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Supplementary Information for

Thermodynamic and kinetic principles for amyloid aggregation inhibitors

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Contents

S1. Kinetic theory of protein aggregation into amyloid fibrils and its inhibition

S1.1. Kinetic equations in the absence of inhibitor. We briefly review here some key aspects of the master equation formalism for amyloid fibril formation. The time course of an amyloid aggregation reaction is described in terms of the underlying microscopic steps (Fig. 1A of the main text) by tracking the evolution of $f(t, j)$, which describes the concentration at time t of fibrillar aggregates consisting of j monomers. $f(t, j)$ satisfies the following (mean-field) master equation (1–4):

$$\frac{\partial f(t,j)}{\partial t} = 2k_+ m(t) f(t, j-1) - 2k_+ m(t) f(t,j) + k_1 m(t)^{n_1} \delta_{j,n_1} + k_2 m(t)^{n_2} \delta_{j,n_2} \sum_i i f(t,j), \quad \text{[S1a]}$$

where $m(t)$ is the concentration of monomers, $\delta_{i,j}$ denotes the Kronecker delta function and

$$k_1 = \text{rate constant for primary nucleation,} \quad [S1b]$$
$$k_2 = \text{rate constant for secondary nucleation,} \quad [S1c]$$
$$k_+ = \text{rate constant for aggregate elongation (growth),} \quad [S1d]$$
$$n_1 = \text{reaction order for primary nucleation,} \quad [S1e]$$
$$n_2 = \text{reaction order for secondary nucleation.} \quad [S1f]$$

A note on reaction orders for fibril nucleation: both primary and secondary nucleation of new filaments are believed to be non-classical, multi-step nucleation processes (4–7). Hence, the reaction orders n_1 and n_2 are in general not equal to the physical size of the critical nuclei (4–7), unlike in classical nucleation theory. Instead, the reaction orders n_1 and n_2 should be thought of as describing the dependence of the rate-limiting step of these nucleation processes on the available monomer (see e.g Refs. (4, 7) for a discussion on the interpretation of reaction orders for amyloid aggregation).

The most common experimental observables in amyloid aggregation typically correspond to coarse-grained fields, including

$$P(t) = \text{aggregate number concentration,} \quad [S2a]$$
$$M(t) = \text{aggregate mass concentration,} \quad [S2b]$$
$$m(t) = \text{monomer concentration.} \quad [S2c]$$

The coarse-grained fields in Eq. (S2) correspond to the lowest principal moments of the aggregate size distribution $f(t, j)$

$$P(t) = \sum_j f(t, j), \quad M(t) = \sum_j j f(t, j). \quad [S3]$$

Hence, the time evolution of $P(t)$ and $M(t)$ is obtained by summation of the master equation Eq. (S1a) over j, yielding (1–4):

$$\frac{\mathrm{d}P(t)}{\mathrm{d}t} = k_1 m(t)^{n_1} + k_2 m(t)^{n_2} M(t), \quad [S4]$$
$$\frac{\mathrm{d}m(t)}{\mathrm{d}t} = -2k_+ m(t)P(t) - n_1 k_1 m(t)^{n_1} - n_2 k_2 m(t)^{n_2} M(t) = -\frac{\mathrm{d}M(t)}{\mathrm{d}t}. \quad [S5]$$

In general, elongation is fast compared to nucleation. Indeed, the steady-state value of the average length of aggregates can be shown to scale as $\sqrt{k_+/(k_2\, m_{\mathrm{tot}}^{n_2-1})}$ (8). Increasing the relative importance of growth over nucleation results in longer fibrils. Since fibrillar aggregates are typically several monomers long ($\sim 10^3$-10^4), secondary (and hence also primary) nucleation must be slow compared to growth. This condition allows us to neglect the nucleation terms in Eq. (S5) in front of the growth term. With this simplification, we thus arrive the following set of differential equations (Eqs. (1) of main text) (1–4):

$$\frac{\mathrm{d}P(t)}{\mathrm{d}t} = k_1 m(t)^{n_1} + k_2 m(t)^{n_2} M(t), \quad [S6a]$$
$$\frac{\mathrm{d}m(t)}{\mathrm{d}t} = -2k_+ m(t)P(t) = -\frac{\mathrm{d}M(t)}{\mathrm{d}t}. \quad [S6b]$$

The terms on the right-hand side of Eq. (S6a) describe the total rate of the formation of new fibrils from primary and secondary nucleation, respectively. Similarly, Eq. (S6b) describes the consumption of monomers (hence buildup of aggregate mass) through elongation. The total mass of monomers m_{tot} is conserved

$$m_{\mathrm{tot}} = m(t) + M(t). \quad [S7]$$

S1.2. Integrated rate laws in the absence of inhibitor. An analytical solution to the aggregation kinetics in the absence of an inhibitor, Eq. (S6), has been obtained previously using self-consistent approaches (1, 2, 4). The underlying idea behind this method consists in using a fixed-point iteration to solve Eq. (S6), a strategy which results is self-consistent solutions of increasing accuracy. In practice, Eq. (S6) can be transformed into a fixed-point equation by formal integration

$$P(t) = k_1 \int_0^t m(s)^{n_1} ds + k_2 \int_0^t m(s)^{n_2} M(s) ds, \quad [S8a]$$
$$M(t) = m_{\mathrm{tot}} \left[1 - \exp\left(-2k_+ \int_0^t P(s) ds\right)\right]. \quad [S8b]$$

Denoting with $\mathcal{A}$ the integral operator on the right-hand side of Eq. (S8) and $\boldsymbol{x} = [P(t), M(t)]$, Eq. (S8) corresponds to a fixed point equation $\boldsymbol{x}(t) = \mathcal{A}[\boldsymbol{x}(t)]$ and the fixed point $\boldsymbol{x}^*$ of $\mathcal{A}$ is precisely the required solution to Eq. (S6). Fixed-point equations can be solved using fixed-point iteration methods by applying the operator $\mathcal{A}$ repeatedly on a starting value $\boldsymbol{x_0}$ sufficiently close to the true solution. In the limit of infinitely many iterations, the fixed-point iteration converges to the true solution

$$\boldsymbol{x}^* = \lim_{n\to\infty} \mathcal{A}^n[\boldsymbol{x_0}]. \quad [S9]$$

As the starting point of our fixed-point iteration we choose the linear solution to Eq. (S6) that emerges by fixing the monomer concentration to a constant and is thus exact at early times, when depletion of monomers is negligible. As we will see below, this starting point yields a highly accurate self-consistent solution already after one step of the fixed-point iteration. Fixing $m(t) \simeq m_{\mathrm{tot}}$ in Eq. (S6) yields a set of linear equations

$$\frac{\mathrm{d}P_0(t)}{\mathrm{d}t} = k_1 m_{\mathrm{tot}}^{n_1} + k_2 m_{\mathrm{tot}}^{n_2} M_0(t), \tag{S10a}$$

$$\frac{\mathrm{d}M_0(t)}{\mathrm{d}t} = 2k_+ m_{\mathrm{tot}} P_0(t), \tag{S10b}$$

where the subscript "0" in P_0 and M_0 indicates the linearised solution. Eq. (S10) can be written in matrix form as

$$\frac{\mathrm{d}\boldsymbol{x_0}}{\mathrm{d}t} = \boldsymbol{A}\boldsymbol{x_0} + \boldsymbol{b} \tag{S11}$$

or, explicitly,

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} P_0(t) \\ M_0(t) \end{pmatrix} = \underbrace{\begin{pmatrix} 0 & k_2 m_{\mathrm{tot}}^{n_2} \\ 2k_+ m_{\mathrm{tot}} & 0 \end{pmatrix}}_{=\boldsymbol{A}} \underbrace{\begin{pmatrix} P_0(t) \\ M_0(t) \end{pmatrix}}_{=\boldsymbol{x_0}} + \underbrace{\begin{pmatrix} k_1 m_{\mathrm{tot}}^{n_1} \\ 0 \end{pmatrix}}_{=\boldsymbol{b}}. \tag{S12}$$

The solution to Eq. (S11) with initial condition $\boldsymbol{x_0}(0) = \boldsymbol{0}$ is

$$\boldsymbol{x_0}(t) = \int_0^t e^{\boldsymbol{A}(t-s)}\boldsymbol{b}\, ds. \tag{S13}$$

To determine the exponential of the matrix $\boldsymbol{A}$ it is convenient to diagonalise $\boldsymbol{A}$ by writing

$$\boldsymbol{A} = \boldsymbol{U}\boldsymbol{D}\boldsymbol{U}^{-1}, \tag{S14}$$

where

$$\boldsymbol{D} = \begin{pmatrix} x_1 & & \\ & x_2 & \\ & & \ddots \end{pmatrix} \tag{S15}$$

is a diagonal matrix consisting of the different eigenvalues $x_1, x_2, \cdots$ of $\boldsymbol{A}$ and the rows of the matrix $\boldsymbol{U}$ are the eigenvectors to the eigenvalues x_i, $i = 1, 2, \cdots$. Hence, the solution to Eq. (S11) can be written as

$$\boldsymbol{x_0}(t) = \int_0^t e^{\boldsymbol{A}(t-s)}\boldsymbol{b}\, ds = \boldsymbol{U}\left(\int_0^t e^{\boldsymbol{D}(t-s)} ds\right)\boldsymbol{U}^{-1}\boldsymbol{b} = \boldsymbol{U}\begin{pmatrix} \frac{\left(e^{x_1 t}-1\right)}{x_1} & & \\ & \frac{\left(e^{x_2 t}-1\right)}{x_2} & \\ & & \ddots \end{pmatrix}\boldsymbol{U}^{-1}\boldsymbol{b}. \tag{S16}$$

The resulting solution for $P_0(t)$ is a sum of exponentials $e^{x_i t}$

$$P_0(t) = k_1 m_{\mathrm{tot}}^{n_1} \sum_{j=1}^{n} U_{1j} \frac{\left(e^{x_j t} - 1\right)}{x_j} \left(U^{-1}\right)_{j1}, \tag{S17}$$

where U_{ij} denotes the ij-th component of the matrix $\boldsymbol{U}$. We obtain a self-consistent solution for the total aggregate mass concentration by substituting Eq. (S17) into Eq. (S8b), hence performing a step of the fixed-point iteration. This yields

$$\boxed{\frac{M(t)}{m_{\mathrm{tot}}} = 1 - \exp\left(-2k_+ k_1 m_{\mathrm{tot}}^{n_1} \sum_{j=1}^{n} U_{1j} \frac{\left(e^{x_j t} - 1\right)}{x_j^2} \left(U^{-1}\right)_{j1}\right)} \tag{S18}$$

For the matrix $\boldsymbol{A}$ in Eq. (S12) the eigenvalues are $x_1 = \kappa$ and $x_2 = -\kappa$, where $\kappa = \sqrt{2k_+ k_2 m_{\mathrm{tot}}^{n_2+1}}$. The associated eigenvectors are $\begin{pmatrix} \frac{\kappa}{2k_+ m_{\mathrm{tot}}} \\ 1 \end{pmatrix}$ and $\begin{pmatrix} -\frac{\kappa}{2k_+ m_{\mathrm{tot}}} \\ 1 \end{pmatrix}$, respectively. Hence:

$$\boldsymbol{U} = \begin{pmatrix} \frac{\kappa}{2k_+ m_{\mathrm{tot}}} & -\frac{\kappa}{2k_+ m_{\mathrm{tot}}} \\ 1 & 1 \end{pmatrix} \quad \Rightarrow \quad \boldsymbol{U}^{-1} = \begin{pmatrix} \frac{k_+ m_{\mathrm{tot}}}{\kappa} & \frac{1}{2} \\ -\frac{k_+ m_{\mathrm{tot}}}{\kappa} & \frac{1}{2} \end{pmatrix}. \tag{S19}$$

