How to Determine the Size of Folding Nuclei of Protofibrils from the Concentration Dependence of the Rate and Lag-Time of Aggregation. I. Modeling the Amyloid Protofibril Formation

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1. Linear regime of growth

This regime (see Fig. 2) is described by the following system of equations:

$$\begin{cases} \dfrac{d[P]}{dt} = 2k_{+}n_{s}[M]^{n^{*}} \\[3mm] \dfrac{d[M]}{dt} \approx -k_{2}[P][M] \;, \end{cases} \qquad (S.1.1)$$

where [M] is the concentration of free monomers, [P] is the total concentration of ends of all stable polymers (which is twice greater than concentration of all stable polymers), n^{*} is the effective number of monomers in the nucleus (i.e., in the most unstable polymer intermediate), n_{s} is the number of monomers in the seed (i.e., in the shortest stable polymer intermediate; $n^{*} < n_{s}$), and k_{+}, k_{2} are the corresponding rate constants for initiation and elongation of polymers (see Fig. 2 and equations (1) of the main text).

Equations (1) can be strictly solved in the following way. Define $Z = ([M]/[M_{\Sigma}])^{n^{*}}$, where $[M_{\Sigma}]$ is the total concentration of free and aggregated monomers (thus, $[M] = [M_{\Sigma}] \cdot Z^{1/n^{*}}$). Then:

$$\begin{cases} \dfrac{d[P]}{dt} = 2k_{+}n_{s}[M_{\Sigma}]^{n^{*}} \cdot Z \;; \\[3mm] \dfrac{d[M]}{[M]\,dt} = -k_{2}[P] \text{, that is: } \dfrac{d}{dt}\ln(Z) = -n^{*}k_{2}[P] \end{cases} \qquad (S.1.2)$$

At the beginning of the process, all monomers are free (i.e., $[M]_{t=0} = [M_{\Sigma}]$) and thus $[P]_{t=0} = 0$; $Z_{t=0} = 1$; $\dfrac{d}{dt}\ln(Z)\big|_{t=0} = 0$; at the end of the process, all monomers are involved in aggregates; thus, $Z_{t=\infty} = 0$.

Excluding [P] from the system (S.1.2) by the differentiation $\dfrac{d^{2}}{dt^{2}}\ln(Z) = -n^{*}k_{2}\dfrac{d}{dt}[P]$, one obtains

$$\frac{d^{2}}{dt^{2}}\ln(Z) = -AZ, \qquad (S.1.3)$$

where

$$A = 2k_{2}k_{+}n_{s}n^{*}[M_{\Sigma}]^{n^{*}} > 0. \qquad (S.1.4)$$

Multiplying both sides of equation (S.1.3) by $\dfrac{d}{dt}\ln(Z)$, one obtains: $\dfrac{1}{2}\dfrac{d}{dt}\left\{\left[\dfrac{d}{dt}\ln(Z)\right]^{2}\right\} = -A\dfrac{dZ}{dt}$,

and thus:

$$\left[\frac{d}{dt}\ln(Z)\right]^2 + 2AZ = const.$$

Here, $const = 2A$, because, at $t=0$, $Z_{t=0}=1$ and $\frac{d}{dt}\ln(Z)\big|_{t=0}= 0$; thus

$$\frac{d}{dt}\ln(Z) = -\sqrt{2A}\sqrt{1-Z};$$

the choice of "-" sign follows from the descent of $Z = ([M]/[M_\Sigma])^{n^*}$ (and of $[M]$) with the growth of t. Thus:

$$\frac{dZ}{Z\sqrt{1-Z}} = -\sqrt{2A}\,dt.$$

Using substitution $x = \sqrt{1-Z}$, one has $Z = 1 - x^2$ (i.e., $dZ = -2xdx$); thus

