SUPPORTING INFORMATION

Dissecting the Kinetic Process of Amyloid Fiber Formation through Asymptotic Analysis

Liu Hong,[1,2] Xianghong Qi,[1] Yang Zhang[1,3*]

[1]*Center for Computational Medicine and Bioinformatics, University of Michigan, 100 Washtenaw Ave, Ann Arbor, MI 48109, USA.*

[2]*Zhou Pei-Yuan Center for Applied Mathematics, Tsinghua University, Beijing, 100084, P. R. China.*

[3]*Department of Biological Chemistry, University of Michigan, 100 Washtenaw Ave, Ann Arbor, MI 48109, USA.*

[*]To whom correspondence should be addressed. E-mail: zhng@umich.edu

Conformational Transition

To consider the process of protein structure unfolding and refolding (or structure conversion), we add a new reaction to the original model, i.e. $A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B$, where A represents proteins with specific conformations before fibrillation, B is proteins with specific conformations after fibrillation, and k_2 represent the forward and backward reaction rates of structure conversion, respectively. Here, all terms concerning $m(t)$ in Eq. 1 should be replaced by $m_B(t)$ -- the concentration of monomers in conformation B. If we further assume that monomers in conformations A and B are in fast equilibrium compared to other fibrillation processes, such that $k_1 m_A(t) = k_2 m_B(t)$, we will recover Eq. 1 by defining

$$\begin{cases} k_+^{'} = \dfrac{k_1}{k_1 + k_2} k_+ \\ k_n^{'} = (\dfrac{k_1}{k_1 + k_2})^{n_c} k_n \end{cases} \qquad \text{(S1)}$$

A comparison of numerical solutions of the original model and the extended models is presented in Figure S1.

As we can see that even the fast equilibrium approximation is so strictly satisfied, our above treatment is still valid as long as enough unfolded monomers can be provided for fiber elongation process (the red and black lines). However, if the reaction rates for protein structure conversion are lowered further more, the results produced by considering protein structure unfolding and refolding will greatly differ from the original case (the purple and green lines.).

FIGURES

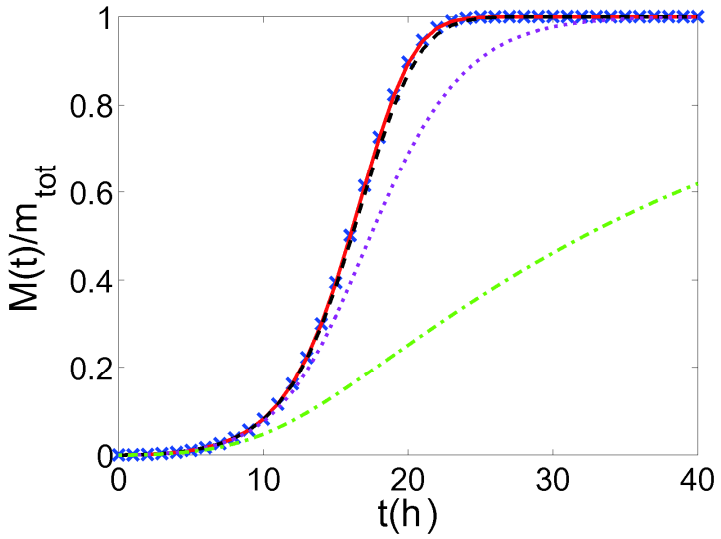

Figure S1. Comparison of numerical solutions of the original model and extended model under different reaction rates for protein structure conversion. The blue crosses represent the solution of the original model based on Eq. 1, with parameters of $k_+ = 5\times10^4 M^{-1}s^{-1}$, $k_- = 2\times10^{-8} s^{-1}$, $k_n = 2\times10^{-5} M^{-1}s^{-1}$, $n_c = 2$, and $m_{tot} = 5\times10^{-6} M$. The numerical solutions of the extended model are calculated under four different sets of reaction rates for protein structure conversion, i.e. $k_1 = 10^{-2} M^{-1}s^{-1}$, $k_2 = 9.9\times10^{-1} M^{-1}s^{-1}$ (red solid line); $k_1 = 10^{-3} M^{-1}s^{-1}$, $k_2 = 9.9\times10^{-2} M^{-1}s^{-1}$ (black dotted line); $k_1 = 10^{-4} M^{-1}s^{-1}$, $k_2 = 9.9\times10^{-3} M^{-1}s^{-1}$ (purple dashed line); and $k_1 = 10^{-5} M^{-1}s^{-1}$, $k_2 = 9.9\times10^{-4} M^{-1}s^{-1}$ (green dashed and dotted line). Examples with even higher reaction rates of k_1, k_2, which will give similar plots as the red solid line, are not further shown for simplicity. Other model parameters are fixed as $k_+ = 5\times10^6 M^{-1}s^{-1}, k_- = 2\times10^{-8} s^{-1}, k_n = 2\times10^{-1} M^{-1}s^{-1}$, $m_{tot} = 5\times10^{-6} M$ and $n_c = 2$.

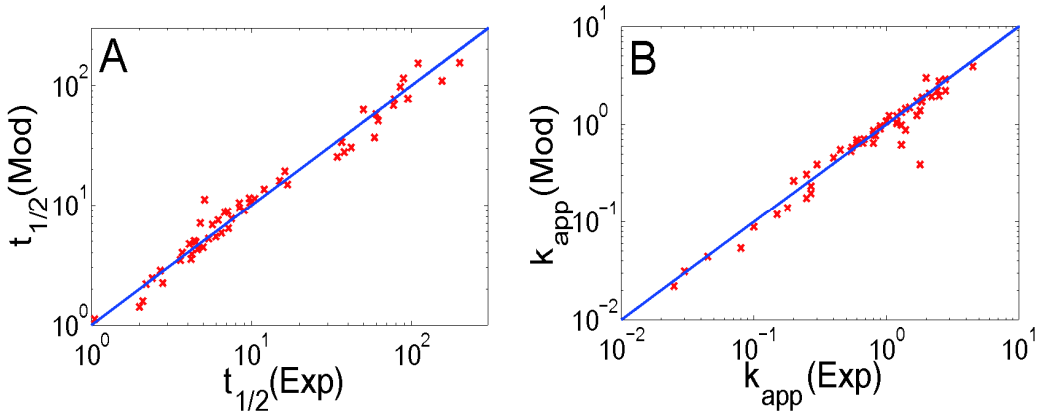

Figure S2. The log-log correlation between the experimental data, taken from eight Type-I amyloid proteins (the yeast prion Sup35 NW region, Csg B_{trunc}, Ure2 protein, β2-microglobulin, stefin B, α-synucleins, WW domain and insulin), and the estimated data via Eqs. 5 and 6 separately. (A) Correlation for the half-time of fiber formation $t_{1/2}$ with a Pearson correlation coefficient $r = 0.95$. (B) Correlation for the apparent fiber growth k_{app} with a Pearson correlation coefficient $r = 0.94$.