Therefore, using Eq. (S17) we find

$$P_0(t) = \frac{k_1 m_{\mathrm{tot}}^{n_1}}{2\kappa}\left(e^{\kappa t} + e^{-\kappa t} - 2\right), \tag{S20}$$

where

$$\lambda = \sqrt{2k_+k_1m_{\text{tot}}^{n_1}}, \tag{S21}$$

$$\kappa = \sqrt{2k_+k_2m_{\text{tot}}^{n_2+1}}. \tag{S22}$$

λ and κ are effective aggregate proliferation rates of aggregates through primary and secondary nucleation, respectively. A self-consistent solution for the aggregation kinetics in the absence of an inhibitor is thus obtained using Eq. (S18) as

$$\boxed{\frac{M(t)}{m_{\text{tot}}} = 1 - \exp\left(-\frac{\lambda^2}{2\kappa^2}\left(e^{\kappa t} + e^{-\kappa t} - 2\right)\right)} \tag{S23}$$

We can simplify the solution Eq. (S18) by noticing that, after a very rapid phase of adaptation, the behaviour of $P_0(t)$ is going to be dominated by the fastest growing exponential term, which corresponds to the largest positive eigenvalue assumed here to be x_1. Thus:

$$P_0(t) \simeq k_1m_{\text{tot}}^{n_1}\frac{U_{11}\left(U^{-1}\right)_{11}}{x_1}\left(e^{x_1t} - 1\right). \tag{S24}$$

For the matrix $\boldsymbol{A}$ in Eq. (S12), which has the eigenvalues $x_1 = \kappa$ and $x_2 = -\kappa$, the dominant term in P_0 is

$$P_0(t) \simeq \frac{k_1m_{\text{tot}}^{n_1}}{2\kappa}\left(e^{\kappa t} - 1\right). \tag{S25}$$

To construct a self-consistent solution for the total aggregate mass concentration, we now substitute Eq. (S25) into Eq. (S8b)

$$\frac{M(t)}{m_{\text{tot}}} = 1 - \exp\left(-2k_+\int_0^t P_0(s)ds\right) \tag{S26}$$

and obtain

$$\boxed{\frac{M(t)}{m_{\text{tot}}} = 1 - \exp\left(-\frac{\lambda^2}{2\kappa^2}\left(e^{\kappa t} - 1\right)\right)} \tag{S27}$$

which is Eq. (2) of the main text.

We note that an alternative analytical solution, which is more accurate than Eq. (S27) for $n_2 \geq 1$, has been obtained (9) by considering a different initial point for the fixed point iteration

$$\frac{P_0(t)}{1 + \frac{P_0(t)}{P(\infty)}}, \tag{S28}$$

where $P_0(t)$ is Eq. (S25) and $P(\infty)$ is the terminal aggregate number concentration. Substituting Eq. (S28) into Eq. (S8b) yields

$$\boxed{\frac{M(t)}{m_{\text{tot}}} = 1 - \left(\frac{B_+ + C_+}{B_+ + C_+e^{\kappa t}}\frac{B_- + C_+e^{\kappa t}}{B_- + C_+}\right)^{\frac{k_\infty^2}{\kappa k_\infty}} e^{-k_\infty t}} \tag{S29a}$$

where

$$C_\pm = \pm\frac{\lambda^2}{2\kappa^2}, \tag{S29b}$$

$$k_\infty = \kappa\sqrt{\frac{2}{n_2(n_2+1)} + \frac{2\lambda^2}{n_1\kappa^2}}, \tag{S29c}$$

$$\tilde{k}_\infty = \sqrt{k_\infty^2 - 4C_+C_-\kappa^2}, \tag{S29d}$$

$$B_\pm = \frac{k_\infty \pm \tilde{k}_\infty}{2\kappa}. \tag{S29e}$$

Also in this case, the solution is dependent on λ and κ.

We conclude this section by mentioning a technical point, which will become useful later in Sec. S2. We note that the self-consistent solution Eq. (S27) can be written using Eq. (S24) as:

$$\boxed{\frac{M(t)}{m_{\text{tot}}} \simeq 1 - \exp\left(-2k_+k_1m_{\text{tot}}^{n_1}\frac{U_{11}\left(U^{-1}\right)_{11}}{x_1^2}\left(e^{x_1t} - 1\right)\right)} \tag{S30}$$

By comparing Eq. (S30) with Eq. (S27) we see that we can express the rate parameters λ and κ as

$$\boxed{\kappa = x_1, \quad \lambda = \sqrt{2k_+k_1m_{\text{tot}}^{n_1}}\sqrt{2U_{11}\left(U^{-1}\right)_{11}}} \tag{S31}$$

The formula in Eq. (S31) provides an explicit way to determine how the rate parameters κ and λ are affected by the presence of an inhibitor from a consideration of the eigenvalues and eigenvectors of the matrix $\boldsymbol{A}$ describing inhibited linearised kinetics.

S1.3. Modes of inhibition. To understand how the presence of inhibitor molecules affects the aggregation dynamics described by Eq. (S6a) and Eq. (S6b), we consider in detail the possible modes of inhibition when a drug-like small molecule is incorporated into the dynamics of aggregation. In general, we distinguish three main scenarios for how the inhibitor molecule can interfere with the aggregation process (Fig. 1B of main text):

1. **Binding to monomers** – The first possibility for the inhibitor to influence the aggregation process is by reversibly binding to the monomers. Through reversible binding and unbinding, the monomers can be activated or deactivated. Deactivated monomers have a reduced propensity to participate to the aggregation process. We denote the rate constants for binding to and unbinding from the monomers as $k_{\mathrm{m}}^{\mathrm{on}}$ and $k_{\mathrm{m}}^{\mathrm{off}}$, respectively. The ratio $k_{\mathrm{m}}^{\mathrm{on}}/k_{\mathrm{m}}^{\mathrm{off}} = K_{\mathrm{m}}$ is the equilibrium constant for monomer binding.

2. **Binding to fibril ends** – Another possibility is that inhibitor molecules block the ends of fibrils, thereby preventing them from growing by recruiting free monomers from solution. The rate constants for binding to and unbinding from the fibril ends are indicated respectively as $k_{\mathrm{e}}^{\mathrm{on}}$ and $k_{\mathrm{e}}^{\mathrm{off}}$, and the associated equilibrium binding constant is $k_{\mathrm{e}}^{\mathrm{on}}/k_{\mathrm{e}}^{\mathrm{off}} = K_{\mathrm{e}}$. For simplicity, we assume that inhibitor binding/unbinding occur with the same rates at both fibril ends; our approach could in principle be generalised to account for different binding and dissociation rates at and from both fibril ends.

3. **Binding to fibril surface** – A third relevant possibility to consider is the binding of inhibitor molecules to the catalytic surface of existing fibrils. Inhibitor molecules bind the surface with rate constant $k_{\mathrm{s}}^{\mathrm{on}}$, thereby potentially blocking the autocatalytic cycle of surface-catalyzed secondary nucleation. Inhibitor molecules can unbind from the fibril surface with rate constant $k_{\mathrm{s}}^{\mathrm{off}}$, thereby allowing aggregates to catalyze again the formation of new aggregates on their surface. The equilibrium constant for binding to the surface of fibrils is $k_{\mathrm{s}}^{\mathrm{on}}/k_{\mathrm{s}}^{\mathrm{off}} = K_{\mathrm{s}}$.

S1.4. Kinetic equations in the presence of inhibitor. Depending on the specific chemical characteristics of the inhibitor molecule under consideration, all or only a subgroup of the various modes of inhibition described in the previous section could be active. In the most general scenario, protein aggregation kinetics in the presence of an inhibitor is captured by the following set of coupled differential equations, as an extension of Eq. (S6a) and Eq. (S6b) (Eq. (3) of main text):

$$\frac{\mathrm{d}P_{\mathrm{f}}(t)}{\mathrm{d}t} = k_1 m_{\mathrm{f}}(t)^{n_1} + k_2 m_{\mathrm{f}}(t)^{n_2} M_{\mathrm{f}}(t) - k_{\mathrm{e}}^{\mathrm{on}} C_i(t) P_{\mathrm{f}}(t) + k_{\mathrm{e}}^{\mathrm{off}} P_{\mathrm{b}}(t), \tag{S32a}$$

$$\frac{\mathrm{d}M_{\mathrm{f}}(t)}{\mathrm{d}t} = 2k_+ m_{\mathrm{f}}(t) P_{\mathrm{f}}(t) - k_{\mathrm{s}}^{\mathrm{on}} C_i(t) M_{\mathrm{f}}(t) + k_{\mathrm{s}}^{\mathrm{off}} M_{\mathrm{b}}(t), \tag{S32b}$$

$$\frac{\mathrm{d}m_{\mathrm{f}}(t)}{\mathrm{d}t} = -2k_+ m_{\mathrm{f}}(t) P_{\mathrm{f}}(t) - k_{\mathrm{m}}^{\mathrm{on}} C_i(t) m_{\mathrm{f}}(t) + k_{\mathrm{m}}^{\mathrm{off}} m_{\mathrm{b}}(t), \tag{S32c}$$

$$\frac{\mathrm{d}P_{\mathrm{b}}(t)}{\mathrm{d}t} = k_{\mathrm{e}}^{\mathrm{on}} C_i(t) P_{\mathrm{f}}(t) - k_{\mathrm{e}}^{\mathrm{off}} P_{\mathrm{b}}(t), \tag{S32d}$$

$$\frac{\mathrm{d}M_{\mathrm{b}}(t)}{\mathrm{d}t} = k_{\mathrm{s}}^{\mathrm{on}} C_i(t) M_{\mathrm{f}}(t) - k_{\mathrm{s}}^{\mathrm{off}} M_{\mathrm{b}}(t), \tag{S32e}$$

$$\frac{\mathrm{d}m_{\mathrm{b}}(t)}{\mathrm{d}t} = k_{\mathrm{m}}^{\mathrm{on}} C_i(t) m_{\mathrm{f}}(t) - k_{\mathrm{m}}^{\mathrm{off}} m_{\mathrm{b}}(t), \tag{S32f}$$

$$\frac{\mathrm{d}C_i(t)}{\mathrm{d}t} = -\frac{\mathrm{d}P_{\mathrm{b}}(t)}{\mathrm{d}t} - \frac{\mathrm{d}M_{\mathrm{b}}(t)}{\mathrm{d}t} - \frac{\mathrm{d}m_{\mathrm{b}}(t)}{\mathrm{d}t}, \tag{S32g}$$

where

$$P_{\mathrm{f}}(t), P_{\mathrm{b}}(t) = \text{free/bound aggregate number concentration}, \tag{S32h}$$

$$M_{\mathrm{f}}(t), M_{\mathrm{b}}(t) = \text{free/bound aggregate mass concentration}, \tag{S32i}$$

$$m_{\mathrm{f}}(t), m_{\mathrm{b}}(t) = \text{free/bound monomer concentration}, \tag{S32j}$$

$$C_i(t) = \text{(free) inhibitor concentration}. \tag{S32k}$$

Eq. (S32) must be coupled to the conservation of total protein mass m_{tot}, which implies:

$$m_{\mathrm{tot}} = m_{\mathrm{f}}(t) + m_{\mathrm{b}}(t) + M_{\mathrm{f}}(t) + M_{\mathrm{b}}(t). \tag{S33}$$

