Dynamic renormalisation group theory reveals sequential mechanism of oligomer generation in protein aggregation

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A key question in modern biochemistry and molecular biology is to determine the molecular pathways that control the overall kinetics of complex biochemical processes. Questions about mechanisms are usually difficult to answer using experimental techniques only, which can give clues, but rarely produce alone conclusive evidence for a given mechanism in systems characterised by the complexity of many biochemical processes. This limitation makes theoretical modelling an important tool as a complement to the experimental techniques.

An important class of biochemical processes, which are increasingly linked with biological function and disfunction, is the self-assembly of filamentous structures from soluble proteins. To date, only solutions to particular cases or solutions to the equations describing average quantities such as filament mass have been derived, which have identified monomer dependent secondary nucleation as the dominant mechanism in the aberrant self-assembly of soluble proteins into filaments[1]. A detailed knowledge of the sequential mechanisms behind the process of secondary nucleation, however, has been challenging to access, yet it is crucial for improving our understanding of the formation of low molecular weight oligomeric species, which appear likely to be the most toxic species.

We used the theoretical framework provided by the time dependent real-space renormalisation group (RG)[2] to connect the macroscopic features of fibril formation to the microscopic mechanisms of secondary nucleation through progressively more coarse-grained descriptions that yield simplified models to be compared with kinetic data. By analysing data from the polymerisation of islet amyloid polypeptides and the amyloid-β peptide Aβ42 into amyloid fibrils, we conclude that pre-critical nuclei stay attached to the aggregates during the process of secondary nucleation.

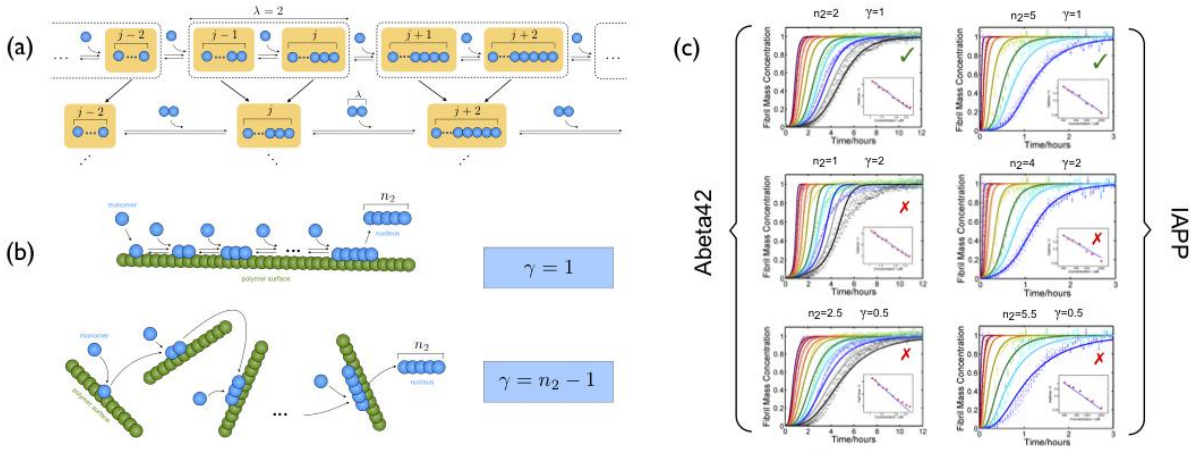

Figure 1 (a) Schematic representation of the RG transformation for nucleated polymerisation processes with representative decimation parameter $\lambda = 2$. (b) The RG analysis predicts that the various possible microscopic pictures of the secondary nucleation process are reflected by a different dependence of the secondary nucleation rate on the concentration of total fibril mass and soluble monomer. In particular, $r_2 = k_2 m(t)^{n2} M(t)^{\gamma}$, where $m(t)$ is the free monomer concentration and $M(t)$ is the polymer mass concentration. We display two limiting mechanisms of secondary nucleation. (c) RG theoretical analysis of the aggregation kinetics of Abeta42 and IAPP. The global fittings indicate clearly that the only combination of parameters compatible with the data corresponds to $\gamma = 1$ and $n_2 = 2, 5$, corresponding to the scenario, where new formed nuclei grow on the fibril surface before detaching.

[1] Cohen, S.I.A., et al. Proliferation of amyloid-β42 aggregates occurs through a secondary nucleation mechanism. Proc. Natl.Acad. Sci. U S A. 110, 9758 (2013)

[2] Suzuki, M.S., et al. Real-space renormalization group approach to critical dynamics. Prog. Theor. Phys. 61, 864 (1979)