Supporting Information:
General integrated rate law for complex self-assembly reactions reveals the mechanism of amyloid-beta co-aggregation

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S1. INTRODUCTION TO LIE GROUP THEORY OF DIFFERENTIAL EQUATIONS

The theory of Lie groups finds diverse application across theoretical physics. It was originally developed by Sophus Lie as a systematic method for exactly solving nonlinear differential equations (DEs) by exploiting their symmetry properties; however, this application is largely unknown today. Consequently, it is widely believed that nonlinear DEs can be solved only by a combination of guesswork and ad-hoc methods of individually narrow applicability. In fact, most such methods may be derived from the Lie group theory of DEs, which provides a unified and general platform for solving DEs of any kind. Here we give a brief summary of those parts of Lie group theory of DEs that are utilized in the paper; for a more in-depth treatment, refs. [1, 2] can be consulted.

A. Continuous transformations

A point transformation maps the independent and dependent variables x and y of the object being acted upon to $\tilde{x}$ and $\tilde{y}$. Point transformations that are indexed by real-valued parameter s may be written $\tilde{x} = \tilde{x}(x, y, s)$, $\tilde{y} = \tilde{x}(x, y, s)$ and are continuous: the extent of the transformation can be "dialled up" or down arbitrarily by increaseing or decreasing s. When these are also invertible, contain the identity at $s = 0$, and obey associativity via $\tilde{x}(\tilde{x}(x, y, s), \tilde{y}(x, y, s), t) = \tilde{x}(x, y, s + t)$, they form a group. Because they are continuous, the infinitesimal transformation exists and can be accessed by expanding around $s = 0$:

$$\tilde{x}(x, y, s) = x + s\xi(x, y) + \ldots, \qquad \xi(x, y) = \left.\frac{\partial \tilde{x}}{\partial s}\right|_{s=0}, \tag{S1}$$

$$\tilde{y}(x, y, s) = y + s\eta(x, y) + \ldots, \qquad \eta(x, y) = \left.\frac{\partial \tilde{y}}{\partial s}\right|_{s=0}. \tag{S2}$$

$(\xi(x, y), \eta(x, y))$ define the tangent vector of the transformation. This can alternatively be expressed as:

$$\tilde{x}(x, y, s) = x + s\boldsymbol{X}x + O(s^2), \qquad \tilde{y}(x, y, s) = y + s\boldsymbol{X}y + O(s^2), \tag{S3}$$

where the operator $\boldsymbol{X}$ is the infinitesimal generator of the point transformation, given by:

$$\boldsymbol{X} = \xi(x,y)\frac{\partial}{\partial x} + \eta(x,y)\frac{\partial}{\partial y}, \tag{S4}$$

Integrating the tangent vector over s will yield a finite transformation.

B. What is a Lie symmetry?

A Lie symmetry of an object is a continuous transformation that leaves the object invariant. A rotational symmetry of a square is not a Lie symmetry, as it is discrete and can only be performed in multiples of $\pi/2$ (Fig. S1**a**). However, a rotational symmetry of a circle can involve any angle, and is thus a Lie symmetry (Fig. S1**b**). A DE can be viewed as a geometrical object: a manifold consisting of the union of all its possible solutions. They often possess Lie point symmetries: transformations of the dependent and independent variables that leave the overall manifold invariant. Applied to a particular solution (that spans a subspace of the DE manifold) a Lie symmetry of the DE transforms it into another solution (see Fig. S1**c**)). By analogy, a rotational Lie symmetry maps a circle to itself but maps a point on the circle to another point.

The ability to express a continuous point transformation in infinitesimal form also makes it possible to calculate systematically the Lie point symmetries possessed by a given object. For DEs this procedure, although algorithmic, can be extremely long-winded because derivatives are not transformed in a straightforward way by Lie point symmetries. To avoid dozens or hundreds of pages of working, it is thus best implemented using computer algebra systems (CAS). On the other hand, for objects without derivatives the procedure is simple. For example, the circle in Fig. S1**b** may be expressed in polar coordinates as $F = r - c = 0$. In these co-ordinates the generator is $\boldsymbol{X} = \xi_r\partial/\partial r + \xi_\theta\partial/\partial\theta$. Trivially, solving $\boldsymbol{X}F = 0$ yields $\xi_r = 0$ and arbitrary ξ_θ: a rotational symmetry. In cartesian co-ordinates $F = x^2 + y^2 - c$, and solving $\boldsymbol{X}F = 0$ yields η in terms of ξ, giving the generator as follows:

$$0 = \boldsymbol{X}F = \left(\xi(x,y)\frac{\partial}{\partial x} + \eta(x,y)\frac{\partial}{\partial y}\right)(x^2 + y^2 - c) \tag{S5}$$

$$\therefore \quad \boldsymbol{X} = \xi(x,y)\left(y\frac{\partial}{\partial x} - x\frac{\partial}{\partial y}\right). \tag{S6}$$

The arbitrary rotational transformation is recovered in cartesian coordinates as expected.

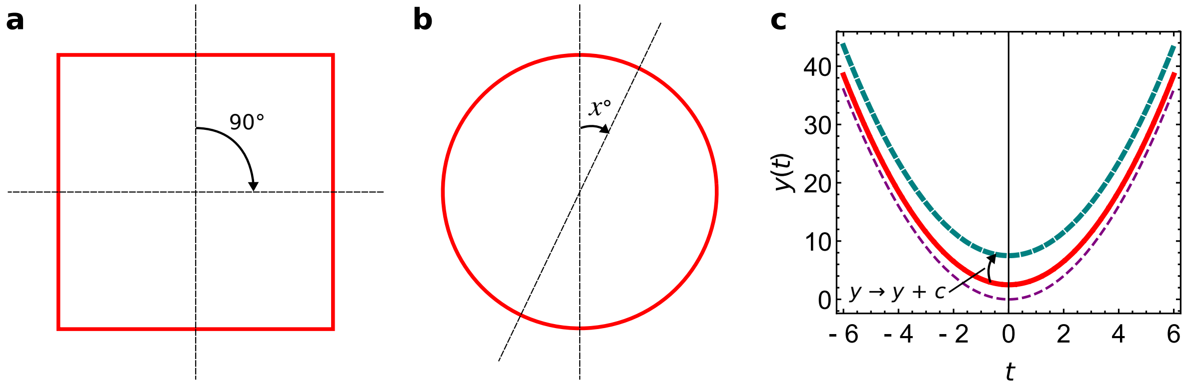

FIG. S1: An overview of Lie symmetries. **a**: Squares have discrete rotational symmetries. These cannot be reduced to infinitesimal form; therefore, they are not Lie symmetries. **b**: Circles can be rotated by any amount; rotation is thus a Lie symmetry of the circle. **c**: In general, symmetries of DEs map solutions to other solutions with different boundary conditions. An arbitrary translation on the y axis is a Lie symmetry of the DE $\dot{y} = 2t$, because this is solved by $y = t^2 + c$, and the translation just changes the value of c, giving the solution to the DE for new boundary conditions.

C. Approximate symmetries

A more recent development in the field of Lie group analysis of DEs is the discovery that perturbed DEs can possess "approximate symmetries" [3]. These leave a perturbed DE invariant only to some finite order in the perturbation parameter ε. They can be identified by solving:

$$(\boldsymbol{X}^{(0)} + \epsilon \boldsymbol{X}^{(1)} + ...)(F_0 + \varepsilon F_1)|_{F_0+\epsilon F_1=0} = 0, \tag{S7}$$

order-by-order [4]. They can often be used to find approximate solutions to perturbed DEs. However, approximate symmetries of DEs are more difficult to compute than exact symmetries, and there exist few if any CAS implementations of the procedure.