Total monomer and aggregate concentrations – effective kinetic equations. It is useful to introduce total aggregate number, aggregate mass and monomer concentrations as

$$P(t) = P_{\mathrm{f}}(t) + P_{\mathrm{b}}(t), \tag{S34a}$$

$$M(t) = M_{\mathrm{f}}(t) + M_{\mathrm{b}}(t), \tag{S34b}$$

$$m(t) = m_{\mathrm{f}}(t) + m_{\mathrm{b}}(t), \tag{S34c}$$

which satisfy the following equations

$$\frac{\mathrm{d}P(t)}{\mathrm{d}t} = k_1 m_{\mathrm{f}}(t)^{n_1} + k_2 m_{\mathrm{f}}(t)^{n_2} M_{\mathrm{f}}(t), \tag{S34d}$$

$$\frac{\mathrm{d}m(t)}{\mathrm{d}t} = -2k_+ m_{\mathrm{f}}(t) P_{\mathrm{f}}(t) = -\frac{\mathrm{d}M(t)}{\mathrm{d}t}. \tag{S34e}$$

Eq. (S34d) and Eq. (S34e) highlight the origin of inhibition: compared to uninhibited kinetics, Eq. (S6a) and Eq. (S6b), free (instead of total) monomer, aggregate number and aggregate mass concentrations appear on the right hand side of the kinetic equations Eq. (S34d) and Eq. (S34e). Thus, different microscopic events of aggregation (elongation, primary and secondary nucleation) are inhibited depending to which of the "aggregate species" P, M or m the inhibitor binds. As we will see in Sec. S2, the speed of inhibitor binding to the targeted species also determines the efficacy of its inhibitory action.

S1.5. Fast inhibitor binding (equilibrium inhibition regime). Important simplifications emerge in the limit of fast binding of the inhibitor to monomers and aggregates (the meaning of "fast" can be quantified rigorously using asymptotic analysis, see Sec. S2 and e.g. Eq. (S62)). We term this regime *equilibrium inhibition regime*. In this case, time variations of bound species can be approximatively set equal to zero in Eq. (S32d)-Eq. (S32f)

$$\frac{\mathrm{d}P_\mathrm{b}(t)}{\mathrm{d}t} \simeq \frac{\mathrm{d}M_\mathrm{b}(t)}{\mathrm{d}t} \simeq \frac{\mathrm{d}m_\mathrm{b}(t)}{\mathrm{d}t} \simeq 0. \tag{S35}$$

This implies

$$\frac{\mathrm{d}C_i(t)}{\mathrm{d}t} \simeq 0, \tag{S36}$$

i.e. the inhibitor concentration is approximately constant. This procedure yields simple relationships that link the concentrations of free and bound material as

$$m_\mathrm{f}(t) = K_\mathrm{m} m_\mathrm{b}(t), \quad P_\mathrm{f}(t) = K_\mathrm{e} P_\mathrm{b}(t), \quad M_\mathrm{f}(t) = K_\mathrm{s} M_\mathrm{b}(t), \tag{S37a}$$

where

$$K_\mathrm{m} = \frac{k_\mathrm{m}^\mathrm{on}}{k_\mathrm{m}^\mathrm{off}}, \quad K_\mathrm{e} = \frac{k_\mathrm{e}^\mathrm{on}}{k_\mathrm{e}^\mathrm{off}}, \quad K_\mathrm{s} = \frac{k_\mathrm{s}^\mathrm{on}}{k_\mathrm{s}^\mathrm{off}} \tag{S37b}$$

are the equilibrium constants for inhibitor binding to monomers, fibril ends or fibril surface, respectively. Using Eq. (S34) we obtain relationships between the amount of free and total material, as:

$$m_\mathrm{f}(t) = \frac{m(t)}{1+K_\mathrm{m}C_i}, \quad P_\mathrm{f}(t) = \frac{P(t)}{1+K_\mathrm{e}C_i}, \quad M_\mathrm{f}(t) = \frac{M(t)}{1+K_\mathrm{s}C_i}. \tag{S38}$$

Thus, Eq. (S34d) and Eq. (S34e) become:

$$\frac{\mathrm{d}M(t)}{\mathrm{d}t} = 2k_+ \left(\frac{m(t)}{1+K_\mathrm{m}C_i}\right)\left(\frac{P(t)}{1+K_\mathrm{e}C_i}\right), \tag{S39}$$

$$\frac{\mathrm{d}P(t)}{\mathrm{d}t} = k_1 \left(\frac{m(t)}{1+K_\mathrm{m}C_i}\right)^{n_1} + k_2 \left(\frac{m(t)}{1+K_\mathrm{m}C_i}\right)^{n_2}\left(\frac{M(t)}{1+K_\mathrm{s}C_i}\right). \tag{S40}$$

Eq. (S39) and Eq. (S40) are equivalent to the kinetic equations in the absence of inhibitor, Eq. (S6a) and Eq. (S6b), but the kinetic parameters are replaced by "effective" rate constants that depend on the inhibitor concentration (Table S1).

$$\frac{k_+^\mathrm{eff}}{k_+} = \left(\frac{1}{1+K_\mathrm{m}C_i}\right)\left(\frac{1}{1+K_\mathrm{e}C_i}\right), \tag{S41}$$

$$\frac{k_1^\mathrm{eff}}{k_1} = \left(\frac{1}{1+K_\mathrm{m}C_i}\right)^{n_1}, \tag{S42}$$

$$\frac{k_2^\mathrm{eff}}{k_2} = \left(\frac{1}{1+K_\mathrm{m}C_i}\right)^{n_2}\left(\frac{1}{1+K_\mathrm{s}C_i}\right). \tag{S43}$$

The time course of aggregate mass concentration in the presence of an inhibitor in the fast binding limit can therefore be obtained by replacing the rate parameters in Eq. (S27) by Eq. (S41)-Eq. (S43), i.e.

$$\frac{M(t)}{m_\mathrm{tot}} = 1 - \exp\left(-\frac{\lambda_\mathrm{eff}^2}{2\kappa_\mathrm{eff}^2}\left(e^{\kappa_\mathrm{eff}t}-1\right)\right), \tag{S44}$$

where the effective kinetic parameters are given by:

$$\frac{\lambda_\mathrm{eff}}{\lambda} = \left(\frac{1}{1+K_\mathrm{m}C_i}\right)^{\frac{n_1+1}{2}}\left(\frac{1}{1+K_\mathrm{e}C_i}\right)^{\frac{1}{2}}, \tag{S45}$$

$$\frac{\kappa_\mathrm{eff}}{\kappa} = \left(\frac{1}{1+K_\mathrm{m}C_i}\right)^{\frac{n_2+1}{2}}\left(\frac{1}{1+K_\mathrm{e}C_i}\right)^{\frac{1}{2}}\left(\frac{1}{1+K_\mathrm{s}C_i}\right)^{\frac{1}{2}}. \tag{S46}$$

When $n_2 \geq 1$, Eq. (S29a) may be used to describe inhibited aggregation kinetics, where λ and κ are replaced by λ_eff and κ_eff, respectively.

Table S1. Effective couplings (rate constants) of the various steps of aggregation in the equilibrium regime.

Targeted species	Monomers	Aggregate ends	Fibril surface
Inhibited steps			
Primary nucleation	✓	✗	✗
Secondary nucleation	✓	✗	✓
Elongation	✓	✓	✗
Effective rate constants (equilibrium inhibition)	$\frac{k_1^{\mathrm{eff}}}{k_1} = \left(\frac{1}{1+K_{\mathrm{m}}C_i}\right)^{n_1}$ $\frac{k_2^{\mathrm{eff}}}{k_2} = \left(\frac{1}{1+K_{\mathrm{m}}C_i}\right)^{n_2}$ $\frac{k_+^{\mathrm{eff}}}{k_+} = \frac{1}{1+K_{\mathrm{m}}C_i}$	$\frac{k_1^{\mathrm{eff}}}{k_1} = 1$ $\frac{k_2^{\mathrm{eff}}}{k_2} = 1$ $\frac{k_+^{\mathrm{eff}}}{k_+} = \frac{1}{1+K_{\mathrm{e}}C_i}$	$\frac{k_1^{\mathrm{eff}}}{k_1} = 1$ $\frac{k_2^{\mathrm{eff}}}{k_2} = \frac{1}{1+K_{\mathrm{s}}C_i}$ $\frac{k_+^{\mathrm{eff}}}{k_+} = 1$

S1.6. Scaling argument to determine inhibition regimes. In Sec. S1.5, we have assumed "fast" inhibitor binding. We can determine the relevant timescale that differentiates the different inhibition regimes using a simple scaling argument. We illustrate this idea for an inhibitor that binds aggregate ends. A rigorous timescale analysis based on matched asymptotics is given in Sec. S2. Successful inhibition requires binding to be sufficiently fast; to quantify the meaning of "fast" in this case, we need to compare the terms $k_{\mathrm{e}}^{\mathrm{on}} P_{\mathrm{f}}(t) C_i(t)$ and $k_2 m_{\mathrm{f}}(t)^{n_2} M_{\mathrm{f}}(t)$ in Eq. (S32). Equating these two terms, using the fact that aggregate number concentration scales as $P \simeq \kappa/(2k_+)$ (8), yields

$$k_2 m_{\mathrm{tot}}^{n_2+1} \simeq \frac{\kappa}{2k_+} k_{\mathrm{e}}^{\mathrm{on}} C_i \quad \Rightarrow \quad k_{\mathrm{e}}^{\mathrm{on}} C_i \simeq \kappa. \tag{S47}$$

This simple argument shows that the relevant timescale for comparing inhibitor binding is $1/\kappa$. In general, $1/\kappa$ emerges as the key timescale to which the inhibitor binding rate $k_\times^{\mathrm{on}} C_i$ to the target $\times = $ m,e,s must be compared.

S2. Integrated rate laws in the presence of an inhibitor

We now discuss the mathematical details associated with the derivation of analytical solutions to the aggregation kinetics in the presence of an inhibitor, Eq. (4) of the main text. In this derivation we do not assume fast inhibitor binding to the target. For clarity of exposition we discuss each inhibition mechanism separately. In each case we follow the steps outlined in Sec. S1.2 to derive a self-consistent solution to the aggregation kinetics.

