Understanding Aggregation Diseases from Physical Principles

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Protein folding, the process by which an amino acid chain finds the stable structure integral to its function, has been a well-defined problem for more than 50 years but a predictive solution has continued to elude us. It is clear that the physical interactions within the chain and with the surrounding water determines which structure has the lowest free energy but neither computation nor experiment can completely describe the path a protein might take to find it, in part because there is a huge range of timescales on which important folding events can occur. Additionally, understanding protein folding in a cell also requires understanding how folding competes with aggregation, which leads to diseases such as Parkinson's and Alzheimer's. The complexity and dynamics of unfolded protein ensembles may be the ultimate speed limit of folding and play a crucial role in aggregation. In my lab over the past several years we have investigated the reconfiguration dynamics unfolded proteins by measuring the rate of intramolecular diffusion, the rate one part of the chain diffuses relative to another. We have measured diffusion coefficients ranging over three orders of magnitude and observed that aggregation-prone sequences tend to fall in the middle of this range. In this talk I shall present our experiments on alpha-synuclein, the protein that aggregates in Parkinson disease, and the Alzheimer's peptide. We correlated intramolecular diffusion of the disordered protein with solution conditions that promote aggregation. Finally we have begun measurements on small molecule aggregation inhibitors and found that some can prevent aggregation by shifting intramolecular diffusion out of the dangerous middle range.