D. Perturbation symmetries

Lie point symmetries of a DE are traditionally thought of as transformations acting on its dependent and independent variables. However, there is nothing to stop us pretending that the perturbation parameter ε in a perturbed DE is an independent variable, and searching for symmetries that act on ε as well [5]. Doing so can significantly extend the power of the Lie group approach. We have previously termed these “perturbation symmetries” (See ref. [6] for a detailed explanation of these symmetries and this choice of terminology).

Crucially, if a reference solution is known for the perturbation problem with $\varepsilon = 0$, this may be converted using a perturbation symmetry of the general solution into a solution valid for arbitrary ε. This is because such a symmetry leaves the space of solutions for all possible ε unchanged. Thus, acting on a solution for a specific ε maps it to another solution with a different ε.

Unfortunately, both exact and approximate perturbation symmetries are often extremely difficult or impossible to compute, due to the high dimensionality of the manifold, which defeats most or all CAS implementations. However, we recently developed a method (explained in detail in [6]) that can compute approximate perturbation symmetries of the *solution* to a perturbed DE directly, with far greater ease than earlier methods.

S2. METHOD OF ASYMPTOTIC LIE SYMMMETRIES FOR SOLVING PROTEIN AGGREGATION KINETICS

In the main text we focus on a highly general rate law for protein aggregation kinetics, which in nondimensional form is given by Eqs. (12). We reproduce these here for convenience:

$$\frac{d\Pi}{d\tau} = 2\varepsilon\frac{\alpha_1(t,m)}{\alpha_1(0,m_{\mathrm{tot}})} + \frac{\alpha_2(m)}{\alpha_2(m_{\mathrm{tot}})}(1-\mu(\tau)) \tag{S8a}$$

$$\frac{d\mu}{d\tau} = -\frac{\alpha_e(m)}{\alpha_e(m_{\mathrm{tot}})}\Pi(\tau). \tag{S8b}$$

As explained in Methods V B, $\mu = m/m_{\mathrm{tot}}$ is the nondimensional monomer concentration, and Π the nondimensional fibril number concentration. The nondimensional time is $\tau = \kappa t$ where $\kappa = \sqrt{\alpha_e(m_{\mathrm{tot}})\alpha_2(m_{\mathrm{tot}})}$. Moreover, the functions α_1, α_2 and α_e are defined as the monomer-dependence of the rates of primary nucleation, secondary nucleation and elongation. Finally, $\varepsilon = \alpha_1(0, m_{\mathrm{tot}})/2m_{\mathrm{tot}}\alpha_2(m_{\mathrm{tot}})$, which can be interpreted as the relative importance of primary nucleation over secondary processes. The initial conditions considered are $\{\mu(0) = 1 - \delta,\ \Pi(0) = p = \delta + O(\delta^2)\}$ where $\delta \ll 1$.

A. Exact, approximate and asymptotic Lie symmetries in protein aggregation

The kinetics of pure Aβ42 aggregation at pH 8.0, among other protein aggregation reactions, obey the simplest possible equations of the form of Eqs. (12), which are:

$$\frac{d\Pi}{d\tau} = 2\varepsilon\mu(\tau)^{n_c} + \mu(\tau)^{n_2}(1-\mu(\tau)) \tag{S9a}$$

$$\frac{d\mu}{d\tau} = -\mu(\tau)\Pi(\tau). \tag{S9b}$$

We will use these equations throughout this subsection as an illustrative example.

Eqs. (S9) (and many other instances of Eqs. (S8)) can be integrated once analytically [7]. The first step is to divide Eq. (S9a) by Eq. (S9b), giving:

$$\Pi\frac{d\Pi}{d\mu} = -2\varepsilon\mu(\tau)^{n_c-1} - \mu(\tau)^{n_2-1}(1-\mu(\tau)). \tag{S10}$$

Then explicitly integrating over μ gives:

$$\Pi(\mu) = \left(p^2 + \frac{4\varepsilon}{n_c}(1-\delta)^{n_c} + 2\frac{(1-\delta)^{n_2} - \mu^{n_2}}{n_2} - 2\frac{(1-\delta)^{n_2+1} - \mu^{n_2+1}}{n_2+1}\right)^{1/2}. \tag{S11}$$

The problem is consequently reduced to quadrature by substituting this into the Eq. (S9b) [7]. However, the second integration cannot be performed analytically. So, an exact analytic solution for μ is not possible. Since all solutions are consequences of Lie symmetries, Eqs (S9) should therefore not possess any non-trivial exact symmetries other than those that yield this quadrature. This can be verified explicitly by their computation using CAS. Surprisingly, moreover, their explicit computation reveals that Eqs (S9) have no non-trivial approximate symmetries (Fig. S2**a**) either.

Yet, these equations have several approximate analytical solutions [7–9], implying they possess some other kind of approximate symmetry property even if they do not possess formal approximate symmetries as defined in [3] and explained in Sec. S1 C. Given that these approximate solutions all become more accurate in the limit $\mu \to 1$, we consider the possibility of Lie symmetries that become exact only *asymptotically* in a given region of phase space (Fig. S2**b**). The concept of exact "asymptotic symmetries" of DEs, involving dependent and independent variables only, has been investigated in at least two prior mathematical papers [10, 11]. However, a systematic method for their computation was not established, and instead they were computed by guesswork from the DE and its exact

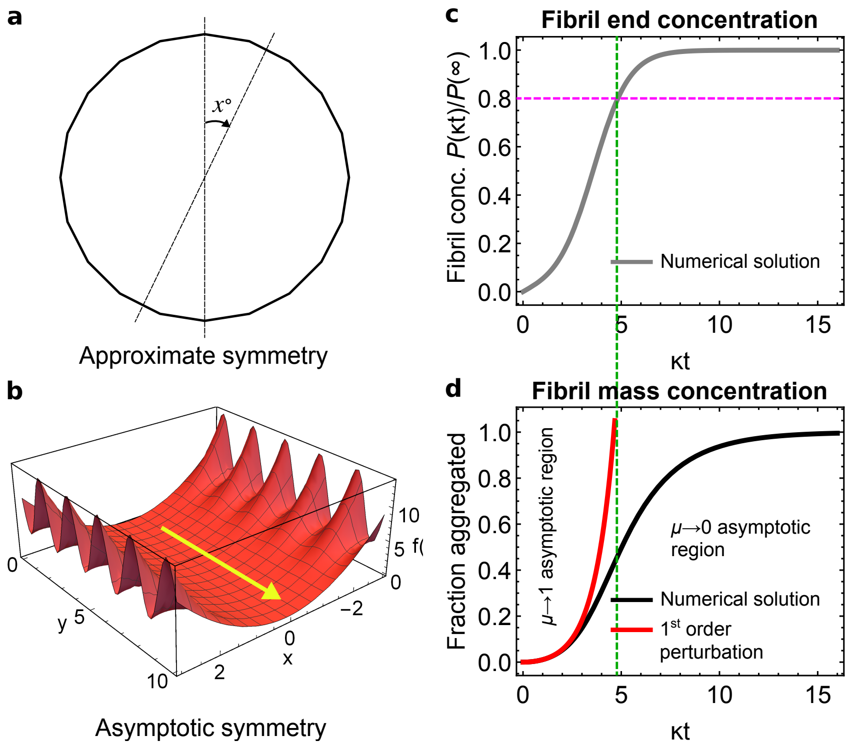

FIG. S2: Illustration of asymptotic symmetries, and asymptotic regions in the kinetics of linear protein self-assembly. **a**: Dodecagons are only approximately invariant under infinitesimal rotational transformations (to $O(\varepsilon)$, where $\varepsilon \sim z \cos\theta$, with θ the external angle and z the side length), which are therefore an approximate Lie symmetry. **b**: $f = x^2 + \varepsilon \sin(\pi y) x^5$ is asymptotically invariant to an arbitrary y-translation in the limit $x \to 0$; such a translation is thus an asymptotic Lie symmetry. **c**: Numerical solution for normalized fibril end concentration Π (rate equation Eq. (S9a), gray); parameters are the same as in Fig. 6. **d**: Numerical solution for normalized fibril mass concentration $1 - \mu$ (rate equation Eq. (S9b), black). The $\mu \to 0$ asymptotic regime, dominated by simple exponential decay of μ, is entered once the fibril number concentration begins to plateau. The local perturbation series (red, Eq. (15a)) is no longer valid in this regime.

symmetries. Hereafter we adopt the name "asymptotic" proposed in these papers for this class of symmetries.