S2.1. Binding to fibril surface. In the case of an inhibitor binding the surface of fibrils, the kinetic equations are

$$\frac{\mathrm{d}P(t)}{\mathrm{d}t} = k_1 m(t)^{n_1} + k_2 m(t)^{n_2} M_\mathrm{f}(t) \tag{S48a}$$

$$\frac{\mathrm{d}M_\mathrm{f}(t)}{\mathrm{d}t} = 2k_+ m(t) P(t) - k_\mathrm{s}^\mathrm{on} C_i M_\mathrm{f}(t) + k_\mathrm{s}^\mathrm{off} M_\mathrm{b}(t), \tag{S48b}$$

$$\frac{\mathrm{d}M_\mathrm{b}(t)}{\mathrm{d}t} = k_\mathrm{s}^\mathrm{on} C_i M_\mathrm{f}(t) - k_\mathrm{s}^\mathrm{off} M_\mathrm{b}(t). \tag{S48c}$$

Summing Eq. (S48b) and Eq. (S48c) we find

$$\frac{\mathrm{d}M(t)}{\mathrm{d}t} = \frac{\mathrm{d}M_\mathrm{f}(t)}{\mathrm{d}t} + \frac{\mathrm{d}M_\mathrm{f}(t)}{\mathrm{d}t} = 2k_+ m(t) P(t), \tag{S49}$$

which can be integrated formally using $M(t) + m(t) = m_\mathrm{tot}$ to yield

$$M(t) = m_\mathrm{tot}\left[1 - \exp\left(-2k_+ \int_0^t P(s) ds\right)\right]. \tag{S50}$$

Crucially, in the presence of an inhibitor that binds fibril surfaces we recover the same fixed-point operator that we obtained in the absence of the inhibitor, Eq. (S8b). Thus, we can obtain a self-consistent solution to inhibited kinetics by the same method described in Sec. S1.2. As the starting point for deriving such a self-consistent solution we linearise Eq. (S48) by setting $m \simeq m_\mathrm{tot}$ throughout, yielding

$$\frac{\mathrm{d}P_0(t)}{\mathrm{d}t} = k_1 m_\mathrm{tot}^{n_1} + k_2 m_\mathrm{tot}^{n_2} M_{\mathrm{f},0}(t) \tag{S51a}$$

$$\frac{\mathrm{d}M_{\mathrm{f},0}(t)}{\mathrm{d}t} = 2k_+ m_\mathrm{tot} P(t) - k_\mathrm{s}^\mathrm{on} C_i M_{\mathrm{f},0}(t) + k_\mathrm{s}^\mathrm{off} M_{\mathrm{b},0}(t), \tag{S51b}$$

$$\frac{\mathrm{d}M_{\mathrm{b},0}(t)}{\mathrm{d}t} = k_\mathrm{s}^\mathrm{on} C_i M_{\mathrm{f},0}(t) - k_\mathrm{s}^\mathrm{off} M_{\mathrm{b},0}(t), \tag{S51c}$$

where the subscript 0 indicates the linearised solution. Eq. (S51) can be written in matrix form as $\frac{\mathrm{d}\boldsymbol{x_0}}{\mathrm{d}t} = \boldsymbol{A}\boldsymbol{x_0} + \boldsymbol{b}$, where

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} P_0(t) \\ M_{\mathrm{f},0}(t) \\ M_{\mathrm{b},0}(t) \end{pmatrix} = \underbrace{\begin{pmatrix} 0 & k_2 m_\mathrm{tot}^{n_2} & 0 \\ 2k_+ m_\mathrm{tot} & -k_\mathrm{s}^\mathrm{on} C_i & k_\mathrm{s}^\mathrm{off} \\ 0 & k_\mathrm{s}^\mathrm{on} C_i & -k_\mathrm{s}^\mathrm{off} \end{pmatrix}}_{=\boldsymbol{A}} \underbrace{\begin{pmatrix} P_0(t) \\ M_{\mathrm{f},0}(t) \\ M_{\mathrm{b},0}(t) \end{pmatrix}}_{=\boldsymbol{x_0}} + \underbrace{\begin{pmatrix} k_1 m_\mathrm{tot}^{n_1} \\ 0 \\ 0 \end{pmatrix}}_{=\boldsymbol{b}}. \tag{S52}$$

To find the eigenvalues of the above matrix $\boldsymbol{A}$, we consider its characteristic polynomial:

$$x^3 + (k_\mathrm{s}^\mathrm{on} C_i + k_\mathrm{s}^\mathrm{off}) x^2 - \kappa^2 x - k_\mathrm{s}^\mathrm{off} \kappa^2 = 0, \tag{S53}$$

where $\kappa = \sqrt{2k_+ k_2 m_\mathrm{tot}^{n_2+1}}$. Eq. (S53) yields 1 positive eigenvalue x_1 and two 2 eigenvalues $x_{2,3}$ with negative real part. The explicit expressions for these eigenvalues are rather complex and can be written in terms of two relevant dimensionless combinations of parameters

$$a = \frac{k_\mathrm{s}^\mathrm{on} C_i}{\kappa} \quad \text{and} \quad b = K_\mathrm{s} C_i \tag{S54}$$

as

$$x_1 = -\frac{1}{3}\left(a + \frac{a}{b} + C + \frac{\Delta_0}{C}\right), \tag{S55a}$$

$$x_2 = -\frac{1}{3}\left(a + \frac{a}{b} + \xi C + \xi^2 \frac{\Delta_0}{C}\right), \tag{S55b}$$

$$x_3 = -\frac{1}{3}\left(a + \frac{a}{b} + \xi^2 C + \xi \frac{\Delta_0}{C}\right), \tag{S55c}$$

where $\xi = \frac{-1+\sqrt{3}i}{2}$, $C = \left(\frac{\Delta_1+\sqrt{\Delta_1^2-4\Delta_0^3}}{2}\right)^{1/3}$, $\Delta_0 = \left(a+\frac{a}{b}\right)^2 + 3$, $\Delta_1 = 2\left(a+\frac{a}{b}\right)^3 + 9\left(a+\frac{a}{b}\right) - 27\frac{a}{b}$. The associated eigenvectors are

$$\begin{pmatrix} \frac{k_2 m_{\rm tot}^{n2}(x_1+k_{\rm s}^{\rm off})}{k_{\rm s}^{\rm on}C_i x_1} \\ \frac{x_1+k_{\rm s}^{\rm off}}{k_{\rm s}^{\rm on}C_i} \\ 1 \end{pmatrix}, \quad \begin{pmatrix} \frac{k_2 m_{\rm tot}^{n2}(x_2+k_{\rm s}^{\rm off})}{k_{\rm s}^{\rm on}C_i x_2} \\ \frac{x_2+k_{\rm s}^{\rm off}}{k_{\rm s}^{\rm on}C_i} \\ 1 \end{pmatrix}, \quad \begin{pmatrix} \frac{k_2 m_{\rm tot}^{n2}(x_3+k_{\rm s}^{\rm off})}{k_{\rm s}^{\rm on}C_i x_3} \\ \frac{x_3+k_{\rm s}^{\rm off}}{k_{\rm s}^{\rm on}C_i} \\ 1 \end{pmatrix}, \tag{S56}$$

The self-consistent solution to the aggregation kinetics in the presence of an inhibitor binding the surface of fibrils is therefore

$$\frac{M(t)}{m_{\rm tot}} = 1 - \exp\left(-2k_+k_1 m_{\rm tot}^{n_1} \sum_{j=1}^{n} U_{1j} \frac{\left(e^{x_j t}-1\right)}{x_j^2} \left(U^{-1}\right)_{j1}\right) \tag{S57}$$

where x_1, x_2, and x_3 are given in Eq. (S55) and the rows of the matrix $\boldsymbol{U}$ are the eigenvectors in Eq. (S56).

As we did in the absence of an inhibitor, we can simplify our self-consistent solution by truncating the sum of exponentials in Eq. (S57). Note that there is only one positive eigenvalue x_1, while the other two eigenvalues x_2 and x_3 have a negative real part. Thus, we keep only the exponentially growing term $e^{x_1 t}-1$ in front of the exponentially decaying terms $e^{x_2 t}-1$ and $e^{x_3 t}-1$. Using

$$U_{11} = \frac{k_2 m_{\rm tot}^{n2}(x_1+k_{\rm s}^{\rm off})}{k_{\rm s}^{\rm on}C_i x_1}, \quad \left(U^{-1}\right)_{11} = \frac{k_{\rm s}^{\rm on}C_i x_1 x_2 x_3}{k_2 m_{\rm tot}^{n2} k_{\rm s}^{\rm off}(x_1-x_2)(x_1-x_3)}. \tag{S58}$$

in combination with Eq. (S24), we obtain

$$P_0(t) \simeq k_1 m_{\rm tot}^{n_1} \frac{x_2 x_3 (x_1+k_{\rm s}^{\rm off})}{x_1 k_{\rm s}^{\rm off}(x_1-x_2)(x_1-x_3)} \left(e^{x_1 t}-1\right). \tag{S59}$$

Finally, using Eq. (S58) in Eq. (S30) and Eq. (S31) we obtain the self-consistent solution to the aggregation kinetics as

$$\frac{M(t)}{m_{\rm tot}} = 1 - \exp\left(-\frac{\lambda_{\rm eff}^2}{2\kappa_{\rm eff}^2}\left(e^{\kappa_{\rm eff} t}-1\right)\right), \tag{S60}$$

where the explicit expressions for $\kappa_{\rm eff}$ and $\lambda_{\rm eff}$ are obtained by substituting Eq. (S58) in Eq. (S31) as

$$\boxed{\kappa_{\rm eff} = x_1, \quad \frac{\lambda_{\rm eff}}{\lambda} = \sqrt{\frac{2x_2 x_3 (x_1+k_{\rm s}^{\rm off})}{k_{\rm s}^{\rm off}(x_1-x_2)(x_1-x_3)}}} \tag{S61}$$

The truncation of the sum of exponentials in Eq. (S57) allows us therefore to relate the solution in the presence of an inhibitor to the solution obtained in the absence of the inhibitor and therefore to interpret inhibited kinetics in terms of effective rate parameters λ and κ.

Dominant balance – fast inhibitor binding limit. In the above section we have solved Eq. (S53) explicitly, but the resulting expressions are complicated. In the limit of fast binding of the inhibitor to fibril surfaces, we can obtain approximate expressions for the roots of the characteristic polynomial using a dominant balance method (10) as follows. Fast binding corresponds to the situation when

$$a = \frac{k_{\rm s}^{\rm on}C_i}{\kappa} \gg 1. \tag{S62}$$

In this case, we can solve the characteristic equation Eq. (S53) considering κ as a small parameter. The possible dominant balances for Eq. (S53) are:

- If $x = \mathcal{O}(1)$, then the leading order terms in the characteristic equation Eq. (S53) for small κ are

$$x^3 + (k_{\rm s}^{\rm on}C_i + k_{\rm s}^{\rm off})x^2 = 0 \quad \Rightarrow \quad x \simeq -(k_{\rm s}^{\rm on}C_i + k_{\rm s}^{\rm off}). \tag{S63}$$

- If $x = \mathcal{O}(\kappa)$, then we write $x = \kappa X$, where $X = \mathcal{O}(1)$. The characteristic equation Eq. (S53) then becomes

$$\kappa\, X^3 + (k_{\rm s}^{\rm on}C_i + k_{\rm s}^{\rm off})x^2 - \kappa\, X - k_{\rm s}^{\rm off} = 0. \tag{S64}$$

Neglecting the terms proportional to κ, we find the leading order terms in the characteristic equation as

$$(k_{\rm s}^{\rm on}C_i + k_{\rm s}^{\rm off})X^2 - k_{\rm s}^{\rm off} = 0 \quad \Rightarrow \quad X \simeq \pm\sqrt{k_{\rm s}^{\rm off}/(k_{\rm s}^{\rm on}C_i + k_{\rm s}^{\rm off})} \quad \Rightarrow \quad x \simeq \pm\kappa\sqrt{1/(1+K_{\rm s}C_i)} \tag{S65}$$

In summary, the three approximate eigenvalues found using dominant balance are:

$$x_1 = \kappa\sqrt{\frac{1}{1+K_\mathrm{s}C_i}}, \quad x_2 = -\kappa\sqrt{\frac{1}{1+K_\mathrm{s}C_i}}, \quad x_3 = -(k_\mathrm{s}^\mathrm{on}C_i + k_\mathrm{s}^\mathrm{off}). \tag{S66}$$

We have one positive and two negative eigenvalues. Using the approximated eigenvalues Eq. (S66) in Eq. (S31) we arrive at the final solution

$$\frac{M(t)}{m_\mathrm{tot}} = 1 - \exp\left(-\frac{\lambda_\mathrm{eff}^2}{2\kappa_\mathrm{eff}^2}\left(e^{\kappa_\mathrm{eff}t} - 1\right)\right), \tag{S67}$$

where using $\kappa \ll K_\mathrm{s}C_i$

$$\frac{\lambda_\mathrm{eff}}{\lambda} = \sqrt{\frac{2x_2x_3(x_1 + k_\mathrm{s}^\mathrm{off})}{k_\mathrm{s}^\mathrm{off}(x_1 - x_2)(x_1 - x_3)}} \simeq 1, \quad \frac{\kappa_\mathrm{eff}}{\kappa} = \frac{x_1}{\kappa} = \left(\frac{1}{1+K_\mathrm{s}C_i}\right)^{\frac{1}{2}}, \tag{S68}$$

which is the same result of Sec. S1.5.