$$\frac{dZ}{Z\sqrt{1-Z}} = \frac{-2xdx}{(1-x^2)x} = \frac{-2dx}{(1-x^2)} = \frac{-dx}{1-x} + \frac{-dx}{1+x} = d\left[\ln\left(\frac{1-x}{1+x}\right)\right] = d\left[\ln\left(\frac{1-\sqrt{1-Z}}{1+\sqrt{1-Z}}\right)\right]$$

or

$$\ln\left(\frac{1-\sqrt{1-Z}}{1+\sqrt{1-Z}}\right) + \sqrt{2A}\,t = const',\ \text{where}\ const' = 0,\ \text{because}\ Z = 1\ \text{at}\ t=0.\ \text{Thus,}$$

$$\frac{1-\sqrt{1-Z}}{1+\sqrt{1-Z}} = \exp\left(-\sqrt{2A}t\right),\ \text{and}$$

$$Z = 1 - \left[\frac{1-\exp\left(-\sqrt{2A}t\right)}{1+\exp\left(-\sqrt{2A}t\right)}\right]^2, \qquad\qquad (S.1.5)$$

or

$$Z \equiv \left(\frac{[M]}{[M_\Sigma]}\right)^{n^*} = \frac{4\exp\left(-\sqrt{2A}t\right)}{\left[1+\exp\left(-\sqrt{2A}t\right)\right]^2}.$$

At last,

$$\frac{[M]}{[M_\Sigma]} = \frac{4^{1/n^*}\exp\left(-\sqrt{2A}t/n^*\right)}{\left[1+\exp\left(-\sqrt{2A}t\right)\right]^{2/n^*}} \equiv \frac{4^{1/n^*}\exp(-t/T)}{\left[1+\exp(-n^*t/T)\right]^{2/n^*}}, \qquad\qquad (S.1.6),$$

where

$$T \equiv n^*/\sqrt{2A} = \sqrt{n^*/(4k_2k_+n_s)}\cdot[M_\Sigma]^{-n^*/2} \qquad\qquad (S.1.7)$$

is a characteristic time of the descent of $[M]$ at $t \to \infty$, i.e., at the end of the polymerization reaction.

The ratio of the lag-phase to the growth phase can be estimated as follows.

1) $\mu(t) \equiv 1 - \frac{[M]_t}{[M_\Sigma]} = \frac{4^{1/n^*}\exp(-t/T)}{\left[1+\exp(-n^*t/T)\right]^{2/n^*}}$ is the degree of involvement of monomers into the

polymers $[\mu(t=0) = 0,\ \mu(t\to\infty) \to 1]$; $v_t = \frac{d\mu}{dt}(t)$ is the rate of involvement of monomers into the polymers at time t.

2) $t_{v_{max}}$ is the time moment at which the rate of involvement of monomers into polymers reaches

its maximum (v_{max}), i.e., $\frac{d^2\mu}{dt^2}(t_{v_{max}}) = 0$. At this time moment, $v_{max} = \frac{d\mu}{dt}(t_{V\,max})$.

3) $T_2 = 1/v_{max}$ is the characteristic duration of the growth period of aggregates;

4) $T_{Lag} = t_{v_{max}} - \mu(t_{v_{max}})/v_{max}$ is the duration of the lag period;

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5) $L_{rel} = T_{Lag}/(1/v_{max}) = T_{Lag} \cdot v_{max}$.

$t_{v_{max}}$ is calculated as follows:

$$\mu = 1 - \frac{4^{1/n^*} x}{\left[1 + x^{n^*}\right]^{2/n^*}} \text{, where } x = \exp(-t/T);$$

$$\nu \equiv \frac{d\mu}{dt} = \left[d\left(1 - \frac{4^{1/n^*} x}{\left[1 + x^{n^*}\right]^{2/n^*}}\right) / dx \right] \cdot \left[\frac{dx}{dt} \right]$$

