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An energy landscape approach to protein aggregation ALEXANDER BUELL, TUOMAS KNOWLES, University of Cambridge, Department of Chemistry — Protein aggregation into ordered fibrillar structures is the hallmark of a class of diseases, the most prominent examples of which are Alzheimer's and Parkinson's disease. Recent results (e.g. Baldwin et al. J. Am. Chem. Soc. 2011) suggest that the aggregated state of a protein is in many cases thermodynamically more stable than the soluble state. Therefore the solubility of proteins in a cellular context appears to be to a large extent under kinetic control. Here, we first present a conceptual framework for the description of protein aggregation (see AK Buell et al., Phys. Rev. Lett. 2010) that is an extension to the generally accepted energy landscape model for protein folding. Then we apply this model to analyse and interpret a large set of experimental data on the kinetics of protein aggregation, acquired mainly with a novel biosensing approach (see TPJK Knowles et al, Proc. Nat. Acad. Sc. 2007). We show how for example the effect of sequence modifications on the kinetics and thermodynamics of human lysozyme aggregation can be understood and quantified (see AK Buell et al., J. Am. Chem. Soc. 2011). These results have important implications for therapeutic strategies against protein aggregation disorders, in this case lysozyme systemic amyloidosis.

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