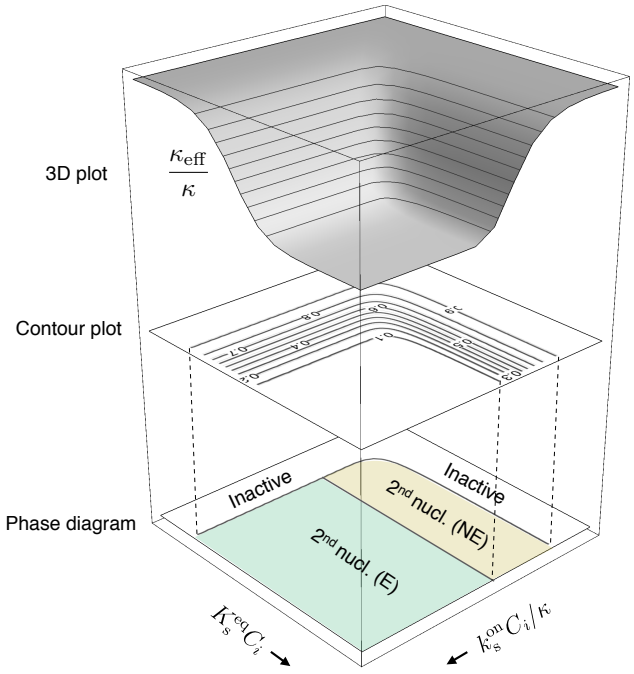

Fig. S1. Construction of phase diagram of possible inhibition regimes for an inhibitor that binds fibril surface sites. Contour lines are shown here in steps of 0.1. Boundary lines are however not sharp: the extent of inhibition is in fact a continuous function of $a = k_\mathrm{s}^\mathrm{on}C_i/\kappa$ and $b = K_\mathrm{s}C_i$.

S2.2. Binding to fibril ends. In the case of an inhibitor that binds fibril ends, the kinetic equations are

$$\frac{\mathrm{d}P_\mathrm{f}(t)}{\mathrm{d}t} = k_1 m(t)^{n_1} + k_2 m(t)^{n_2} M(t) - k_\mathrm{e}^\mathrm{on} C_i P_\mathrm{f}(t) + k_\mathrm{e}^\mathrm{off} P_\mathrm{b}(t), \tag{S69a}$$

$$\frac{\mathrm{d}M(t)}{\mathrm{d}t} = 2k_+ m(t) P_\mathrm{f}(t), \tag{S69b}$$

$$\frac{\mathrm{d}P_\mathrm{b}(t)}{\mathrm{d}t} = k_\mathrm{e}^\mathrm{on} C_i P_\mathrm{f}(t) - k_\mathrm{e}^\mathrm{off} P_\mathrm{b}(t). \tag{S69c}$$

Formal integration of Eq. (S69b) in this case yields

$$M(t) = m_\mathrm{tot}\left[1 - \exp\left(-2k_+ \int_0^t P_\mathrm{f}(s)ds\right)\right]. \tag{S70}$$

Therefore, we can obtain a self-consistent solution for the case of an inhibitor that bind fibril ends by obtaining an expression for P_f in the linearised Eq. (S69). To this end, we set $m \simeq m_\mathrm{tot}$ in Eq. (S69), which yields the following linearised equations

$$\frac{\mathrm{d}P_\mathrm{f}(t)}{\mathrm{d}t} = k_1 m_\mathrm{tot}^{n_1} + k_2 m_\mathrm{tot}^{n_2} M_0(t) - k_\mathrm{e}^\mathrm{on} C_i P_{\mathrm{f},0}(t) + k_\mathrm{e}^\mathrm{off} P_{\mathrm{b},0}(t), \tag{S71a}$$

$$\frac{\mathrm{d}M_0(t)}{\mathrm{d}t} = 2k_+ m_\mathrm{tot} P_{\mathrm{f},0}(t), \tag{S71b}$$

$$\frac{\mathrm{d}P_{\mathrm{b},0}(t)}{\mathrm{d}t} = k_\mathrm{e}^\mathrm{on} C_i P_{\mathrm{f},0}(t) - k_\mathrm{e}^\mathrm{off} P_{\mathrm{b},0}(t), \tag{S71c}$$

or in matrix form

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} P_{\mathrm{f},0}(t) \\ M_0(t) \\ P_{\mathrm{b},0}(t) \end{pmatrix} = \underbrace{\begin{pmatrix} -k_\mathrm{e}^\mathrm{on} C_i & k_2 m_\mathrm{tot}^{n_2} & k_\mathrm{e}^\mathrm{off} \\ 2k_+ m_\mathrm{tot} & 0 & 0 \\ k_\mathrm{e}^\mathrm{on} C_i & 0 & -k_\mathrm{e}^\mathrm{off} \end{pmatrix}}_{=\boldsymbol{A}} \underbrace{\begin{pmatrix} P_{\mathrm{f},0}(t) \\ M_0(t) \\ P_{\mathrm{b},0}(t) \end{pmatrix}}_{=\boldsymbol{x_0}} + \underbrace{\begin{pmatrix} k_1 m_\mathrm{tot}^{n_1} \\ 0 \\ 0 \end{pmatrix}}_{=\boldsymbol{b}}. \tag{S72}$$

Next, we determine the eigenvalues of $\boldsymbol{A}$ by considering the characteristic polynomial:

$$x^3 + (k_\mathrm{e}^\mathrm{on} C_i + k_\mathrm{e}^\mathrm{off}) x^2 - \kappa^2 x - k_\mathrm{e}^\mathrm{off} \kappa^2 = 0. \tag{S73}$$

We see that the characteristic polynomial in Eq. (S73) is identical to the one we found in the case of an inhibitor that binds the surface of fibrils, Eq. (S53). Therefore, the eigenvalues x_1, x_2, x_3 are given by Eq. (S55) where k_s^on and $k_\mathrm{s}^\mathrm{off}$ are replaced by k_e^on respectively $k_\mathrm{e}^\mathrm{off}$. The associated eigenvectors are

$$\begin{pmatrix} \frac{x_1 + k_\mathrm{e}^\mathrm{off}}{k_\mathrm{e}^\mathrm{on} C_i} \\ \frac{2k_+ m_\mathrm{tot}(x_1 + k_\mathrm{e}^\mathrm{off})}{k_\mathrm{e}^\mathrm{on} C_i x_1} \\ 1 \end{pmatrix}, \quad \begin{pmatrix} \frac{x_2 + k_\mathrm{e}^\mathrm{off}}{k_\mathrm{e}^\mathrm{on} C_i} \\ \frac{2k_+ m_\mathrm{tot}(x_2 + k_\mathrm{e}^\mathrm{off})}{k_\mathrm{e}^\mathrm{on} C_i x_2} \\ 1 \end{pmatrix}, \quad \begin{pmatrix} \frac{x_3 + k_\mathrm{e}^\mathrm{off}}{k_\mathrm{e}^\mathrm{on} C_i} \\ \frac{2k_+ m_\mathrm{tot}(x_3 + k_\mathrm{e}^\mathrm{off})}{k_\mathrm{e}^\mathrm{on} C_i x_3} \\ 1 \end{pmatrix}, \tag{S74}$$

such that

$$U_{11} = \frac{x_2 + k_\mathrm{e}^\mathrm{off}}{k_\mathrm{e}^\mathrm{on} C_i}, \quad \left(U^{-1}\right)_{11} = \frac{k_\mathrm{e}^\mathrm{on} C_i x_1}{(x_1 - x_2)(x_1 - x_3)}. \tag{S75}$$

Thus using Eq. (S75) in Eq. (S24), we obtain

$$P_0(t) \simeq k_1 m_\mathrm{tot}^{n_1} \frac{x_2 x_3 (x_1 + k_\mathrm{s}^\mathrm{off})}{x_1 k_\mathrm{s}^\mathrm{off} (x_1 - x_2)(x_1 - x_3)} \left(e^{x_1 t} - 1\right). \tag{S76}$$

Finally, using Eq. (S75) in Eq. (S30) and Eq. (S31) we obtain the required self-consistent solution for the case of an inhibitor of aggregate elongation

$$\frac{M(t)}{m_\mathrm{tot}} = 1 - \exp\left(-\frac{\lambda_\mathrm{eff}^2}{2\kappa_\mathrm{eff}^2}\left(e^{\kappa_\mathrm{eff} t} - 1\right)\right), \tag{S77}$$

where κ_eff and λ_eff are determined by substituting Eq. (S58) in Eq. (S31) as

$$\boxed{\kappa_\mathrm{eff} = x_1, \quad \frac{\lambda_\mathrm{eff}}{\lambda} = \sqrt{\frac{2x_1(x_1 + k_\mathrm{e}^\mathrm{off})}{(x_1 - x_2)(x_1 - x_3)}}} \tag{S78}$$

Dominant balance – fast binding limit. In the limit of fast binding to fibril surfaces, $\frac{k_e^{on} C_i}{\kappa} \gg 1$, we can obtain approximate expressions for the roots of the characteristic polynomial using a dominant balance argument as above. The eigenvalues are approximatively given by

$$x_1 = \kappa\sqrt{\frac{1}{1+K_e C_i}}, \quad x_2 = -\kappa\sqrt{\frac{1}{1+K_e C_i}}, \quad x_3 = -(k_e^{on} C_i + k_e^{off}). \tag{S79}$$

Using Eq. (S79) in Eq. (S58) with Eq. (S62) in the limit $\kappa \ll k_e^{on} C_i$, we arrive at the final solution

$$\frac{M(t)}{m_{tot}} = 1 - \exp\left(-\frac{\lambda_{eff}^2}{2\kappa_{eff}^2}\left(e^{\kappa_{eff} t} - 1\right)\right), \tag{S80}$$

where

$$\frac{\lambda_{eff}}{\lambda} = \sqrt{\frac{2x_1(x_1 + k_e^{off})}{(x_1 - x_2)(x_1 - x_3)}} = \left(\frac{k_e^{off}}{k_e^{on} C_i + k_e^{off}}\right)^{\frac{1}{2}} = \left(\frac{1}{1+K_e C_i}\right)^{\frac{1}{2}}, \quad \frac{\kappa_{eff}}{\kappa} = \frac{x_1}{\kappa} = \left(\frac{1}{1+K_e C_i}\right)^{\frac{1}{2}}. \tag{S81}$$

Our asymptotic analysis thus recovers the pre-equilibrium solution found in Sec. S1.5 in the limit of fast inhibitor binding.