$$= \left[-4^{1/n^*} \left(\frac{1 \cdot \left[1 + x^{n^*}\right]^{2/n^*} - x \frac{2}{n^*}\left[1 + x^{n^*}\right]^{(2/n^*-1)} \cdot n^* x^{n^*-1}}{\left[1 + x^{n^*}\right]^{4/n^*}} \right) \right] \cdot \left[-\frac{x}{T} \right]$$

$$= 4^{1/n^*} \left[1 + x^{n^*}\right]^{(2/n^*-1)} \left[\left(\frac{1 + x^{n^*} - x \frac{2}{n^*} \cdot n^* x^{n^*-1}}{\left[1 + x^{n^*}\right]^{4/n^*}} \right) \right] \cdot \left[\frac{x}{T} \right]$$

$$= \frac{4^{1/n^*}}{T} \left(\frac{x - x^{n^*+1}}{\left[1 + x^{n^*}\right]^{(2/n^*+1)}} \right);$$

$$\frac{d^2\mu}{dt^2} = \frac{4^{1/n^*}}{T} \left[d\left(\frac{x - x^{n^*+1}}{\left[1 + x^{n^*}\right]^{(2/n^*+1)}} \right) / dx \right] \cdot \left[\frac{dx}{dt} \right] \propto \left[d\left(\frac{x - x^{n^*+1}}{\left[1 + x^{n^*}\right]^{(2/n^*+1)}} \right) / dx \right]$$

$$= \frac{(x - x^{n^*+1})' \left[1 + x^{n^*}\right]^{(2/n^*+1)} - (x - x^{n^*+1})\{\left[1 + x^{n^*}\right]^{(2/n^*+1)}\}'}{\left[1 + x^{n^*}\right]^{(4/n^*+2)}}$$

$$\propto [1 - (n^*+1)x^{n^*}] \cdot \left[1 + x^{n^*}\right]^{(2/n^*+1)} - (x - x^{n^*+1})(2/n^*+1)\left[1 + x^{n^*}\right]^{(2/n^*)} n^* x^{n^*-1}$$

$$\propto [1 - (n^*+1)x^{n^*}] \cdot \left[1 + x^{n^*}\right] - (1 - x^{n^*})(2 + n^*)x^{n^*}$$

$$= [1 + x^{n^*} - (n^*+1)x^{n^*} - (n^*+1)x^{2n^*}] + [-(2 + n^*)x^{n^*} + (2 + n^*)x^{2n^*}]$$

$$= 1 + [x^{n^*} - (n^*+1)x^{n^*} - (2 + n^*)x^{n^*}] - [(n^*+1)x^{2n^*} - (2 + n^*)x^{2n^*}]$$

$$= 1 + x^{n^*}[1 - n^* - 1 - 2 - n^*)] - x^{2n^*}[n^*+1 - 2 - n^*)]$$

$$= 1 - x^{n^*} \cdot 2(n^*+1) + x^{2n^*}.$$

Because $\frac{d^2\mu}{dt^2} = 0$ at $t = t_{v_{max}}$, the corresponding x value is obtained from $x^{2n^*} - x^{n^*} \cdot 2(n^*+1) + 1 = 0$. Thus,

$$x^{n^*} = (n^*+1) \pm \sqrt{(n^*+1)^2 - 1}.$$

Because $x = \exp(-t/T)$ and $T, t \geq 0$, we have $0 \leq x \leq 1$ and $0 \leq x^{n^*} \leq 1$ at $n^* \geq 0$. So,

$$x_{v_{max}}^{n^*} = (n^*+1) - \sqrt{(n^*+1)^2 - 1}.$$

Thus,

$$\exp\!\left(-\,t_{v_{\max}}/\mathrm{T}\right)=x_{v_{\max}}=\left((n^{*}+1)-\sqrt{(n^{*}+1)^{2}-1}\right)^{1/n^{*}}$$

$$t_{v_{\max}}/\mathrm{T}=-\ln(x_{v_{\max}})=-\frac{1}{n^{*}}\ln\!\left((n^{*}+1)-\sqrt{(n^{*}+1)^{2}-1}\right).$$

