587f Computer Simulation of Fibril Forming Peptides

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Assembly of normally soluble proteins into ordered aggregates, known as amyloid fibrils, is a cause or associated symptom of numerous human disorders, including Alzheimer's and the prion diseases. The long term goal of our work is to determine the underlying physical forces responsible for the misfolding and aggregation of proteins. Our objective is to extend the intermediate-resolution protein model, PRIME (Protein Intermediate Resolution Model), that we have already developed for polyalanine to the description of disease-specific proteins, such as the protein implicated in Alzheimer's disease, β-Amyloid, and the short oligomers found in the Syrian hamster prion protein (AGAAAAGA) and the mouse prion protein (VAGAAAAGAV). PRIME is well suited for modeling protein aggregation because it provides a faithful representation of protein geometry while also capturing the essential features of the forces responsible for protein folding, hydrogen bonding and hydrophobicity. We apply discontinuous molecular dynamics (DMD) to PRIME models of AGAAAAGA or VAGAAAAGAV to study the assembly of systems containing 48 peptides into ordered structures at various peptide concentrations and temperatures. Both the Syrian hamster prion oligomers and the mouse prion oligomers form fibrils at concentration, c = 5 mM and reduced temperatures at or around T*=0.12, starting from an initial configuration of random coils. At temperatures less than or equal to T*=0.11, the peptides form amorphous aggregates, but at temperatures greater than or equal to T*=0.13, the peptides remain as random coils. Preliminary results on the aggregation of the Alzheimer's peptide, β-Amyloid (10-40) and (10-42) will also be presented. Movies will be shown of the aggregation process.