S2.3. Binding to monomers. The kinetic equations in the presence of an inhibitor that binds monomers are:

$$\frac{\mathrm{d}P(t)}{\mathrm{d}t} = k_1 m_\mathrm{f}(t)^{n_1} + k_2 m_\mathrm{f}(t)^{n_2} M(t), \tag{S82a}$$
$$\frac{\mathrm{d}M(t)}{\mathrm{d}t} = 2k_+ m_\mathrm{f}(t) P(t), \tag{S82b}$$
$$\frac{\mathrm{d}m_\mathrm{f}(t)}{\mathrm{d}t} = -2k_+ m_\mathrm{f}(t) P(t) - k_\mathrm{m}^\mathrm{on} C_i m_\mathrm{f}(t) + k_\mathrm{m}^\mathrm{off} m_\mathrm{b}(t), \tag{S82c}$$
$$\frac{\mathrm{d}m_\mathrm{b}(t)}{\mathrm{d}t} = k_\mathrm{m}^\mathrm{on} C_i m_\mathrm{f}(t) - k_\mathrm{m}^\mathrm{off} m_\mathrm{b}(t), \tag{S82d}$$

The derivation of an analytical solution in this case requires more careful considerations, since the linearization procedure for Eq. (S82) does not occur simply by fixing the monomer concentration to a constant. A rigorous linearization of the equations in this limit can be obtained by using the method of matched asymptotics (see e.g. Ref. (10)). Asymptotic analysis is useful in the context of protein aggregation kinetics, since there is a separation of timescales between primary nucleation (which is very slow) and the subsequent growth of aggregates (which is comparatively very fast). This timescale separation is formalised in terms of the the following parameter

$$\varepsilon = \frac{k_1 m_\mathrm{tot}^{n_1-2}}{2k_+} \ll 1, \tag{S83}$$

which is typically much less than unity. For example, typical values for ε in the case of the amyloid-β peptide are $\varepsilon = 5 \times 10^{-11}$ for Aβ42 (3) or $\varepsilon = 3 \times 10^{-12}$ for Aβ40 (11). Physically, a small ε is necessary to ensure that the aggregates that are formed during the reaction are long. If nucleation is slow compared to growth, few nuclei will form which can grow very long. On the contrary, when nucleation is fast compared to growth, many nuclei can form; fewer monomers, however, will be available for growth, causing aggregates to be shorter on average (see discussion after Eq. (S5)).

Perturbation expansion. Since $\varepsilon \ll 1$ can be considered as small perturbation parameter, we construct a perturbation solution to Eq. (S82). To this end, it is convenient to rewrite Eq. (S32) in dimensionless form first:

$$\frac{\mathrm{d}\bar{P}(\tau)}{\mathrm{d}\tau} = \varepsilon\, \bar{m}_\mathrm{f}(\tau)^{n_1} + \nu_2\, \bar{m}_\mathrm{f}(\tau)^{n_2} \Big(1 - \bar{m}_\mathrm{f}(\tau) - \bar{m}_\mathrm{b}(\tau)\Big), \tag{S84a}$$
$$\frac{\mathrm{d}\bar{m}_\mathrm{f}(\tau)}{\mathrm{d}\tau} = -\bar{m}_\mathrm{f}(\tau)\bar{P}(\tau) - \beta_\mathrm{m}\, \bar{m}_\mathrm{f}(\tau) + \alpha_\mathrm{m}\, \bar{m}_\mathrm{b}(\tau), \tag{S84b}$$
$$\frac{\mathrm{d}\bar{m}_\mathrm{b}(\tau)}{\mathrm{d}\tau} = \beta_\mathrm{m}\, \bar{m}_\mathrm{f}(\tau) - \alpha_\mathrm{m}\, \bar{m}_\mathrm{b}(\tau), \tag{S84c}$$

where we have eliminated the equation for $M(t)$ using conservation of mass, Eq. (S33), we have defined

$$\bar{P} = \frac{P_\mathrm{f}(t)}{m_\mathrm{tot}}, \tag{S84d}$$
$$\bar{m}_\mathrm{f} = \frac{m_\mathrm{f}(t)}{m_\mathrm{tot}}, \tag{S84e}$$
$$\bar{m}_\mathrm{b} = \frac{m_\mathrm{b}(t)}{m_\mathrm{tot}}, \tag{S84f}$$
$$\tau = 2k_+ m_\mathrm{tot} t, \tag{S84g}$$

and we have introduced the following dimensionless parameters:

$$\nu_2 = \frac{k_2 m_\mathrm{tot}^{n_2-1}}{2k_+}, \tag{S84h}$$
$$\beta_\mathrm{m} = \frac{k_\mathrm{m}^\mathrm{on} C_i}{2k_+ m_\mathrm{tot}}, \tag{S84i}$$
$$\alpha_\mathrm{m} = \frac{k_\mathrm{m}^\mathrm{off}}{2k_+ m_\mathrm{tot}}. \tag{S84j}$$

A perturbation series solution of Eq. (S84) can now be constructed as

$$\bar{P}(\tau) = \bar{P}^{(0)}(\tau) + \varepsilon\, \bar{P}^{(1)}(\tau) + \mathcal{O}(\varepsilon^2), \tag{S85a}$$
$$\bar{m}_\mathrm{f}(\tau) = \bar{m}_\mathrm{f}{}^{(0)}(\tau) + \varepsilon\, \bar{m}_\mathrm{f}{}^{(1)}(\tau) + \mathcal{O}(\varepsilon^2), \tag{S85b}$$
$$\bar{m}_\mathrm{b}(\tau) = \bar{m}_\mathrm{b}{}^{(0)}(\tau) + \varepsilon\, \bar{m}_\mathrm{b}{}^{(1)}(\tau) + \mathcal{O}(\varepsilon^2). \tag{S85c}$$

$\mathcal{O}(\varepsilon^0)$ ***solution – initial layer dynamics.*** After inserting the perturbation expansions Eq. (S85) in Eq. (S84) and then collecting terms for each order of ε, we arrive at the equations at order ε^0:

$$\frac{\mathrm{d}\bar{P}^{(0)}(\tau)}{\mathrm{d}\tau} = \nu_2\, \bar{m_{\mathrm{f}}}^{(0)}(\tau)^{n_2}\left(1 - \bar{m_{\mathrm{f}}}^{(0)}(\tau) - \bar{m_{\mathrm{b}}}^{(0)}(\tau)\right), \tag{S86a}$$

$$\frac{\mathrm{d}\bar{m_{\mathrm{f}}}^{(0)}(\tau)}{\mathrm{d}\tau} = -\bar{m_{\mathrm{f}}}^{(0)}(\tau)\bar{P}^{(0)}(\tau) - \beta_{\mathrm{m}}\, \bar{m_{\mathrm{f}}}^{(0)}(\tau) + \alpha_{\mathrm{m}}\, \bar{m_{\mathrm{b}}}^{(0)}(\tau), \tag{S86b}$$

$$\frac{\mathrm{d}\bar{m_{\mathrm{b}}}^{(0)}(\tau)}{\mathrm{d}\tau} = \beta_{\mathrm{m}}\, \bar{m_{\mathrm{f}}}^{(0)}(\tau) - \alpha_{\mathrm{m}}\, \bar{m_{\mathrm{b}}}^{(0)}(\tau), \tag{S86c}$$

Applying the initial conditions $\bar{m_{\mathrm{f}}}^{(0)}(0) = 1$ and $\bar{P}^{(0)}(0) = \bar{m_{\mathrm{b}}}^{(0)}(0) = 0$, we see immediately that the solution to the $O(\varepsilon^0)$ equation, Eq. (S86), is:

$$\bar{P}^{(0)} \equiv 0, \tag{S87a}$$

$$\bar{m_{\mathrm{f}}}^{(0)} = 1 - \frac{\beta_{\mathrm{m}}}{\alpha_{\mathrm{m}} + \beta_{\mathrm{m}}}\left(1 - e^{-(\alpha_{\mathrm{m}}+\beta_{\mathrm{m}})\tau}\right), \tag{S87b}$$

$$\bar{m_{\mathrm{b}}}^{(0)} = \frac{\beta_{\mathrm{m}}}{\alpha_{\mathrm{m}} + \beta_{\mathrm{m}}}\left(1 - e^{-(\alpha_{\mathrm{m}}+\beta_{\mathrm{m}})\tau}\right). \tag{S87c}$$

Hence, due to to the separation of timescales between nucleation and growth, the dynamics of the system evolves initially through a rapid phase of equilibration, where the inhibitor binds monomers but no aggregates form at leading order in ε. Note that during this initial phase, the total monomer concentration $\bar{m}^{(0)} = \bar{m_{\mathrm{f}}}^{(0)} + \bar{m_{\mathrm{b}}}^{(0)} = 1$ is constant at leading order in ε. During the initial layer phase, which is the temporal equivalent of a boundary layer (e.g. in fluid dynamics), the initial value of the monomer concentration relaxes quickly to the equilibrium value $\frac{\beta_{\mathrm{m}}}{\alpha_{\mathrm{m}}+\beta_{\mathrm{m}}}$ before any aggregation occurs (see Figs. S2 and Fig. 2 of the main text).

$\mathcal{O}(\varepsilon^1)$ ***solution – slow manifold.*** After this initial, rapid phase of monomer redistribution through inhibitor binding, the system enters a slower phase of dynamics where, at leading order in ε, the system stays on the slow manifold

$$\bar{m_{\mathrm{f}}}(\tau) = \frac{\alpha_{\mathrm{m}}}{\alpha_{\mathrm{m}} + \beta_{\mathrm{m}}}\bar{m}(\tau) \tag{S88}$$

at all times. This relationship, valid in the slow manifold, is verified against numerical integration of Eq. (S32) in Fig. S2d.

To obtain a solution valid for the slow manifold, we collect terms of order ε^1 in our perturbation expansion of Eq. (S84). Using Eq. (S87), we arrive at the following first order equations:

$$\frac{\mathrm{d}\bar{P}^{(1)}(\tau)}{\mathrm{d}\tau} = \bar{m_{\mathrm{f}}}^{(0)}(\tau)^{n_1} + \nu_2\, \bar{m_{\mathrm{f}}}^{(0)}(\tau)^{n_2}\left(-\bar{m_{\mathrm{f}}}^{(1)}(\tau) - \bar{m_{\mathrm{b}}}^{(1)}(\tau)\right) \tag{S89a}$$

$$\frac{\mathrm{d}\bar{m_{\mathrm{f}}}^{(1)}(\tau)}{\mathrm{d}\tau} = -\bar{m_{\mathrm{f}}}^{(0)}(\tau)\bar{P}^{(1)}(\tau) - \beta_{\mathrm{m}}\, \bar{m_{\mathrm{f}}}^{(1)}(\tau) + \alpha_{\mathrm{m}}\, \bar{m_{\mathrm{b}}}^{(1)}(\tau), \tag{S89b}$$

$$\frac{\mathrm{d}\bar{m_{\mathrm{b}}}^{(1)}(\tau)}{\mathrm{d}\tau} = \beta_{\mathrm{m}}\, \bar{m_{\mathrm{f}}}^{(1)}(\tau) - \alpha_{\mathrm{m}}\, \bar{m_{\mathrm{b}}}^{(1)}(\tau), \tag{S89c}$$

where, to match with the $O(\varepsilon^0)$ solution, we set

$$\bar{m_{\mathrm{f}}}^{(0)} = \frac{1 - e^{-\frac{\kappa}{\lambda}\left(a + \frac{a}{b}\right)}}{1 + b} =: \mu_0, \tag{S90}$$

