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Spontaneous Formation of Oligomers and Fibrils in Large-Scale Molecular Dynamics Simulations of A-beta Peptides[1]

CAROL HALL, North Carolina State University

Protein aggregation is associated with serious and eventually-fatal neurodegenerative diseases including Alzheimer's and Parkinson's. While atomic resolution molecular dynamics simulations have been useful in this regard, they are limited to examination of either oligomer formation by a small number of peptides or analysis of the stability of a moderate number of peptides placed in trial or known experimental structures. We describe large scale intermediate-resolution molecular dynamics simulations of the spontaneous formation of fibrils by systems containing large numbers (48) of peptides including A-beta (16-22), and A-beta (17-42) peptides. We trace out the aggregation process from an initial configuration of random coils to proto-filaments with cross-β structures and demonstrate how kinetics dictates the structural details of the fully formed fibril. Fibrillization kinetics depends strongly on the temperature. Nucleation and templated growth via monomer addition occur at and near a transition temperature above which fibrils are unlikely to form. Oligomeric merging and structural rearrangement are observed at lower temperatures.

[1]In collaboration with Mookyung Cheon, Iksoo Chang, Pusan University; and David Latshaw, North Carolina State University.