Now, we can find $v_{\max}=\dfrac{d\mu}{dt}(t_{v_{\max}})$:

$$\frac{d\mu}{dt}=\left[d\!\left(1-\frac{4^{1/n^{*}}x}{\left[1+x^{n^{*}}\right]^{2/n^{*}}}\right)\!/dx\right]\cdot\left[\frac{dx}{dt}\right]=\frac{4^{1/n^{*}}}{\mathrm{T}}\!\left(\frac{x-x^{n^{*}+1}}{\left[1+x^{n^{*}}\right]^{(2/n^{*}+1)}}\right),$$

where (and below) $x\equiv x_{v_{\max}}=\left[(n^{*}+1)-\sqrt{(n^{*}+1)^{2}-1}\right]^{1/n^{*}}$ is a function of n^{*} only and does not depend on $[\mathrm{M}_{\Sigma}]$.

Now we can calculate $\mathrm{T}_{2}=1/v_{\max}$, which is a characteristic duration of the growth of aggregates;

$$\mathrm{T}_{2}=1/v_{\max}=\frac{\mathrm{T}}{4^{1/n^{*}}}\!\left(\frac{\left[1+x^{n^{*}}\right]^{(2/n^{*}+1)}}{x-x^{n^{*}+1}}\right),\tag{S.1.8}$$

Now, we can find $\mathrm{T}_{\mathrm{Lag}}=t_{v_{\max}}-\mu(t_{v_{\max}})\times[1/v_{\max}]$, the duration of the lag-period:

$$\mathrm{T}_{\mathrm{Lag}}=-\frac{\mathrm{T}}{n^{*}}\ln\!\left((n^{*}+1)-\sqrt{(n^{*}+1)^{2}-1}\right)-\left(1-\frac{4^{1/n^{*}}x}{\left[1+x^{n^{*}}\right]^{2/n^{*}}}\right)\times\frac{\mathrm{T}}{4^{1/n^{*}}}\!\left(\frac{\left[1+x^{n^{*}}\right]^{(2/n^{*}+1)}}{x-x^{n^{*}+1}}\right)$$

$$=-\mathrm{T}\ln(x)-\mathrm{T}\!\left(\frac{\left[1+x^{n^{*}}\right]^{(2/n^{*}+1)}}{4^{1/n^{*}}(x-x^{n^{*}+1})}-\frac{1+x^{n^{*}}}{1-x^{n^{*}}}\right),\tag{S.1.9}$$

At last, we can find $\mathrm{L}_{\mathrm{rel}}=\mathrm{T}_{\mathrm{Lag}}/(1/v_{\max})=\mathrm{T}_{\mathrm{Lag}}\cdot v_{\max}$.

$$\mathrm{L}_{\mathrm{rel}}=\mathrm{T}_{\mathrm{Lag}}\cdot v_{\max}=\left\{-\mathrm{T}\ln(x)-\mathrm{T}\!\left(\frac{\left[1+x^{n^{*}}\right]^{(2/n^{*}+1)}}{4^{1/n^{*}}(x-x^{n^{*}+1})}-\frac{1+x^{n^{*}}}{1-x^{n^{*}}}\right)\right\}\frac{4^{1/n^{*}}}{\mathrm{T}}\!\left(\frac{x-x^{n^{*}+1}}{\left[1+x^{n^{*}}\right]^{(2/n^{*}+1)}}\right)$$

$$=\left\{-4^{1/n^{*}}\ln(x)-\left(\frac{\left[1+x^{n_{s}}\right]^{(2/n^{*}+1)}}{(x-x^{n^{*}+1})}-4^{1/n^{*}}\frac{1+x^{n^{*}}}{1-x^{n^{*}}}\right)\right\}\!\left(\frac{x-x^{n^{*}+1}}{\left[1+x^{n^{*}}\right]^{(2/n^{*}+1)}}\right),\tag{S.1.10}$$

where $x\equiv x_{v_{\max}}=\left[(n^{*}+1)-\sqrt{(n^{*}+1)^{2}-1}\right]^{1/n^{*}}$.

