

NETWORK THERMODYNAMIC ANALYSIS OF PROTEIN AGGREGATION

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ABSTRACT

The formation of A-beta fibril plaques in the human brain has been widely studied and considered important in the pathogenesis of Alzheimer-disease (AD). Low-molecular weight A-beta oligomers are however; now thought to be a primary precursor in early AD affected brains. Prior conjectures and new experiments emphasize the interaction between A-beta and fatty acids which catalyzes an alternative, off-pathway aggregation mechanism. These off-pathway aggregates are being singled out as especially related to AD. In our theoretical study, we aspire to better understand the origins of the off-pathway kinetics and explore ways to control their aggregation. To such ends, we develop a reduced order chemical network model which captures the essential biophysical traits of the on- and off-pathway aggregation processes. We employ a game-theoretic approach to the mass-action based complex dynamical system representing the evolutions of the various species. Numerical computations of the system help us determine the conditions under which like species in each of the pathways dominate which are aptly represented using a phase diagram. A very useful outcome of this phase analysis is the identification of specific reaction topologies along which the dominant reactions occur. Of the eight identified four end up as on-pathway fibrils while the other half end up as off-pathway fibrils. The question we wish to address next is seek out interventions which can help change some of these outcomes, i.e. change network topologies to terminate in an on-pathway. This is mathematically performed by means of seeding by appropriate oligomers and fibrils which is seen to significantly change the observed phases. The presentation will provide details of the seeding studies and the favorable interventions. By varying the parameters and studying their interplay we can determine regimes where pathologically preferential pathways are dominant. The network complexity gives rise to intense dependence on parameters and initial conditions. One further focus of our study is in the thermodynamic properties of our network. We examine quantities integral to the underlying chemical networks like free energy. The tools of classic network thermodynamics help us better understand the stability of the network models.

Keywords: network thermodynamics, game-theory, protein aggregation