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The Mechanisms of Aberrant Protein Aggregation SAMUEL COHEN, Harvard University, University of Cambridge, MICHELE VENDRUSCOLO, CHRIS DOBSON, TUOMAS KNOWLES, University of Cambridge — We discuss the development of a kinetic theory for understanding the aberrant loss of solubility of proteins. The failure to maintain protein solubility results often in the assembly of organized linear structures, commonly known as amyloid fibrils, the formation of which is associated with over 50 clinical disorders including Alzheimer's and Parkinson's diseases. A true microscopic understanding of the mechanisms that drive these aggregation processes has proved difficult to achieve. To address this challenge, we apply the methodologies of chemical kinetics to the biomolecular self-assembly pathways related to protein aggregation. We discuss the relevant master equation and analytical approaches to studying it. In particular, we derive the underlying rate laws in closed-form using a self-consistent solution scheme; the solutions that we obtain reveal scaling behaviors that are very generally present in systems of growing linear aggregates, and, moreover, provide a general route through which to relate experimental measurements to mechanistic information. We conclude by outlining a study of the aggregation of the Alzheimer's amyloid-beta peptide. The study identifies the dominant microscopic mechanism of aggregation and reveals previously unidentified therapeutic strategies.

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