One can see that $\mathrm{L}_{\mathrm{rel}}$ depends on n^{*} only (and does not depend on $[\mathrm{M}_{\Sigma}]$ or n_{s}, k_{2}, k_{+}), while T, T_{2} and $\mathrm{T}_{\mathrm{Lag}}$ can be presented as some constants (depending on n_{s}, n^{*}, k_{2}, k_{+}), multiplied by $[\mathrm{M}_{\Sigma}]^{-n^{*}/2}$.

2. Exponential regime of growth with "growth from the surface" scenario

The equation that satisfies this regime (see Fig. 4) is:

$$\frac{d[\mathrm{M}]}{dt}=-2k_{+}n_{s}[\mathrm{M}]^{n^{*}}-k_{2}([\mathrm{M}_{\Sigma}]-[\mathrm{M}])\cdot[\mathrm{M}];\tag{S.2.1}$$

here $[\mathrm{M}]$ is the concentration of free monomers, $[\mathrm{M}_{\Sigma}]$ is the total concentration of free and aggregated monomers, $[\mathrm{M}_{\Sigma}]-[\mathrm{M}]$ is the number of sites on amyloid structure available for the

further monomer attachment, $n*$ is the effective number of monomers in the nucleus, n_s is the number of monomers in the seed, and k_+, k_2 are the rate constants for initiation and elongation of polymers (see Fig. 4 and equation (2) of the main text).

Because the difference between $[M_\Sigma]$ and $[M]$ at the beginning of a process is small, this equation can be rewritten in a form that is easy to integrate:

$$\frac{d[M]}{dt} \approx -2k_+n_s[M_\Sigma]^{n*-1}\cdot[M] - k_2([M_\Sigma]-[M])\cdot[M],$$ (S.2.2)

or

$$\frac{d[M]}{dt} \approx -k_2\left(\frac{2k_+n_s[M_\Sigma]^{n*}}{k_2[M_\Sigma]}+[M_\Sigma]-[M]\right)\cdot[M].$$ (S.2.3)

That is, for the early stages of the reaction (until $[M] \ll [M_\Sigma]$):

$$\frac{d[M]}{\left(\frac{2k_+n_s[M_\Sigma]^{n*}}{k_2[M_\Sigma]}+[M_\Sigma]-[M]\right)\cdot[M]} \approx -k_2\,dt,$$ (S.2.4)

or

$$\ln\left(\frac{[M]}{\left(\frac{2k_+n_s[M_\Sigma]^{n*}}{k_2[M_\Sigma]}+[M_\Sigma]-[M]\right)}\right) \approx -k_2\left(\frac{2k_+n_s[M_\Sigma]^{n*}}{k_2[M_\Sigma]}+[M_\Sigma]\right)t+const.$$

At $t=0$, $[M_\Sigma]-[M]=0$, so the constant $const$ equals to

$$\ln\left\{\frac{[M_\Sigma]}{(2k_+n_s[M_\Sigma]^{n*})/(k_2[M_\Sigma])}\right\}.$$

The final solution is:

$$\frac{[M]}{[M_\Sigma]}=\frac{\left(\frac{2k_+n_s[M_\Sigma]^{n*}}{k_2[M_\Sigma]}+[M_\Sigma]\right)\cdot\exp\left(-k_2\left(\frac{2k_+n_s[M_\Sigma]^{n*}}{k_2[M_\Sigma]}+[M_\Sigma]\right)t\right)}{\frac{2k_+n_s[M_\Sigma]^{n*}}{k_2[M_\Sigma]}+[M_\Sigma]\cdot\exp\left(-k_2\left(\frac{2k_+n_s[M_\Sigma]^{n*}}{k_2[M_\Sigma]}+[M_\Sigma]\right)t\right)}$$ (S.2.5)

