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On the construction of amiloid growth models

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Amyloid diseases are group of widespread neurodegenerative disorders such as Alzheimer's, Parkinson's, Creutzfeldt–Jakob's, Huntington's diseases, etc. They all are associated with starch-like deposits of insoluble 80 to 150 nm protein fibrils in the brain neurons causing neuronal death or deterioration of the interneuron contacts. In different diseases, the insoluble fibrils include different misfolded proteins enriched in beta-sheet structures, which is the reason reason to classify these diseases as beta-sheet diseases. The most common among the amyloid neuropathies is the Alzheimer's disease, affecting 6–10% of the population over the age above 65. The cost of their medical and social care worldwide is estimated at more than one trillion US dollars annually. Amyloid plaques in Alzheimer's disease are formed mainly by the aggregation of the amyloid beta proteins (Aβ). It is composed of 39 to 43 amino acids polypeptides originating from a larger transmembrane protein known as amyloid-beta precursor protein (APP). The shorter Aβ peptides are released by two proteases called gamma secretase and beta secretase. Since the Aβ structures are dominated by beta-sheets, they easily aggregate in the form of fibrils.

The formation of amyloid fibrils is a multi-step process, involving nucleation, elongation and maturation. This complex process can be studied both in terms of of molecular mechanism of protein interaction and kinetics of amyloid fibrils formation. In the first case, a good knowledge on the fine molecular structure of the monomeric proteins is required, whereas for studying the kinetics of fibril growth the molecular mechanism of interaction is not essential since the fibril growth can be regarded as an act of joining new particles (monomers) to a linearly growing chain.

The kinetics of formation and growth of amyloid fibrils depends on many factors such as the concentration of the reacting components, temperature, viscosity, binding energy, etc. From a practical point of view, it is important to know

the growth phases details and also how the polymerization/depolymerization equilibrium can be shifted towards depolymerization, i.e. how the amyloid plaques can be dissolved.

In this work we discuss some methodological aspects of the creation and formulation of mathematical models describing amyloid fibrils growth from the point of view of reaction kinetics. We propose and study several reaction network models for the amiloid fibrillation processes in the citoplasm. Recent intensive research into the physicochemical properties of amyloid and its formation into fibrils points attention to mathematical growth models [1, 2]. In [2] the authors consider the growth of single amyloid fibrils and look for a mechanistic explanation of the process in terms of a biochemical reaction network.

Fibril is an olygomer composed by monomers, thus model [2] involves two reactants: fibril F and monomer M, and additionally an intermediate reactant C. Reacrant C is the fibril "in action", that is the fibril that at the given time instant is in the process of storing the monomer molecule (adding it to self in a compact form). We present several reaction kinetic models that upgrade models presented in [1] and [2] based on recent research in the detailed fibril growth mechanisms, see e.g. [3, 4, 5]. Our models may be useful in explaining certain particular steps of the fibril growth process and certain issues of interest (such as the lag phase). Our discussion is based on familiar case studies of biological growth models using reaction network theory, such as enzyme kinetics, logistic and Gompertz growth. The solutions of the presented models are sigmoidal functions graphically visualized using computer algebra systems [1, 2, 3, 4, 5].

Keywords: amiloid fibril growth, reaction kinetic

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