Structures and Kinetics of Amyloid-like Superstructures I: Experiments

Structures and Kinetics of Amyloid-like Superstructures II: Theory and Modeling

Vito Foderà

Sector for Biologics, Department of Pharmacy, University of Copenhagen, Denmark

Background: Protein deposits are mainly formed by elongated amyloid fibrils that are characterized by a common cross-β structure, possibly presenting different isoforms. Moreover, both *in vivo* and *in vitro*, amyloid aggregates may generally conserve their basic structural arrangement of cross β-sheet, yet exhibit significantly different packing into three-dimensional superstructures. Specifically, a number of model proteins have been shown to aggregate into different forms (i.e. particulates and spherulites), mainly depending on the pH of the solution [1]. Recently, such superstructures have been suggested to potentially have a role in human amyloid pathologies [2].

Questions addressed and Methods: We wanted to address the physical origin of the formation of the above mentioned superstructures and connect the thermodynamics of the aggregation process to the development of the structure. In parallel, an experimental characterization of both kinetics and structures at different time and length scales is necessary to validate the models. Standard biophysical techniques combined with advanced optical microscopy and ab initio modeling of small angle X-ray scattering data are used. Theoretical models are based on free energy calculations and simulations are performed by means of Metropolis Monte Carlo (MC) simulations and the fibrillation dynamics by means of dynamic Monte Carlo.

Results and discussion: The developed theoretical model for superstructures predicts the formation of multi-fractal structures with the geometry of the growth determined by the electrostatic interactions between single proteins [3]. The model predictions are successfully verified in comparison with experimental curves for aggregate growth allowing us to reveal the mechanism of formation of spherulites. Moreover, our 2D model for protein allowed as to study the amyloid-like fibril formation and is able to recover the main features of a fibrillation process [4]. From an experimental point of view we revealed the origin of particulate formation, isolating the low-resolution structural features of the intermediate species from which such superstructure may originate [5].

References:

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Info: http://www.vitofodera.com/
Email: vito.fodera@sund.ku.dk