where $a = k_{\mathrm{m}}^{\mathrm{on}} C_i/\kappa$ and $b = K_{\mathrm{m}} C_i$. In terms of the original dimensional variables, Eq. (S89) can be written as

$$\frac{d}{dt}\begin{pmatrix} P_{\mathrm{f}}^{(1)} \\ m_{\mathrm{f}}^{(1)} \\ m_{\mathrm{b}}^{(1)} \end{pmatrix} = \begin{pmatrix} 0 & -k_2 m_{\mathrm{tot}}^{n_2}\mu_0^{n_2} & -k_2 m_{\mathrm{tot}}^{n_2}\mu_0^{n_2} \\ -2k_+ m_{\mathrm{tot}}\mu_0 & -k_{\mathrm{m}}^{\mathrm{on}} C_i & k_{\mathrm{m}}^{\mathrm{off}} \\ 0 & k_{\mathrm{m}}^{\mathrm{on}} C_i & -k_{\mathrm{m}}^{\mathrm{off}} \end{pmatrix}\begin{pmatrix} P_{\mathrm{f}}^{(1)} \\ m_{\mathrm{f}}^{(1)} \\ m_{\mathrm{b}}^{(1)} \end{pmatrix} + \begin{pmatrix} k_1 m_{\mathrm{tot}}^{n_1}\mu_0^{n_1} \\ 0 \\ 0 \end{pmatrix}, \tag{S91}$$

and can be considered to be the equivalent of the linearised equations Eq. (**??**) and Eq. (S72). The eigenvalues of the above matrix are

$$x_1 = \kappa\sqrt{\mu_0^{n_2+1}}, \quad x_2 = -\kappa\sqrt{\mu_0^{n_2+1}}, \quad x_3 = -(k_{\mathrm{m}}^{\mathrm{on}} C_i + k_{\mathrm{m}}^{\mathrm{off}}) \tag{S92}$$

with associated eigenvectors

$$\begin{pmatrix} -\frac{x_1(k_{\mathrm{m}}^{\mathrm{off}} + k_{\mathrm{m}}^{\mathrm{on}} C_i + x_1)}{k_{\mathrm{m}}^{\mathrm{on}} C_i\, 2k_+ m_{\mathrm{tot}}\mu_0} \\ \frac{k_{\mathrm{m}}^{\mathrm{off}} + x_1}{k_{\mathrm{m}}^{\mathrm{on}} C_i} \\ 1 \end{pmatrix}, \quad \begin{pmatrix} -\frac{x_2(k_{\mathrm{m}}^{\mathrm{off}} + k_{\mathrm{m}}^{\mathrm{on}} C_i + x_2)}{k_{\mathrm{m}}^{\mathrm{on}} C_i\, 2k_+ m_{\mathrm{tot}}\mu_0} \\ \frac{k_{\mathrm{m}}^{\mathrm{off}} + x_2}{k_{\mathrm{m}}^{\mathrm{on}} C_i} \\ 1 \end{pmatrix}, \quad \begin{pmatrix} 0 \\ -1 \\ 1 \end{pmatrix} \tag{S93}$$

It follows

$$U_{11} = -\frac{x_1(k_{\rm m}^{\rm off} + k_{\rm m}^{\rm on} C_i + x_1)}{k_{\rm m}^{\rm on} C_i \, 2k_+ m_{\rm tot}\mu_0} \qquad \left(U^{-1}\right)_{11} = -\frac{k_{\rm m}^{\rm on} C_i \, 2k_+ m_{\rm tot}\mu_0}{2x_1(k_{\rm m}^{\rm off} + k_{\rm m}^{\rm on} C_i + x_1)} \tag{S94}$$

Formal integration of Eq. (S82b) yields

$$M(t) = m_{\rm tot}\left[1 - \exp\left(-2k_+\mu_0 \int_0^t P(s)ds\right)\right], \tag{S95}$$

where we used Eq. (S90). Therefore using Eq. (S94), we find the following self-consistent solution to the aggregation kinetics with a monomer binder

$$\frac{M(t)}{m_{\rm tot}} = 1 - \exp\left(-\frac{\lambda_{\rm eff}^2}{2\kappa_{\rm eff}^2}\left(e^{\kappa_{\rm eff} t} - 1\right)\right), \tag{S96}$$

where the expressions for the effective λ and κ are

$$\boxed{\frac{\lambda_{\rm eff}}{\lambda} = \sqrt{2\mu_0^{n_1+1} U_{11}\left(U^{-1}\right)_{11}} = \mu_0^{\frac{n_1+1}{2}}} \tag{S97a}$$

$$\boxed{\frac{\kappa_{\rm eff}}{\kappa} = \frac{x_1}{\kappa} = \mu_0^{\frac{n_2+1}{2}}} \tag{S97b}$$

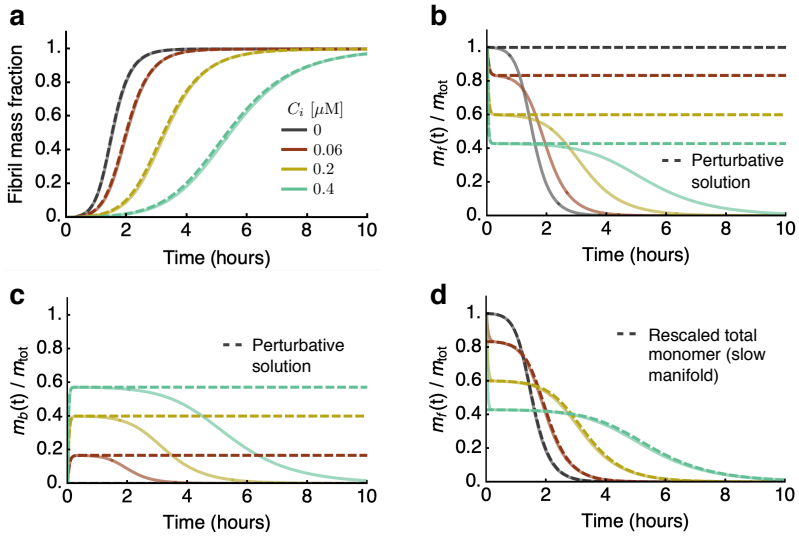

Fig. S2. (a) Time course of aggregate mass concentration in the presence of increasing concentrations of an inhibitor of that binds monomers calculated using numerical integration of the master equation Eq. (S32) (solid lines) and our analytical solution (dashed line). (b-c) Free and bound monomer concentrations. In the initial layer phase, there is rapid binding of the inhibitor to the free monomers (dashed lines indicate the $\mathcal{O}(\varepsilon^0)$ perturbation solution Eq. (S87)); no aggregation occurs during this phase. A slow manifold phase follows, where the both the free and bound monomer concentrations decrease slowly due to aggregation. (d) In the slow manifold, there is a relationship linking the free monomer concentration to the total monomer concentration Eq. (S88). This relationship is verified here numerically through integration of the master equation Eq. (S32) (solid line: free monomer concentration, dashed line: Eq. (S88)). Calculation parameters are the same as in the left column of Fig. 2 of the main text.

S2.4. Combining binding to monomers, fibril ends and fibril surface. We now consider the case when the inhibitor can bind all protein species, i.e. monomers, fibril ends and surfaces. We proceed in a similar way to the previous sections and we first nondimensionalise Eq. (S32) by introducing a rescaled time coordinate $\tau = 2k_+ m_{\rm tot} t$, the variables

$$\bar{P}_{\rm f} = \frac{P_{\rm f}(t)}{m_{\rm tot}}, \quad \bar{P}_{\rm b} = \frac{P_{\rm b}(t)}{m_{\rm tot}}, \quad \bar{M}_{\rm f} = \frac{M_{\rm f}(t)}{m_{\rm tot}}, \quad \bar{M}_{\rm b} = \frac{M_{\rm b}(t)}{m_{\rm tot}}, \quad \bar{m}_{\rm f} = \frac{m_{\rm f}(t)}{m_{\rm tot}}, \quad \bar{m}_{\rm b} = \frac{m_{\rm b}(t)}{m_{\rm tot}}, \tag{S98a}$$

and the following dimensionless parameters:

$$\nu_2 = \frac{k_2 m_{\rm tot}^{n_2-1}}{2k_+}, \quad \beta_\times = \frac{k_\times^{\rm on} C_i}{2k_+ m_{\rm tot}}, \quad \beta_\times = \frac{k_\times^{\rm on} C_i}{2k_+ m_{\rm tot}}, \quad \times = {\rm m, s, e} \tag{S98b}$$

By seeking for a perturbation solution $\bar{P}_{\rm f}(\tau) = \bar{P}_{\rm f}^{\,(0)}(\tau) + \varepsilon\, \bar{P}_{\rm f}^{\,(1)}(\tau) + \mathcal{O}(\varepsilon^2)$, etc. we arrive at the following equations at order $\mathcal{O}(\varepsilon^0)$

$$\frac{d}{dt}\begin{pmatrix} \bar{P}_{\rm f}^{\,(1)} \\ \bar{m}_{\rm f}^{\,(1)} \\ \bar{m}_{\rm b}^{\,(1)} \\ \bar{P}_{\rm b}^{\,(1)} \\ \bar{M}_{\rm b}^{\,(1)} \end{pmatrix} = \begin{pmatrix} -\beta_{\rm e} & -\nu_2\mu_0^{n_2} & -\nu_2\mu_0^{n_2} & \alpha_{\rm e} & -\nu_2\mu_0^{n_2} \\ -\mu_0 & -\beta_{\rm m} & \alpha_{\rm m} & 0 & 0 \\ 0 & \beta_{\rm m} & -\alpha_{\rm m} & 0 & 0 \\ \beta_{\rm e} & 0 & 0 & -\alpha_{\rm e} & 0 \\ 0 & -\beta_{\rm s} & -\beta_{\rm s} & 0 & -(\alpha_{\rm s}+\beta_{\rm s}) \end{pmatrix} \begin{pmatrix} \bar{P}_{\rm f}^{\,(1)} \\ \bar{m}_{\rm f}^{\,(1)} \\ \bar{m}_{\rm b}^{\,(1)} \\ \bar{P}_{\rm b}^{\,(1)} \\ \bar{M}_{\rm b}^{\,(1)} \end{pmatrix} + \begin{pmatrix} \mu_0^{n_1} \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \tag{S99}$$

where $\mu_0 = \alpha_m/(\alpha_m + \beta_m)$. The characteristic polynomial of the above matrix is

$$(x+\alpha_m+\beta_m)\Big[x^4 + (\alpha_e+\beta_e+\alpha_s+\beta_s)x^3 + [(\alpha_e+\beta_e)(\alpha_s+\beta_s) - \nu_2\mu_0^{n_2+1}]x^2 - (\alpha_e+\alpha_s)\nu_2\mu_0^{n_2+1}x - \alpha_e\alpha_s\nu_2\mu_0^{n_2+1}\Big] = 0. \tag{S100}$$

Using dominant balance argument, we can find an approximated expression for the largest (positive) eigenvalue x_1 by writing $x_1 = \sqrt{\nu_2}X_1$ leading to $(\alpha_e+\beta_e)(\alpha_s+\beta_s)X_1^2 - \alpha_e\alpha_s\mu_0^{n_2+1} = 0$, i.e.

$$x_1 \simeq \sqrt{\nu_2 \left(\frac{\alpha_e}{\alpha_e+\beta_e}\right)\left(\frac{\alpha_s}{\alpha_s+\beta_s}\right)\left(\frac{\alpha_m}{\alpha_m+\beta_m}\right)^{n_2+1}}. \tag{S101}$$