Now, we propose asymptotic symmetries of *solutions* to DEs rather than of DEs themselves, and acting on all parameters in the problem, not just the dependent and independent variables. We also propose a systematic method for their computation. If a local approximation to the solution of a DE is available (such as a "local perturbation series", as defined in Methods Sec. V B and also explored in ref. [6]), then exact or approximate symmetries of this local approximation will be asymptotic symmetries of the solution to the DE. Since these approximations do not contain derivatives, computation of their Lie symmetries can easily be done by hand with no need for the usual computer algebra approaches.

Asymptotic symmetries computed from a local perturbation series are generally only valid near the initial or boundary conditions $C_j(0)$. They are clearly also only valid to the same order in the perturbation parameter as their parent series. For example, solving Eqs (S9) perturbatively to first order with initial conditions $\{\mu(0) = 1 - \delta,\ \Pi(0) = \delta + O(\delta^2)\}$, and premultiplying δ and ε by indexing parameter s, yields the following local perturbation series for μ:

$$\mu(\tau) = \mu^{(0)} + s\mu^{(1)} = 1 -\ s\big[\varepsilon(e^{\tau} + e^{-\tau} - 2) + \delta e^{\tau}\big]\,. \tag{S12}$$

We can then seek from this a zeroth-order approximate $\mu \to 1$ asymptotic perturbation symmetry for the exact solution to Eqs. (S9), acting solely on parameters ε and δ:

$$\boldsymbol{X}^{(0)}_{\varepsilon,\delta} = \xi^{(0)}_{\varepsilon}\frac{\partial}{\partial\varepsilon} + \xi^{(0)}_{\delta}\frac{\partial}{\partial\delta} \tag{S13}$$

Solving $\boldsymbol{X}^{(0)}_{\varepsilon,\delta}\left(\mu^{(0)} + s\mu^{(1)}\right) = 0$ yields the zeroth-order symmetry:

$$\boldsymbol{X}^{(0)}_{\varepsilon,\delta} = \xi^{(0)}\left(e^{\tau}\frac{\partial}{\partial\varepsilon} - (e^{\tau} + e^{-\tau} - 2)\frac{\partial}{\partial\delta}\right), \tag{S14}$$

where $\xi^{(0)}$ is an arbitrary function of ε and δ. Note, although zeroth-order in s, this symmetry correctly describes the solution manifold to $O(s^1)$ in the $\mu \to 1$ asymptotic regime.

B. Conditions for global validity of asymptotic symmetry

Finally, we propose that asymptotic perturbation symmetries may often remain approximately valid throughout the entire phase space of interest. If so, they may in principle be employed to find global approximate solutions. To evaluate whether a given such symmetry is indeed globally valid requires an examination of the bifurcations of the DEs it was calculated for.

By definition, $1 \geq \mu(0)$ and $\Pi(0) \geq 0$. Moreover, $\alpha_1,\ \alpha_2$ and α_e are never negative in protein aggregation reactions. Consequently, Π is monotonic increasing, and μ is monotonic decreasing in Eqs. (S8). The structure of the parameter space relevant to protein aggregation is therefore simple, featuring only an attractive fixed point at $\mu = m_c$. If we make the approximation of irreversibility, $m_c = 0$ and the parameter space can be partitioned into two parts: the $\mu \to 0$ asymptotic region, characterized by linearized kinetics about the fixed point, and the remainder, the $\mu \to 1$ asymptotic region. For small ε the kinetics described by Eqs. (S8) approximately linearize when $\alpha_2(m_{\text{tot}}\mu)/\alpha_2(m_{\text{tot}}) \to 0$ such that $\Pi(\tau) \to \Pi_\infty =$ const., and when $\alpha_e(m_{\text{tot}}\mu)/\alpha_e(m_{\text{tot}})$ becomes linear in μ. The $\mu \to 0$ asymptotic region thus corresponds to the kinetics becoming dominated by single-step elongation of fibrils, with nucleation no longer being important. The μ value at which this occurs represents the boundary between these two asymptotic regimes. Often, the dynamics within the $\mu \to 1$ region are uniform and no meaningful further subdivision of the parameter space exists, in which case the global dynamics are partitioned into two asymptotic limits: $\mu \to 1$ and $\mu \to 0$ (Fig. S2**c**-**d**). The boundary between these regions of phase space is marked by the linearization of the kinetics.

$\mu \to 1$ asymptotic perturbation symmetries are then approximately valid globally under two circumstances. First, if the parameters transformed by the symmetry in response to an increase in the perturbation parameters drop out of the $\mu \to 0$ kinetics at the order in s the $\mu \to 1$ symmetry was calculated at. For example, Eqs. (S9) lose memory of the initial conditions $\{\mu(0) = 1 - s\delta,\ \Pi(0) = s\delta + O(s^2)\}$ in the $\mu \to 0$ asymptotic region, becoming independent of δ at $O(s)$. This is because the initial conditions then enter the dynamics only via $\Pi_\infty = \Pi(\mu = 0)$, which from Eq. (S11) can be shown to depend on δ only at $O(s^2)$. Thus, although the $\mu \to 1$ asymptotic symmetry Eq. (S14) in principle transforms δ incorrectly here, this leads only to an $O(s^2)$ error in the $\mu \to 0$ asymptotic region, and so Eq. (S14) is actually universally valid to $O(s)$. The second circumstance is if the boundary between asymptotic regions is sufficiently close to $\mu = 0$, the second region may be neglected. We consider examples of this in Methods Sec. V D.

C. Special solution for $\varepsilon = d = 0$

A critical requirement of the method we develop in this section is the knowledge of a special solution, valid for a specific choice of the constant parameters on which the DE in question depends and on which the asymptotic perturbation symmetry calculated operates. It must be uniformly convergent and so valid globally, and consequently nonperturbative. We derive such a solution in this subsection.

