOMERS: A MM-GBSA APPLICATION TO MOLECULAR DYNAMICS SIMULATIONS

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Low-weight amyloid-β (Aβ) oligomers formed at early stages of oligomerization rather than fibril assemblies seem to be the toxic components that drive neurodegeneration in Alzheimer's disease. Unfortunately, detailed knowledge of the structure of these early oligomers at the residue level is not yet available. All-atom explicit solvent molecular dynamics (MD) simulations were performed to examine the oligomerization process of $A\beta_{10-35}$ monomers when forming dimers, trimers, tetramers and octamers, with four independent simulations of a total simulated time of 3 μs for each oligomer system.[1] The decomposition of the relative free energy of the molecular dynamics simulations into residues and residue-pairwise terms by MM-GBSA methodology (molecular mechanics energies with implicit solvent approach)[2] allowed us to unravel the network of energetic interactions that stabilize such oligomers. The contribution of the intermonomeric van der Waals term is the most significant energy feature of the oligomerization process, consistent with the so-called hydrophobic effect. Furthermore, interactions between three specific hydrophobic fragments 31–35 (C-terminal region), 17–20 (central hydrophobic core) and 12–14 (N-terminal region) are responsible for such a favourable effect. Recently this systematic and general methodology for the analysis of MD simulations has been extended to replica exchange MD simulations of $A\beta_{1-40}$ and $A\beta_{1-42}$ dimers with similar results at the global and residue level of analysis. Understanding the mechanism of Aβ oligomerization at the residue level will lead to more efficient design of inhibitors of this process.

1) Pouplana, R.; Campanera, J. M., *Phys. Chem. Chem. Phys.* **2015**, *17*, 2823.

2) Zamora, W. ; Campanera, J. M.; Luque, F. J., Implicit Solvation Methods in the Study of Ligand–Protein Interactions. In *In Silico Drug Discovery and Design: Theory, Methods, Challenges, and Applications*; C. N. Cavasotto, ed., to be published.