52e Simulation of Polyglutamine Aggregation with an Intermediate Resolution Protein Model

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Aggregation of fibril forming peptides in the brain is either a cause or an associated symptom of many neurodegenerative disorders including Huntington's disease. The molecular level mechanisms by which these proteins aggregate are still unclear. In an effort to shed light on this important phenomenon, we are investigating the aggregation of model fibril-forming peptides using molecular-level computer simulation. A simplified model of polyglutamine, the protein that is known to form fibrils (ordered aggregates of proteins in beta-sheet conformations) in the brains of victims of Huntington's disease, has been developed. This model accounts for the most important types of intra- and inter-molecular interactions - hydrogen bonding and hydrophobic interactions - while allowing the folding process to be simulated in a reasonable time frame. The model utilizes discontinuous potentials such as hard spheres and square wells in order to take advantage of discontinuous molecular dynamics (DMD), a fast simulation technique that is very computationally efficient. DMD is used to examine the folding and aggregation of systems of model polyglutamine peptide ranging in size from isolated peptides to systems of 96 peptides. The effects of chain length, concentration, temperature, interaction strengths, and system size will be presented. Our model peptides form amorphous aggregates at low temperatures, ordered aggregates with significant beta sheet character at intermediate temperatures, and random coils at high temperatures. We have found that the temperature at which the model peptides undergo the transition from amorphous aggregates to ordered aggregates and the temperature at which the model peptides undergo the transition from ordered aggregates to random coils increase with increasing chain length. This may explain the experimentally observed relation between polyglutamine tract length and aggregation in vitro and disease progression in vivo.