When $\alpha_1,\ \alpha_2$ and α_e are finite constants and $\varepsilon = 0$, Eqs. (S8) reduce to:

$$\frac{d\Pi}{d\tau} = \mu(\tau)^{n_2}(1-\mu(\tau)) \tag{S15}$$

$$\frac{d\mu}{d\tau} = -\mu(\tau)\Pi(\tau). \tag{S16}$$

Integrating once, with boundary conditions $\mu(0) = 1-\delta,\ \Pi(0) = p$ yields for $n_2 > 0$:

$$\Pi(\tau) = \left(p^2 + 2\frac{(1-\delta)^{n_2} - \mu(\tau)^{n_2}}{n_2} - 2\frac{(1-\delta)^{n_2+1} - \mu(\tau)^{n_2+1}}{n_2+1}\right)^{1/2}. \tag{S17}$$

$n_2 = 0$ is also possible and indicates fibril fragmentation rather than secondary nucleation. In this case, we instead obtain:

$$\Pi(\tau) = \left(p^2 - 2\ln\frac{\mu}{1-\delta} - 2\left((1-\delta) - \mu(\tau)\right)\right)^{1/2}. \tag{S18}$$

At this point, the problem is reduced to quadrature, with:

$$t = -\int_{1-\delta}^{\mu} \frac{d\mu}{\mu\Pi(\mu)}. \tag{S19}$$

If we choose $p = p_0(\delta) = \delta + O(\delta^2)$, where:

$$p_0 = \sqrt{2\frac{1-(1-\delta)^{n_2}}{n_2} - 2\frac{1-(1-\delta)^{n_2+1}}{n_2+1}}, \tag{S20}$$

then Eq. (S19) reduces to:

$$t = -\int_{1-\delta}^{\mu} \frac{d\mu}{\mu\left(2\frac{1-\mu^{n_2}}{n_2} - 2\frac{1-\mu^{n_2+1}}{n_2+1}\right)^{1/2}}, \tag{S21}$$

with the first term in the square root replaced by $-2\ln\mu$ if $n_2 = 0$. To evaluate this integral, it is necessary to find an accurate approximate expression $g(\mu)$ for the denominator $f(\mu)$. We start by investigating $f(\mu)$ in the interval $[0,1]$ containing all possible values of μ. We find the following basic properties:

$$f(0) = f(1) = 0 \tag{S22}$$

$$f(\mu) > 0, \quad 0 < \mu < 1 \tag{S23}$$

$$f'(0) = c, \quad f'(1) = -1 \tag{S24}$$

$$f''(\mu) \leq 0, \quad 0 \leq \mu \leq 1. \tag{S25}$$

If we instead restrict our attention to the interval $[0, 1-\delta]$, with small positive δ, we find furthermore that:

$$f(1-\delta) = \delta + O(\delta^2), \quad f'(1-\delta) = -1 + \frac{2n_2+4}{3}\delta + O(\delta^2). \tag{S26}$$

Also, there is a single turning point (a maximum) in this interval. When $n_2 = 1$ the maximum value is $f_{\max} = 1/4$, occurring at $\mu_{\max} = 1/2$. As $n_2 \to \infty$, $f_{\max} \to c$, and occurs at $\mu_{\max} \to 1$. Taken together, these results indicate that f is a low hill, rising from 0 at either end of the interval $[0, 1]$ to a value $\leq 1/4$. Thus neither f nor f' have poles.

Such simple behaviour should be adequately captured by the simple functional form:

$$g(\mu) = c_1\mu^{p_1} + c_2\mu^{p_2} + c_3, \quad p_2 > p_1 \geq 1. \tag{S27}$$

This is fortunate, because more complicated polynomials in μ are unlikely to lead to an integrable g^{-1}. Now we constrain the parameters in g by matching to the properties of f. First imposing $g(0) = f(0) = 0$ requires $c_3 = 0$. Imposing $g(1-\delta) = f(1-\delta) = \delta + O(\delta^2)$ then leads to $c_2 = -c_1$ and $p_2 - p_1 = 1/c_1 > 0$, so g has the form:

$$g(\mu) = c_1\mu^{p_1}\left(1 - \mu^{1/c_1}\right). \tag{S28}$$

To inherit the property that $f'(0) > 0$ requires $p_1 = 1$. This is also fortunate, since otherwise g^{-1} would not be integrable. With this form of g we can already evaluate (and invert) $t = \int_{1-\delta}^{\mu} g^{-1} d\mu$, yielding:

$$\mu(\tau) = \frac{1}{\left(1 + e^t\left[(1-\delta)^{-1/c_1} - 1\right]\right)^{c_1}}. \tag{S29}$$

Our asymptotic symmetry transformation method requires that our special solution have the correct $\mu \to 1$ asymptotic dynamics. Therefore, to choose c_1, we match $g'(1-\delta) = f'(1-\delta)$ ($g'(1)$ already equals $f'(1) = -1$), yielding finally $c_1 = 3/(2n_2+1)$.

(If we had instead matched $g'(0) = f'(0)$, we would have obtained $c_1 = \sqrt{2/(n_2(n_2+1))}$. This would give a slightly more accurate solution for $n_2 > 1$, because for larger values of n_2 secondary nucleation decreases significantly at a larger value of μ, and the $\mu \to 0$ region is more important to the overall dynamics. However, there is not a great difference between these choices for c_1, with the maximum difference of 6% attained as $n_2 \to \infty$.)

Since $\delta \ll 1$, Eq. (S29) reduces to:

$$\mu_0(\tau, c_1, \delta) = \frac{1}{(1 + \delta e^{\tau}/c_1)^{c_1}}, \tag{S30a}$$

$$c_1 = \frac{3}{2n_2+1}. \tag{S30b}$$

We will use this as the special solution throughout, taking advantage of its greater simplicity than the "exact" special solution.

D. Regularizing local perturbation series using asymptotic symmetries

Globally valid perturbation symmetries can in principle be used to regularize a singular perturbation problem by transforming a known special solution, such as Eq. (S30), which is valid when $\varepsilon = 0$, for arbitrary δ, and for p as a function of δ satisfying $p(\delta = 0) = 0$. Since c_1 does not enter into the $\mu \to 1$ asymptotic dynamics Eq. (S12), a global solution to Eqs. (S9) for $\delta = 0$ can be obtained simply by transforming the special solution with the globally valid asymptotic perturbation symmetry generator Eq. (S14). First, the generator is integrated to obtain the finite transformation from $(0, \delta)$ to $(\varepsilon, 0)$:

$$\frac{d\varepsilon}{ds} = e^{\tau},\ \frac{d\delta}{ds} = -(e^{\tau} + e^{-\tau} - 2) \tag{S31a}$$

$$\varepsilon = se^{\tau},\ -\delta = -s(e^{\tau} + e^{-\tau} - 2) \tag{S31b}$$

$$\therefore \delta \to \varepsilon(e^{\tau} + e^{-\tau} - 2)/e^{\tau}. \tag{S31c}$$

Then, this finite transformation is substituted into the special solution. Replacing δ in Eq. (S30) accordingly yields:

$$\mu(\tau) = \frac{1}{\left(1 + \frac{\varepsilon}{c_1}(e^{\tau} + e^{-\tau} - 2)\right)^{c_1}}, \tag{S32}$$

with c_1 defined as before.

The same special solution is often available for the more complicated Eqs. (S8) with arbitrary initial conditions when $\varepsilon = 0$ and $p = p_0$ (with p_0 a function of δ given by Eq. (S20)). This requires that α_1, α_2 and α_e depend on parameters $\boldsymbol{d}$ in such a way that $\boldsymbol{d} = 0$ reduces them to finite constants. An asymptotic perturbation symmetry connecting (c_1, δ) with $(\boldsymbol{d}, \varepsilon, p)$ may then be used to transform the special solution Eq. (S30) to a general solution to Eqs. (S8).