Using Eq. (**??**) the final solution for the aggregate mass is found to be:

$$\frac{M(t)}{m(0)} = 1 - \exp\left(-\frac{\lambda_{\rm eff}^2}{2\kappa_{\rm eff}^2}\left[e^{\kappa_{\rm eff}t} - 1\right]\right), \tag{S102}$$

where

$$\frac{\lambda_{\rm eff}}{\lambda} = \left(\frac{\alpha_{\rm e}}{\alpha_{\rm e}+\beta_{\rm e}}\right)^{\frac{1}{2}}\left(\frac{\alpha_{\rm m}}{\alpha_{\rm m}+\beta_{\rm m}}\right)^{\frac{n_1+1}{2}} = \left(\frac{1}{1+K_{\rm m}C_i}\right)^{\frac{n_1+1}{2}}\left(\frac{1}{1+K_{\rm e}C_i}\right)^{\frac{1}{2}}, \tag{S103}$$

$$\frac{\kappa_{\rm eff}}{\kappa} = \left(\frac{\alpha_{\rm e}}{\alpha_{\rm e}+\beta_{\rm e}}\right)^{\frac{1}{2}}\left(\frac{\alpha_{\rm s}}{\alpha_{\rm s}+\beta_{\rm s}}\right)^{\frac{1}{2}}\left(\frac{\alpha_{\rm m}}{\alpha_{\rm m}+\beta_{\rm m}}\right)^{\frac{n_2+1}{2}} = \left(\frac{1}{1+K_{\rm m}C_i}\right)^{\frac{n_2+1}{2}}\left(\frac{1}{1+K_{\rm e}C_i}\right)^{\frac{1}{2}}\left(\frac{1}{1+K_{\rm s}C_i}\right)^{\frac{1}{2}}. \tag{S104}$$

In summary, our asymptotic analysis of Eq. (S32) shows that, in the case when the inhibitor can bind monomers, fibril ends and surfaces, the rate parameters are renormalized according to the following scheme:

$$\frac{k_+^{\rm eff}}{k_+} = \left(\frac{1}{1+K_{\rm m}C_i}\right)\left(\frac{1}{1+K_{\rm e}C_i}\right), \tag{S105}$$

$$\frac{k_1^{\rm eff}}{k_1} = \left(\frac{1}{1+K_{\rm m}C_i}\right)^{n_1}, \tag{S106}$$

$$\frac{k_2^{\rm eff}}{k_2} = \left(\frac{1}{1+K_{\rm m}C_i}\right)^{n_2}\left(\frac{1}{1+K_{\rm s}C_i}\right), \tag{S107}$$

which recovers Eq. (S41). The effect of the individual modes of inhibition on λ and κ combine multiplicatively.

Table S2. Effective rates of aggregation $\frac{\lambda^{\rm eff}}{\lambda}$ and $\frac{\kappa^{\rm eff}}{\kappa}$ as a function of $a = k_\times^{\rm on} C_i/\kappa$ and $b = K_\times C_i$. These functions yield the plots in Fig. 3a,b of the main text. In this table x_1, x_2, x_3 are the 3 roots of the equation $x^3 + \left(a + \frac{a}{b}\right) x^2 - x - \frac{a}{b} = 0$.

Targeted species	Monomers	Aggregate ends	Fibril surface
Effective rate of 1. pathways $\frac{\lambda^{\rm eff}}{\lambda}$	$\left(\frac{1-e^{-\frac{\kappa}{\lambda}\left(a+\frac{a}{b}\right)}}{1+b}\right)^{\frac{n_1+1}{2}}$	$\left(\frac{2x_1\left(x_1+\frac{a}{b}\right)}{(x_1-x_2)(x_1-x_3)}\right)^{\frac{1}{2}}$	1
Effective rate of 2. pathways $\frac{\kappa^{\rm eff}}{\kappa}$	$\left(\frac{1-e^{-\left(a+\frac{a}{b}\right)}}{1+b}\right)^{\frac{n_2+1}{2}}$	x_1	x_1
Parameter definition	$x_1 = -\frac{1}{3}\left(a+\frac{a}{b}+C+\frac{\Delta_0}{C}\right)$ $a = \frac{k_\times^{\rm on} C_i}{\kappa}$ $C = \left(\frac{\Delta_1+\sqrt{\Delta_1^2-4\Delta_0^3}}{2}\right)^{1/3}$	$x_2 = -\frac{1}{3}\left(a+\frac{a}{b}+\xi C+\xi^2\frac{\Delta_0}{C}\right)$ $b = K_\times C_i$ $\Delta_0 = \left(a+\frac{a}{b}\right)^2+3$	$x_3 = -\frac{1}{3}\left(a+\frac{a}{b}+\xi^2 C+\xi\frac{\Delta_0}{C}\right)$ $\xi = \frac{-1+\sqrt{3}i}{2}$ $\Delta_1 = 2\left(a+\frac{a}{b}\right)^3+9\left(a+\frac{a}{b}\right)-27\frac{a}{b}$

S3. Asymptotic solutions to aggregation kinetics with variable inhibitor concentration

Our asymptotic approach for solving Eq. (S32) can be generalized straightforwardly to account for the situation of variable binder concentration. We discuss here this idea on the example of monomer binding; the treatment for binding to fibril ends or fibril surfaces is fully analogous. On accounting for a variable binder concentration, the non-dimensionalized moment equations (see Eq. (S84)) in this case are:

$$\frac{\mathrm{d}\bar{P}(\tau)}{\mathrm{d}\tau} = \varepsilon\,\bar{m}_{\rm f}(\tau)^{n_1} + \nu_2\,\bar{m}_{\rm f}(\tau)^{n_2}\Big(1-\bar{m}_{\rm f}(\tau)-\bar{m}_{\rm b}(\tau)\Big), \tag{S108a}$$

$$\frac{\mathrm{d}\bar{m}_{\rm f}(\tau)}{\mathrm{d}\tau} = -\bar{m}_{\rm f}(\tau)\bar{P}(\tau) - \beta\,\bar{C}_i(\tau)\bar{m}_{\rm f}(\tau) + \alpha\,\bar{m}_{\rm b}(\tau), \tag{S108b}$$

$$\frac{\mathrm{d}\bar{m}_{\rm b}(\tau)}{\mathrm{d}\tau} = \beta\,\bar{C}_i(\tau)\bar{m}_{\rm f}(\tau) - \alpha\,\bar{m}_{\rm b}(\tau) = -\frac{\mathrm{d}\bar{C}_i(\tau)}{\mathrm{d}\tau}, \tag{S108c}$$

where

$$\bar{C}_i = \frac{C_i}{m_{\rm tot}}, \tag{S108d}$$

$$\beta = \frac{k_{\rm m}^{\rm on}}{2k_+ m_{\rm tot}}, \tag{S108e}$$

$$\alpha = \frac{k_{\rm m}^{\rm off}}{2k_+ m_{\rm tot}}. \tag{S108f}$$

Using a perturbation expansion $\bar{P} = \bar{P}^{(0)} + \varepsilon\bar{P}^{(0)} + \cdots$, etc., the equations at order ε^0 are found to be:

$$\frac{\mathrm{d}\bar{P}^{(0)}(\tau)}{\mathrm{d}\tau} = \nu_2\,\bar{m}_{\rm f}{}^{(0)}(\tau)^{n_2}\Big(1-\bar{m}_{\rm f}{}^{(0)}(\tau)-\bar{m}_{\rm b}{}^{(0)}(\tau)\Big), \tag{S109a}$$

$$\frac{\mathrm{d}\bar{m}_{\rm f}{}^{(0)}(\tau)}{\mathrm{d}\tau} = -\bar{m}_{\rm f}{}^{(0)}(\tau)\bar{P}^{(0)}(\tau) - \beta\,\bar{C}_i{}^{(0)}(\tau)\bar{m}_{\rm f}{}^{(0)}(\tau) + \alpha\,\bar{m}_{\rm b}{}^{(0)}(\tau), \tag{S109b}$$

$$\frac{\mathrm{d}\bar{m}_{\rm b}{}^{(0)}(\tau)}{\mathrm{d}\tau} = \beta\,\bar{C}_i{}^{(0)}(\tau)\bar{m}_{\rm f}{}^{(0)}(\tau) - \alpha\,\bar{m}_{\rm b}{}^{(0)}(\tau) = -\frac{\mathrm{d}\bar{C}_i{}^{(0)}(\tau)}{\mathrm{d}\tau}. \tag{S109c}$$

The solution, subject to initial conditions $\bar{m}_{\rm f}{}^{(0)}(0) = 1$, $\bar{C}_i{}^{(0)} = \gamma_0$, $\bar{P}^{(0)}(0) = \bar{m}_{\rm f}{}^{(0)}(0) = 0$, is:

$$\bar{P}^{(0)} \equiv 0, \tag{S110}$$

$$\bar{m}_{\rm b}{}^{(0)} = \frac{A_1A_2\left(1-e^{\beta\xi\tau}\right)}{A_2 - A_1e^{\beta\xi\tau}}, \tag{S111}$$

$$\bar{m}_{\rm f}{}^{(0)} = 1 - \frac{A_1A_2\left(1-e^{\beta\xi\tau}\right)}{A_2 - A_1e^{\beta\xi\tau}}, \tag{S112}$$

$$\bar{C}_i{}^{(0)} = \gamma_0 - \bar{m}_{\rm b}{}^{(0)}, \tag{S113}$$

where

$$A_{1,2} = \frac{1+\gamma_0+\frac{\alpha}{\beta}}{2} \pm \sqrt{\left(\frac{1+\gamma_0+\frac{\alpha}{\beta}}{2}\right)^2 - \gamma_0} \tag{S114}$$

and $\xi = A_1 - A_2$. Thus, we have separation of timescales and the solution is given by

$$\frac{M(t)}{m_{\rm tot}} = 1 - \exp\left(-\frac{\lambda_{\rm eff}^2}{2\kappa_{\rm eff}^2}\left(e^{\kappa_{\rm eff}t} - 1\right)\right), \tag{S115}$$

where

$$\frac{\lambda_{\rm eff}}{\lambda} = (1 - A_2)^{\frac{n_1+1}{2}} = \left(\frac{1}{1 + K_{\rm m}C_i^{\rm eq}}\right)^{\frac{n_1+1}{2}}, \tag{S116}$$

$$\frac{\kappa_{\rm eff}}{\kappa} = (1 - A_2)^{\frac{n_2+1}{2}} = \left(\frac{1}{1 + K_{\rm m}C_i^{\rm eq}}\right)^{\frac{n_2+1}{2}}. \tag{S117}$$

Hence, $1 - A_2$ corresponds to the equilibrium concentration of free monomers. The kinetics are expressed in terms effective rate parameters which are renormalized by the presence of inhibitor according to the following scheme:

$$\frac{k_+^{\rm inhibition}}{k_+} = \frac{1}{1 + K_{\rm m}C_i^{\rm eq}}, \tag{S118}$$

$$\frac{k_n^{\rm inhibition}}{k_n} = \left(\frac{1}{1 + K_{\rm m}C_i^{\rm eq}}\right)^{n_1}, \tag{S119}$$

$$\frac{k_2^{\rm inhibition}}{k_2} = \left(\frac{1}{1 + K_{\rm m}C_i^{\rm eq}}\right)^{n_2}, \tag{S120}$$

where $C_i^{\rm eq}$ is the equilibrium concentration of inhibitor.

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