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Computer Simulation Model of Polymorphisms of Beta-Amyloid Crystals

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Research has established a strong link between symptoms of Alzheimer's disease (AD) to 36-43 amino acid residues peptides, called the amyloid beta (Aβ) peptides. Patients with AD are usually diagnosed with aggregates of Aβ peptides, also called plaques, which can be as large as several μm. The structures of the plaques display a wide variety of polymorphisms that depends on the environments, and are very difficult to reproduce in experiments. This has greatly hindered the efforts to discover the microscopic origin of AD. Recently, Eisenberg *et al.* (Proc Natl Acad Sci USA, 108, 16938-16943, 2011) resolved the structures of segments of Aβ of 5 to 10 amino acid residues. The crystals are very stable, and display a complex polymorphisms of stacked parallel and anti-parallel β-sheet that may be in-register or out-of-register. At this point over 20 micro-crystals have been identified, and in many cases the same segment of Aβ can form several structures.

This submission considers an all-atom simulation model that uses an interaction force field based on the Eisenberg's crystal structures. In the spirit of Go models of folding of single proteins, the force field biased the peptides to the micro-crystal structures, but also exploit the symmetry of the crystals.The model has two adjustable parameters: the strength of the hydrogen bonds that stabilize the β-sheet structure, ϵ_{HB} ; the strength of van der Waals (vdW) interactions that stabilizes the stacking of the β-sheet, ϵ_{vdW}. Computer simulations of the model found that for $\epsilon_{vdW}/\epsilon_{HB} > 0.5$, and at low temperature the layers tends to form stacked three-dimensional structures. However, for $\epsilon_{vdW}/\epsilon_{HB} < 0.5$, the A$\beta$ segments long single-layer β-sheet similar plaques observed in full length Aβ. The implication of the results to AD will be discussed.

Author: LINHANANTA, Apichart (Lakehead University)

Co-author: GIRARDIN, Robert (Lakehead University)

Presenter: LINHANANTA, Apichart (Lakehead University)

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