One can obtain L_{rel} from equation (S.2.5). It is convenient to rewrite (S.2.5) in the following form:

$$\frac{[M]}{[M_\Sigma]}=\frac{(1+\lambda)e^{-xt}}{1+\lambda\cdot e^{-xt}},\text{ and}$$

$$\mu\equiv 1-\frac{[M]}{[M_\Sigma]}=\frac{1-e^{-xt}}{1+\lambda\cdot e^{-xt}},$$ (S.2.6)

where

$$\lambda = \frac{k_2}{2k_+ n_s [M_\Sigma]^{n^*-2}},$$

$$x = k_2 [M_\Sigma](1 + 1/\lambda). \tag{S.2.7}$$

It should be noted that $\lambda \gg 1$ when, as usually, the rate of initiation (connected with k_+) is much smaller than the rate of growth (connected with k_2).

Given the formula (S.2.6), one can easy derive the length of the lag-time and the characteristic time of transition of all monomers into the aggregates.

First, we find the time point $t_{v_{max}}$ where the aggregation rate $v_t = \dfrac{d\mu}{dt} \equiv \dfrac{e^{-xt} \cdot x \cdot (1+\lambda)}{(1 + \lambda \cdot e^{-xt})^2}$

achieves its maximum: $\dfrac{d^2\mu}{dt^2} = \dfrac{(1+\lambda) \cdot e^{-xt} \cdot x^2}{(1 + \lambda e^{-xt})^3}(\lambda e^{-xt} - 1) = 0$, which means that $t_{v_{max}} = \ln(\lambda)/x$.

Now, $\mu(t_{v_{max}}) = \dfrac{\lambda - 1}{2\lambda}$ and $v_{max} = x \cdot \dfrac{1+\lambda}{4\lambda}$. The latter means that a characteristic duration of the growth period is

$$T_2 = 1/v_{max} = \frac{4\lambda}{(1+\lambda)x} = \frac{4}{k_2[M_\Sigma]}, \tag{S.2.8}$$

and the duration of the lag period is

$$T_{Lag} = t_{v_{max}} - \mu(t_{v_{max}})/v_{max} = \frac{\ln(\lambda)}{x} - \frac{\lambda-1}{2\lambda} \cdot \frac{4\lambda}{(1+\lambda)x} = \frac{1}{x}\left(\ln\lambda - 2\frac{\lambda-1}{\lambda+1}\right). \tag{S.2.9}$$

Thus,

$$L_{rel} = T_{Lag}/T_2 = \frac{(\lambda-1)}{4\lambda} \cdot \left(\cdot\frac{\lambda+1}{\lambda-1}\ln(\lambda) - 2\right). \tag{S.2.10}$$

When, as usually (see above) $\lambda = \dfrac{k_2}{2k_+ n_s[M_\Sigma]^{n^*-2}} \gg 1$, the formula for L_{rel} can be rewritten as

$$L_{rel} \approx \frac{1}{4}\left(\ln\lambda - 2\right) = \frac{1}{4}\left(\ln\left\{\frac{k_2}{2k_+ n_s[M_\Sigma]^{n^*-2}}\right\} - 2\right) \tag{S.2.11}$$

3. Exponential regime of growth with the "fragmentation" scenario

This regime (see Fig. 5) is described by the following system of equations at the beginning of the process:

$$\begin{cases} \dfrac{d[P]}{dt} \approx 2k_+[M_\Sigma]^{n^*} + 2\lambda_+ ([M_\Sigma] - [M]) ; \\[2mm] \dfrac{d[M]}{dt} \approx -k_2[P][M_\Sigma]. \end{cases} \tag{S.3.1}$$