Because this kind of symmetry does not transform the dependent and independent variables, a shortcut in this procedure may be taken: it is not necessary to explicitly compute the symmetry and its finite transformations. To see why, suppose such a symmetry connecting (c_1, δ) with $(\boldsymbol{d}, \varepsilon)$ has been found. From these, finite transformations taking $(\tilde{c}_1, \tilde{\delta}, 0, 0)$

to $(c_1, \delta, \boldsymbol{d}, \varepsilon)$ can be calculated. Whatever they may be, they can always be expressed in inverse form as $\tilde{\delta} = g_\delta(\tau, c_1, \delta, \boldsymbol{d}, \varepsilon)$, $\tilde{c}_1 = g_{c_1}(\tau, c_1, \delta, \boldsymbol{d}, \varepsilon)$ where a tilde over a parameter signifies it is at its pre-transformation value. Our global solution is then $\mu_0(\tau, \tilde{c}_1, \tilde{\delta})$. Now, since transforming one asymptotic expansion must yield another, g_δ and g_{c_1} must satisfy:

$$\mu_{0,\text{asy}}(\tau, \tilde{c}_1, \tilde{\delta}) \equiv \mu_{\text{asy}}(\tau, c_1, \delta, \boldsymbol{d}, \varepsilon), \tag{S33}$$

where $\mu_{0,\text{asy}}$ is the asymptotic expansion of the special solution μ_0 in this region of phase space, and $\mu_{\text{asy}}(\tau, c_1, \delta, \boldsymbol{d}, \varepsilon)$ is the asymptotic limit of the full dynamics in the same region (e.g. Eq. (15), or a higher-order series). So, the finite transformations can be identified by inspection of μ_{asy}; a globally valid solution is then obtained by substituting these transformations into Eq. (S30).

S3. SOLUTION OF GENERAL PROTEIN AGGREGATION RATE EQUATIONS BY ASYMPTOTIC LIE SYMMETRY

The general equations Eqs. (S8) can be rewritten for simplicity as:

$$\frac{d\Pi}{d\tau} = 2s\varepsilon\tilde{\alpha}_1(t, \mu) + \tilde{\alpha}_2(\mu)(1 - \mu(\tau)) \tag{S34a}$$

$$\frac{d\mu}{d\tau} = -\tilde{\alpha}_e(\mu)\Pi(\tau), \tag{S34b}$$

$$\mu(0) = 1 - s\delta, \qquad \Pi(0) = sp \tag{S34c}$$

where $\tilde{\alpha}_x(\tau, \mu) = \alpha_x(t, m_{\text{tot}}\mu)/\alpha_x(0, m_{\text{tot}})$, $\varepsilon = \alpha_1(0, m_{\text{tot}})/(2m_{\text{tot}}\alpha_2(m_{\text{tot}}))$ and s is the perturbation bookkeeping parameter, the zeroth order perturbation solutions are, as outlined in the main text, given by:

$$\Pi^{(0)} = 0, \qquad \mu^{(0)} = 1. \tag{S35}$$

A. Perturbative solution to first order

The first order perturbation equations are given by:

$$\frac{d\Pi^{(1)}}{d\tau} = 2\varepsilon\tilde{\alpha}_1(\tau, 1) - \mu^{(1)} \tag{S36a}$$

$$\frac{d\mu^{(1)}}{d\tau} = -\Pi^{(1)}, \tag{S36b}$$

$$\mu^{(1)}(0) = -\delta, \qquad \Pi^{(1)}(0) = p. \tag{S36c}$$

In the case of $\alpha_1(t,m) \equiv \alpha_1(m)$, they are solved by:

$$\Pi^{(0)} = 0, \qquad \mu^{(0)} = 1 \tag{S37a}$$

$$\Pi^{(1)} = \varepsilon(e^{\tau} - e^{-\tau}) + \frac{\delta}{2}(e^{\tau} - e^{-\tau}) + \frac{p}{2}(e^{\tau} + e^{-\tau}), \tag{S37b}$$

$$\mu^{(1)} = -\varepsilon(e^{\tau} + e^{-\tau} - 2) - \frac{\delta}{2}(e^{\tau} + e^{-\tau}) - \frac{p}{2}(e^{\tau} - e^{-\tau}). \tag{S37c}$$

For the remainder, of the section, however, we will not make this assumption. We instead consider the more general condition, introduced in Methods Sec. V A, that the kinetics are secondary-dominated such that α_1 grows less rapidly with τ than e^{τ}. In this case, the particular integral of $\mu^{(1)}$ will also grow less rapidly than e^{τ}. We can then write the first order perturbation terms as:

$$\Pi^{(1)} = qe^{\tau} + \mathcal{R}, \quad \mu^{(1)} = -qe^{\tau} + \mathcal{R} \tag{S38a}$$

$$q = c_{\varepsilon} + \delta/2 + p/2, \tag{S38b}$$

where $\mathcal{R}$ consists of terms that diverge less rapidly with τ, and c_{ε} is a positive constant. In the case that $\alpha_1(t,m) \equiv \alpha_1(m)$, $c_{\varepsilon} = \varepsilon$.

B. Perturbative solution to second order

Now, consider the expansion in s of $\tilde{\alpha}$:

$$\tilde{\alpha} = 1 + s\left.\frac{d\tilde{\alpha}}{ds}\right|_{s=0} + O(s^2) \quad = 1 + s\left.\frac{\partial\tilde{\alpha}}{\partial\mu}\frac{d\mu}{ds}\right|_{s=0} + O(s^2) \tag{S39a}$$

$$= 1 + s\mu^{(1)}\left.\frac{\partial\tilde{\alpha}}{\partial\mu}\right|_{s=0} + O(s^2) \tag{S39b}$$

$$= 1 + s\mu^{(1)}\tilde{\alpha}'(1) + O(s^2), \tag{S39c}$$

where the prime indicates differentiation with respect to μ. The second order perturbation equation is then:

$$\frac{d\Pi^{(2)}}{d\tau} = 2\varepsilon\mu^{(1)}\tilde{\alpha}_1'(\tau,1) - \mu^{(1)2}\tilde{\alpha}_2'(1) - \mu^{(2)} \tag{S40a}$$

$$\frac{d\mu^{(2)}}{d\tau} = -\mu^{(1)}\tilde{\alpha}_e'(1)\Pi^{(1)} - \Pi^{(2)}, \tag{S40b}$$

$$\mu^{(2)}(0) = \Pi^{(2)}(0) = 0. \tag{S40c}$$

These can be combined into:

$$\frac{d^2\mu^{(2)}}{d\tau^2} - \mu^{(2)} = -\tilde{\alpha}_e'(1)\frac{d}{d\tau}\left(\mu^{(1)}\Pi^{(1)}\right) - 2\varepsilon\tilde{\alpha}_1'(\tau,1)\mu^{(1)} + \tilde{\alpha}_2'(1)\mu^{(1)2}. \tag{S41}$$

Since $\tilde{\alpha}_1 = o(e^{\tau})$, so is $\tilde{\alpha}_1'$, and consequently the complementary function of $\mu^{(2)}$ will be $o(e^{2\tau})$.

