Phase behaviour and transitions in complex biological systems

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Introduction

My research is focused on the application of theoretical computational tools developed in soft condensed matter physics to investigate the phase behaviour and transitions of complex systems of biomolecules. From a purely statistical mechanical point of view an ensemble of many peptides and proteins represents a new and important system which should bridge our understanding of colloidal systems, polymers, and proteins. The research highlights in the year 2012 were our Molecular Dynamics simulation of a model peptide system addressing the question of the importance of kinetics and thermodynamics in protein aggregation and the application of nucleation theory to describe the two-step nucleation of amyloid fibrils.

Protein aggregation: kinetics versus thermodynamics

In this study, we address the questions of how important are the kinetics in protein aggregation, and what are the intrinsic properties of proteins that cause this behavior. On the basis of our recent quantitative calculation of the equilibrium phase diagram of natively folded α-helical and β-sheet forming peptides, we perform molecular dynamics simulations to demonstrate how the aggregation mechanism and end product depend on the temperature, concentration, and starting point in the phase diagram. The results obtained show that there are severe differences between the thermodynamically predicted and the kinetically obtained aggregate structures. The observed differences help to rationalize the suggestion that monomeric proteins in their native functional structure can be metastable with respect to the amyloid state, and that the native fold is a special property that protects them from aggregation.

Two-step nucleation of amyloid fibrils: omnipresent or not?

Amyloid protein fibrils feature in various diseases and nanotechnological products. Currently, it is debated whether they nucleate in one step (i.e. directly from the protein solution) or in two steps (step one being the appearance of nonfibrillar oligomers in the solution and step two being the oligomer conversion into fibrils). In this work we employ nucleation theory to gain insight into the idiosyncrasy of two-step fibril nucleation (Figure 1) and to determine the conditions

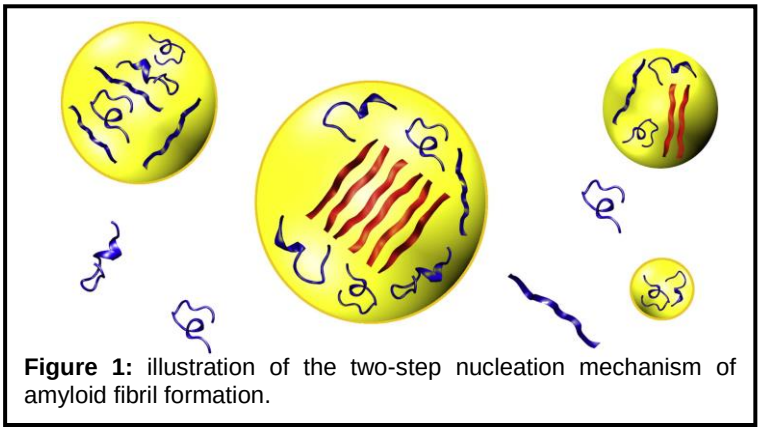

Figure 1: illustration of the two-step nucleation mechanism of amyloid fibril formation.

under which this process can take place. Presenting an expression for the rate of two-step fibril nucleation, we use it to qualitatively describe experimental data for two-step nucleated amyloid-β fibrils. Our analysis helps in understanding why, in some experiments, oligomers

rather than fibrils form and remain structurally unchanged and why, in others, the oligomers convert into fibrils.

Publications

Auer, S., Ricchiuto, P. & Kashchiev, D. (2012) Two-step nucleation of amyloid fibrils: omnipresent or not? *J. Mol. Biol.* **422:** 723-730.

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Collaborators

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