Here [M] is the concentration of free monomers, $[M_\Sigma]$ is the total concentration of free and aggregated monomers, [P] is the total concentration of ends of all stable polymers (which is twice greater than concentration of the stable polymers), n^* is the effective number of monomers in the nucleus, λ_+ is the rate constant of bifurcations, and k_+, k_2 are the corresponding rate constants for initiation and elongation of polymers (see Fig. 5). The system (S.3.1) is valid for the beginning of the process where $[M_\Sigma]-[M]<<[M_\Sigma]$ and thus the approximations $[M]^{n^*}\approx[M_\Sigma]^{n^*}$ and $[P][M]\approx[P][M_\Sigma]$ are possible (cf. equations (4) and (4a) of the main text).

Denoting $1-[M]/[M_\Sigma]$ as μ, we have $[M_\Sigma]-[M]\equiv[M_\Sigma]\cdot\mu$. Now we can transform the second equation to $-\dfrac{d\mu}{dt}\approx-k_2[P]$, and, further, $-\dfrac{d^2\mu}{dt^2}\approx-k_2\dfrac{d[P]}{dt}$; now we obtain

$$-\frac{d^2\mu}{dt^2}\approx-k_2(2k_+[M_\Sigma]^{n^*}+2\lambda_+\mu[M_\Sigma])=-(\mu+k_+[M_\Sigma]^{n^*-1}/\lambda_+)/T_2^2,\qquad(S.3.2)$$

where

$$T_2=1/\sqrt{4\lambda_+k_2[M_\Sigma]}\qquad(S.3.3)$$

is the characteristic time of the exponential growth of μ, the fraction of aggregated monomers (thus, $1/T_2$ is the geometric mean between the rate constant for the fragmentation process, λ_+, and the rate $k_2[M_\Sigma]$ for attachment of monomers to the aggregate).

Equation of the type (S.3.2) has a solution of the type

$$\mu=A\exp(t/T_2)+B\exp(-t/T_2)+C\qquad(S.3.4)$$

with $\dfrac{d\mu}{dt}=\left[A\exp(t/T_2)-B\exp(-t/T_2)\right]/T_2$.

At t=0, $[P]=0$, thus, not only $\mu_{t=0}=0$ (whence $A+B+C=0$), but also $-\dfrac{d\mu}{dt}\Big|_{t=0}=0$, so that $A=B=-C/2$, and thus $\mu=A\left[\exp(t/T_2)+\exp(-t/T_2)-2\right]$.

Substitution of this μ in equation (S.3.2) gives

$$-A\left[\exp(t/T_2)+\exp(-t/T_2)\right]/T_2^2=-\left\{A\left[\exp(t/T_2)+\exp(-t/T_2)-2\right]+k_+[M_\Sigma]^{n^*-1}/\lambda_+\right\}/T_2^2;$$

hence

$$2A=k_+[M_\Sigma]^{n^*-1}/\lambda_+\qquad(S.3.5),$$

So,

$$\mu=\frac{k_+[M_\Sigma]^{n^*-1}}{2\lambda_+}\left[\exp(t/T_2)+\exp(-t/T_2)-2\right].\qquad(S.3.6)$$

This equation is valid for the beginning of the process where [M] is still close to $[M_\Sigma]$ (so that $\mu\equiv\{[M_\Sigma]-[M]\}/[M_\Sigma]<1/2$), and the introduced approximations $[M]^{n^*}\approx[M_\Sigma]^{n^*}$ and $[P][M]\approx[P][M_\Sigma]$ are possible (cf. equations (4) and (4a) of the main text).