We seek the most-divergent terms of the second-order perturbation solution. These will be the $O(e^{2\tau})$ components of the particular integral. These can be computed without the need for retaining the less-divergent parts of the inhomogeneous terms of Eq. (S41). With this simplification Eq. (S41) becomes:

$$\frac{d^2\mu^{(2)}}{d\tau^2} - \mu^{(2)} = 2q^2\tilde{\alpha}_e'(1)e^{2\tau} + q^2\tilde{\alpha}_2'(1)e^{2\tau}. \tag{S42}$$

Its solution can therefore be written as:

$$\mu^{(2)} = \frac{q^2}{3}e^{2\tau}\left(\tilde{\alpha}_2'(1) + 2\tilde{\alpha}_e'(1)\right) + \mathcal{R}. \tag{S43}$$

C. Asymptotic symmetry transformation

To second order in s, the expansion of the special solution Eq. (S30) (where bookkeeping parameter s has again been introduced to pre-multiply δ) is:

$$\tilde{\mu}_2 = 1 - s\tilde{\delta}e^{\tau} + s^2\frac{\tilde{c}_1 + 1}{2\tilde{c}_1}\tilde{\delta}^2 e^{2\tau} + O(\delta^3), \tag{S44}$$

where we have already made the substitutions $\delta \to \tilde{\delta}$ and $c_1 \to \tilde{c}_1$ required by Eq. (S33). The first order perturbation solution can therefore be matched with the following finite transformation:

$$\tilde{\delta}e^{\tau} = -\mu^{(1)}(\tau) + O(s). \tag{S45}$$

The expansion of the special solution is then:

$$\tilde{\mu}_2 = 1 - s\mu^{(1)} + s^2\frac{\tilde{c}_1 + 1}{2\tilde{c}_1}\mu^{(1)2} + O(s^3). \tag{S46}$$

We can only in general match to second order the most-divergent terms in τ (proportional to $e^{2\tau}$), if we desire a simple, time-independent c_1. (There is no great purpose in seeking a time-dependent c_1 since the $\mu \to 1$ kinetics are already captured exactly by the first-order matching, and the asymptotic symmetry loses validity as $\tau \to \infty$.) The matching then requires:

$$\frac{\tilde{c}_1 + 1}{2\tilde{c}_1} = \frac{1}{3}\left(\tilde{\alpha}_2'(1) + 2\tilde{\alpha}_e'(1)\right) \tag{S47a}$$

$$\frac{1}{\tilde{c}_1} = \frac{2}{3}\left(\tilde{\alpha}_2'(1) + 2\tilde{\alpha}_e'(1)\right) - 1 \tag{S47b}$$

$$\Rightarrow \tilde{c}_1 = \frac{3}{2\left(\tilde{\alpha}_2'(1) + 2\tilde{\alpha}_e'(1)\right) - 3}. \tag{S47c}$$

D. Construction of general solution

To remove some superfluous terminology:

$$\tilde{\alpha}_i'(1) = \frac{d}{d\mu}\frac{\alpha_i(m)}{\alpha_i(m_{\text{tot}})}\bigg|_{m=m_{\text{tot}}} = m_{\text{tot}}\frac{d}{dm}\frac{\alpha_i(m)}{\alpha_i(m_{\text{tot}})}\bigg|_{m=m_{\text{tot}}} = m\frac{d}{dm}\ln\alpha_i(m)\bigg|_{m=m_{\text{tot}}}$$

$$\Rightarrow \tilde{\alpha}_i'(1) = \frac{d\ln\alpha_i(m)}{d\ln m}\bigg|_{m=m_{\text{tot}}}. \tag{S48}$$

The general solution is then given by using the substitutions Eq. (S45) and Eq. (S47c) on the special solution Eq. (S29). Setting $s = 1$ and using Eq. (S48), this gives finally the formula Eq. (16) presented in Methods Sec. (V D):

$$\mu = \left(1 - \frac{\mu^{(1)}(\tau)}{c_1}\right)^{-c_1} \tag{S49a}$$

$$c_1 = \left(\frac{2}{3}\frac{d\ln[\alpha_2(m)\alpha_e(m)^2]}{d\ln m}\bigg|_{m=m_{\text{tot}}} - 1\right)^{-1}. \tag{S49b}$$

S4. APPLICABILITY OF NONLINEAR TECHNIQUES TO THE SOLUTION OF PROTEIN AGGREGATION KINETICS

A. Fixed-point theory

In the context of protein aggregation, the fixed-point method is employed by turning the rate equation for monomer concentration into an integral equation that acts as a fixed-point operator [12, 13]. So, the first condition for applicability of the fixed-point method is that this transformation into a closed-form integral equation is possible. This proves to be the case for the most common forms of α_e and is not too restrictive a condition [12–14].

After this transformation, an initial guess is then supplied for the fibril concentration, and the operator applied to this initial guess to generate an improved approximation for the monomer concentration and (by conservation of mass) the fibril concentration. The second condition for fixed-point applicability is that this integral equation is a contractive mapping for the right initial guess. This is easiest evaluated by trial-and-error, simply by testing that the output of the fixed-point iteration is indeed an improved approximation. This has proven to be the case in most systems studied to date [12–14].

The final condition for applicability is that a sufficiently accurate and simple initial guess can be provided for the fixed-point iteration to result in an accurate approximate solution that is still simple enough for insight to be gained from it. This is the hardest condition to satisfy. Under certain circumstances the unmodified early-time (or first-order perturbative) solution is a suitable initial guess [12, 13]. Often, however, this is insufficient, with fixed-point iteration giving a rather inaccurate solution, even for relatively simple rate equations [15, 16]. In such situations accuracy can sometimes be obtained by higher-order iteration. (This means using the result of a single iteration as an initial guess for a second iteration, etc.) However, for all but the simplest systems this is analytically intractable. Moreover, even when tractable the resultant solutions are usually not closed-form and/or are far too complex for insight to be easily derived from them [15]. (An exception is the kinetics of co-aggregation with cross-elongation but without any secondary processes, where the second-order self-consistent solution turns out to be relatively simple in form [16].)

The other potential fix is to use an improved initial guess. However, their identification can be extremely difficult and is entirely non-algorithmic. Interestingly, for instance, higher-order perturbative solutions are not generally better initial guesses; indeed, even-order perturbative solutions can be easily shown to yield divergent expressions after fixed-point iteration. The only other type of initial guess that has been identified previously and that can sometimes be adapted to new systems is a composite solution that interpolates between the early-time fibril concentration and its late-time limit [15]. This can sometimes succeed where the early-time solution fails as an initial guess [8, 17]. However, its iteration leads to expressions that are both more complex (and thus harder to interpret) and less accurate than the approach we consider here. Moreover, it succeeds only when two conditions are satisfied. First, the late-time limit of the fibril concentration must be possible to calculate analytically. Second, there must be no other dominant timescales beyond those that dominate the early-time solution and the fixed point operator for the monomer concentration, as otherwise fixed-point iteration to first order cannot introduce these additional timescales. (Higher-order iteration may be able to do so, since this involves converting the other rate equations to fixed-point operators too, not just the monomer concentration rate equation. However, here we are discussing providing an alternative to iterating to higher order.)

In the case of coaggregation the latter condition is violated, as outlined in Methods Sec. V C. This is because mechanistic analysis of protein aggregation requires data from reactions featuring multiple starting concentrations [12, 14]. One species therefore always depletes before the other for at least some of the coaggregation reactions to be modelled. The kinetics of the remaining species subsequently transitions from coaggregation to self-aggregation, changing the dominant timescales. The transition to self-aggregation-dominated timescales cannot be captured by first-order fixed-point approaches, at least not without some very inspired guesswork that has hitherto not been successfully performed.

B. Chen-Goldenfeld-Oono Renormalization Group (CGO RG)

Ref. [9] considered the kinetics of homomolecular amyloid fibril formation featuring either a fragmentation step, a branching step or an unsaturated secondary nucleation step. The obligate primary nucleation and elongation steps were also restricted to be unsaturated, and only unseeded initial conditions were considered (i.e. starting from pure monomeric protein). Simplified rate equations were written down and nondimensionalized. They were then solved perturbatively to second order in ε, a parameter which had the same definition as in the present study. This divergent solution was then converted into a globally valid convergent solution using CGO RG. This would appear to contradict our finding in Methods Sec. V C that CGO is formally inapplicable to protein aggregation rate equations.

