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Understanding how unfolded protein dynamics affects neurodegenerative diseases

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Many neurodegenerative diseases, such as Parkinson's and Alzheimer's, are caused by uncontrolled aggregation of proteins. While many aggregation-prone proteins ultimately form fibrillary structures, evidence suggests that early, unstructured aggregates are toxic to neurons. 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 of 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 Alzheimer's peptide and various prion sequences. 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.