However, when the rate of fragmentation is significant (i.e., $k_+[M_\Sigma]^{n^*-1}/2\lambda_+<<1$, which means that the rate of fragmentation is much greater than the rate of fibril initiation) the value μ

$\approx {}^1/_2$ is achieved at the time $t_{1/2} >> T_2$. Then this characteristic time of appearance of a half of monomers in an aggregated form, $t_{1/2}$, can be obtained from the equation

$$\frac{k_+[M_\Sigma]^{n^*-1}}{2\lambda_+} \exp(t_{1/2}/T_2) \approx \frac{1}{2} . \tag{S.3.7}$$

Thus,

$$t_{1/2} \approx T_2 \ln\left(\frac{\lambda_+}{k_+[M_\Sigma]^{n^*-1}}\right). \tag{S.3.8}$$

This means that $t_{1/2}/T_2$ is logarithmically dependent on the ratio between velocity of fragmentation and velocity of initiation of aggregation. The characteristic lag-phase duration is

$$T_{lag} \approx t_{1/2} - T_2/2. \tag{S.3.9}$$

Thus, the relative (as compared to growth time T_2) duration of the lag-phase in the case of a significant ($\lambda_+ >> k_+[M_\Sigma]^{n^*-1}$) rate of fragmentation is:

$$L_{rel} = (t_{1/2} - \frac{T_2}{2})/T_2 = \ln\left(\frac{\lambda_+}{k_+[M_\Sigma]^{n^*-1}}\right) - \frac{1}{2} . \tag{S.3.10}$$

4. Exponential regime of growth with the "bifurcation" scenario

This regime (see Fig. 6) is described by the following system of equations:

$$\begin{cases} \dfrac{d[P]}{dt} \approx 2k_+[M_\Sigma]^{n^*} + \lambda'_+[M_\Sigma]^{n_2} \cdot ([M_\Sigma]-[M]) \\ \dfrac{d[M]}{dt} \approx -k_2[P][M_\Sigma] \ , \end{cases} \tag{S.4.1}$$

here [M] is the concentration of free monomers, $[M_\Sigma]$ is the total concentration of free and aggregated monomers, [P] is the concentration of ends of all stable polymers and branches, n^* is the effective number of monomers in the nucleus of a linear polymer, n_2 is the effective number of monomers in the nucleus of a branch, λ'_+ is the rate constant of branching, and k_+, k_2, are the corresponding rate constants for initiation and elongation of polymers (see Fig. 6). The system (S.4.1) is valid for the beginning of the process where $[M_\Sigma]-[M] << [M_\Sigma]$ and thus the approximations $[M]^{n^*} \approx [M_\Sigma]^{n^*}$ and $[P][M] \approx [P][M_\Sigma]$ are possible (cf. equations (6) of the main text).

Generally speaking, the mathematical description of the process of bifurcation, equation (S.4.1), is almost identical to the one used in equation (S.3.1) for the process of fragmentation, with the only substitution $2\lambda_+ \Rightarrow \lambda'_+[M_\Sigma]^{n_2}$. Thus, the solution of this system is:

$$\mu = \frac{k_+[M_\Sigma]^{n^*-1}}{\lambda'_+[M_\Sigma]^{n_2}}\left[\exp(t/T_2) + \exp(t/T_2) - 2\right], \tag{S.4.2}$$

where

$$T_2 = 1/\sqrt{2\lambda'_+ k_2 [M_\Sigma]^{n_2+1}} \;.$$ (S.4.3)

As a result (cf. equations (S.3.8), (S.3.9)), in the case of a significant rate of branching
($\lambda'_+ \gg k_+[M_\Sigma]^{n^*-n_2-1}$),the characteristic time at which aggregation is well developed is

$$t_{1/2} \approx T_2 \ln\left(\frac{\lambda'_+}{2k_+[M_\Sigma]^{n^*-n_2-1}}\right),$$ (S.4.4)

and the relative duration of the lag-phase is

$$L_{rel} = (t_{1/2} - \frac{T_2}{2})/T_2 = \ln\left(\frac{\lambda'_+}{2k_+[M_\Sigma]^{n^*-n_2-1}}\right) - \frac{1}{2}\;.$$ (S.4.5).