To resolve this apparent contradiction, we look in more detail at the calculation in ref. [9]. A key step in the workflow of CGO RG is the calculation of an “RG equation”, whose subsequent integration can produce the desired convergent solution. Unfortunately, however, a direct integration of the RG equation identified in ref. [9] instead produces a divergent expression. To rectify this, it was necessary to make the challenging guess that two terms in the RG equation are the second-order expansion in ε of a very specific function. Substituting in this specific function finally allowed the integration of the RG equation to produce a convergent solution. Since this guess was no easier than guessing the convergent solution directly from the second-order local perturbation series, in reality CGO RG does not aid in finding the solution presented in ref. [9]. Instead, this solution was effectively guessed from the second-order local perturbation series. This is far from the only case in which CGO RG has required this kind of guesswork to succeed. Such cases stem from a widespread misunderstanding of the mathematical origins of the method and, consequently, of the circumstances of its applicability, as discussed extensively in ref. [6].

The solution of ref. [9] can in fact be easily derived using our general solution, Eq. (16). This is done by simply identifying $\alpha_1 = k_n m^{n_c}$, $\alpha_e = 2k_+ m$ and $\alpha_2 = k_2 m^{n_2}$. After this, Eqs. (15)-(16) trivially reduce to the solution of ref. [9]. (Although the limit $\kappa t \gg 1$ of Eq. (15) must also be taken to complete the reduction.) The reasons for this are both the fortunate guesswork of ref. [9] and also because by construction the solutions of both approaches must be consistent with the second order perturbation series.

In certain other papers the solution of ref. [9] was generalized to account for other mechanisms. A notable example is ref. [18], where it was extended to allow for any of primary nucleation, elongation or secondary nucleation to saturate. (Also, the assumption that $\kappa t \gg 1$ was dropped.) This was achieved first by calculating the second-order local perturbation series in ε for the rate equations governing this more complicated reaction mechanism. Next, the parameters in the solution of ref. [9] were modified in such a way that its second order expansion in ε still matched this more complicated perturbation series. This is effectively the same procedure we used to generate our general solution here. In other words, ref. [18] unwittingly applied a $\mu \to 1$ asymptotic symmetry transformation to the simpler solution to generalize it for non-infinite dissociation constants. Consequently, given its shared origins, the solution of ref. [18] can also be derived using our general solution, Eq. (16). We do so with significantly reduced difficulty compared to the original approach in SI Sec. S5.

C. Method of asymptotic Lie symmetries and Aβ42-Aβxx coaggregation

As discussed in Methods Sec. V E, Eqs. (1) can be nondimensionalized into Eqs. (12)/Eqs. (S8) if subscripts $_a$ are added to the latter. This gives:

$$\begin{aligned}
&\frac{d\Pi_a}{d\tau_a} = 2\varepsilon_a \mu_a^{n_c(a)} + \\
&\mu_a^{n_2(a)}(1-\mu_a)\frac{1 + 1/\mathcal{K}_S(a)^{n_2(a)} + 1/\mathcal{K}_S(ba)^{n_2(aa)+n_2(ab)}}{1 + \mu_a^{n_2(a)}/\mathcal{K}_S(a)^{n_2(a)} + \mu_a^{n_2(aa)}/\mathcal{K}_S(ba)^{n_2(aa)+n_2(ab)}}, \qquad \text{(S50a)}\\
&\frac{d\mu_a}{d\tau_a} = -\mu_a(\tau_a)\Pi_a(\tau_a), \qquad \text{(S50b)}\\
&\varepsilon_a = \frac{\alpha_{1,a}(m_{\text{tot},a})}{2m_{\text{tot},a}\alpha_{2,a}(m_{\text{tot},a})}, \qquad \text{(S50c)}
\end{aligned}$$

where $\mu_a(t) = m_a(t)/m_{\text{tot},a}$, $\Pi_a(t) = 2k_+(a)P_a(t)/\kappa_a$ and $\tau_a = \kappa_a t$, with $\kappa_a = \sqrt{\alpha_{e,a}(m_{\text{tot},a})\alpha_{2,a}(m_{\text{tot},a})}$.Additionally, we define $\mathcal{K}_S(a) = K_S(a)/m_{\text{tot},a}$ and $\mathcal{K}_S(ba) = K_S(ba)m_{\text{tot},a}^{-n_2(aa)/(n_2(aa)+n_2(ab))}m_{\text{tot},b}^{-n_2(ab)/(n_2(aa)+n_2(ab))}$ as the dimensionless average per-monomer dissociation constants for monomer clusters from secondary nucleation sites on Aβ42 fibrils.

Eqs. (4) can be nondimensionalized by the same strategy, yielding:

$$\begin{aligned}
\frac{d\Pi_b}{d\tau_b} &= 2\varepsilon_b\mu_b(\tau_b)^{n_c(b)} + 2\varepsilon_{1,ba}\mu_a(\tau_a)^{n_c(ba)}\mu_b(\tau_b)^{n_c(bb)} \\
&+ 2\varepsilon_{2,ba}\mu_a(\tau_a)^{n_2(ba)}\mu_b(\tau_b)^{n_2(bb)}(1-\mu_a(\tau_a)) \\
&+ \frac{1+\mathcal{K}_S(b)^{n_2(b)}}{\mu_b(\tau_b)^{n_2(b)} + \mathcal{K}_S(b)^{n_2(b)}}\mu_b(\tau_b)^{n_2(b)}\big(1-\mu_b(\tau_b)\big), \qquad \text{(S51a)}\\
\frac{d\mu_b}{d\tau_b} &= -\mu_b(\tau_b)\Pi_b(\tau_b), \qquad \text{(S51b)}\\
\mu_b(0) &= 1-\delta,\ \Pi_b(0) = p, \qquad \text{(S51c)}
\end{aligned}$$

where $\mu_b(t) = m_b(t)/m_{\text{tot},b}$, $\Pi_b(t) = 2k_+(b)P_b(t)/\kappa_b$ and $\tau_b = \kappa_b t$ and $\mu_b = m_b/m_{\text{tot},b}$, with $\kappa_b = \sqrt{\alpha_{e,b}(m_{\text{tot},b})\alpha_{2,b}(m_{\text{tot},b})}$. Moreover, $\mathcal{K}_S(b) = K_S(b)/m_{\text{tot},b}$ and:

$$\begin{aligned}
\varepsilon_{1,ba} &= \frac{\alpha_{1,ba}(m_{\text{tot},a}, m_{\text{tot},b})}{2m_{\text{tot},b}\alpha_{2,b}(m_{\text{tot},b})}, \qquad \text{(S52a)}\\
\varepsilon_{2,ba} &= \frac{m_{\text{tot},a}\alpha_{2,ba}(m_{\text{tot},a}, m_{\text{tot},b})}{2m_{\text{tot},b}\alpha_{2,b}(m_{\text{tot},b})}, \qquad \text{(S52b)}\\
\varepsilon_b &= \frac{\alpha_{1,b}(m_{\text{tot},b})}{2m_{\text{tot},b}\alpha_{2,b}(m_{\text{tot},b})}. \qquad \text{(S52c)}
\end{aligned}$$

Importantly, we can identify $(\mathcal{K}_S(a)^{-1}, \mathcal{K}_S(ba)^{-1})$ with parameter $\boldsymbol{d}$ from the Methods; when set to zero alongside ε_a, Eqs. (S50) reduce to Eqs. (S9) with $\varepsilon = 0$ and thus possess the same special solution, i.e. Eq. (S30) (identifying $\tau = \tau_a$ and $n_2 = n_2(a)$).

Asymptotic symmetries involving $\mathcal{K}_S(a)^{-1}, \mathcal{K}_S(ba)^{-1}$ and ε_a computed from the local perturbation series of Eq. (S50) around $\mu_a = 1 - \delta$, $\Pi_a = p_0(\delta)$ are valid globally, provided ε_a is small (as is the case in unseeded Aβ kinetics, and indeed in most protein aggregation reactions hitherto studied[19]). For large values of $\mathcal{K}_S(a)^{-1}$, this is because secondary nucleation does not now reduce significantly until $\mu_a \ll 1$. As a consequence, the $\mu_a \to 0$ asymptotic limit is visited too late during saturating aggregation for its perturbation by the introduction of non-zero $\mathcal{K}_S(a)^{-1}$ and ε to be important for the overall kinetics.

For small values of $\mathcal{K}_S(a)^{-1}$ this is because ε_a and $\mathcal{K}_S(a)^{-1}$ then drop out of the $\mu \to 0$ kinetics at leading order, and such symmetries therefore have no effect in this regime. This may be seen as follows. Using the approximation $\mu_a^{n_2(aa)} = 1$, which is reasonable since inhibiting secondary nucleation affects the kinetics only in the early stages before significant monomer is depleted, integrating Eqs. (S50) once with $\Pi(\mu = 1) = 1$ then yields Π as a function of μ. Next, taking the limit $\mu \to 0$ yields $\Pi(\infty)$:

$$\Pi_a(\infty) = \left(\frac{2(A+B)}{Bn_2(a)} \ln\left[1 + \frac{B}{A}\right] + 4\frac{\varepsilon_a}{n_c} \right.$$
$$\left. - \frac{2(A+B)}{A(1+n_2(a))} {}_2F_1\left[1, 1 + \frac{1}{n_2(a)}, 2 + \frac{1}{n_2(a)}, -\frac{B}{A}\right] \right)^{1/2}, \quad \text{(S53)}$$

where $A = 1 + 1/\mathcal{K}_S(ba)^{n_2(aa)+n_2(ab)}$, and $B = 1/\mathcal{K}_S(a)^{n_2(a)}$. In the limit of small $\mathcal{K}_S(a)^{-1}$, and noting that the first-order Taylor series around $z = 0$ of ${}_2F_1[a, b, c, z]$ is $1 + abz/c$, the hypergeometric becomes:

$${}_2F_1\left[1, \frac{n_2(a)+1}{n_2(a)}, \frac{2n_2(a)+1}{n_2(a)}, -\frac{B}{A}\right] \to 1 - \frac{n_2(a)+1}{2n_2(a)+1}\frac{B}{A} + O(\mathcal{K}_S(a)^{-2n_2(a)}), \quad \text{(S54)}$$

and $\Pi_a(\infty)$ reduces to:

$$\Pi_a(\infty) = \sqrt{\frac{2}{n_2(a)} - \frac{2}{n_2(a)+1}} + O(\mathcal{K}_S(a)^{-n_2(a)}, \varepsilon_a). \quad \text{(S55)}$$

Thus, to leading order, $\mu_a \to 1$ asymptotic symmetries in $\mathcal{K}_S(a)^{-n_2(a)}, \varepsilon_a$ have no effect on the $\mu_a \to 0$ dynamics.

Since Aβ42 aggregation is complete before Aβxx aggregation begins, the solution to the kinetics of Aβ42 aggregation in the presence of constant Aβxx monomer concentration, Eq. (7), may be substituted for $m_a(t)$ and $M_a(t)$ (or Eq. (22) when Aβ42 fibril seeds are present). Once more, Eq. (S30) is a special solution to Eq. (4) with the right initial conditions when $\{\varepsilon_b,\ \varepsilon_{1,ba},\ \varepsilon_{2,ba},\ \mathcal{K}_S(b)^{-1}\} = 0$. Because Eqs. (S51) are also of the same form as Eqs. (S50), asymptotic symmetries around $\mu_b = 1-\delta$, $\Pi_a = p_0(\delta)$ are again valid globally; the method of solution by asymptotic symmetries can thus again be used.

S5. EXAMPLE APPLICATION: UNSEEDED, SATURATED HOMOGENEOUS PROTEIN AGGREGATION KINETICS

The kinetics of protein aggregation in which any reaction step can saturate are given by [18]:

$$\frac{dP}{dt} = \frac{k_n m(t)^{n_c}}{1+(m(t)/K_P)^{n_c}} + \frac{k_2 m(t)^{n_2}}{1+(m(t)/K_S)^{n_2}} M(t) \tag{S56a}$$

$$\frac{dM}{dt} = \frac{2k_+ m(t)}{1+m(t)/K_E} P(t) \tag{S56b}$$

$$m_{\text{tot}} = m(t) + M(t), \tag{S56c}$$

where $k_n,\ k_+$ and k_2 are the rate constants for primary nucleation, elongation and secondary nucleation respectively. $K_P,\ K_E$ and K_S are the half-saturation concentrations for the same reaction steps, or equivalently the geometric mean per-monomer dissociation constants from the sites at which these steps occur [18]. Finally, n_c and n_2 are the reaction orders for primary and secondary nucleation with respect to monomers.

We can identify the monomer-dependence of the reaction step rates as:

$$\alpha_1(m) = \frac{k_n m(t)^{n_c}}{1+(m(t)/K_P)^{n_c}} \tag{S57a}$$

$$\alpha_e(m) = \frac{2k_+ m(t)}{1+m(t)/K_E} \tag{S57b}$$

$$\alpha_2(m) = \frac{k_2 m(t)^{n_2}}{1+(m(t)/K_S)^{n_2}}. \tag{S57c}$$

In the case of no seed, $\delta = p = 0$ and the first order term of the perturbation series can be immediately written down using Eq. (15) of the main text:

$$\mu^{(1)}(t) = -\varepsilon(e^{\kappa t} + e^{-\kappa t} - 2), \tag{S58}$$

where we identified $\mathcal{F} = e^{\kappa t} + e^{-\kappa t} - 2$ since α_1 has no explicit t-dependence. As in the main text, $\kappa = \sqrt{\alpha_2(m_{\text{tot}})\alpha_e(m_{\text{tot}})}$. Moreover, $\varepsilon = \alpha_1(m_{\text{tot}})/2m_{\text{tot}}\alpha_2(m_{\text{tot}})$.

Next, we compute $\ln[\alpha_2(m)\alpha_e(m)^2]$:

$$\ln\big[\alpha_2(m)\alpha_e(m)^2\big] = \text{const.} + \ln m^{n_2+2} - 2\ln[1 + m(t)/K_E] - \ln[1 + (m(t)/K_S)^{n_2}]\,. \quad \text{(S59)}$$

Differentiating by $\ln m$:

$$\frac{d\ln[\alpha_2(m)\alpha_e(m)^2]}{d\ln m} = n_2 + 2 - \frac{2m(t)/K_E}{1 + m(t)/K_E} - \frac{n_2\,(m(t)/K_S)^{n_2}}{1 + (m(t)/K_S)^{n_2}}. \quad \text{(S60)}$$

Finally, combining all these results, we can use the general solution formula Eq. (16) in the main text, which gives:

$$\frac{M(t)}{m_{\text{tot}}} = 1 - \left(1 - \frac{\varepsilon}{c_1}(e^{\kappa t} + e^{-\kappa t} - 2)\right)^{-c_1} \quad \text{(S61a)}$$

$$\kappa = \sqrt{\frac{2k_+k_2m_{\text{tot}}^{n_2+1}}{(1 + m_{\text{tot}}/K_E)(1 + (m_{\text{tot}}/K_S)^{n_2})}} \quad \text{(S61b)}$$

$$c_1 = \frac{3}{2n_2' + 1} \quad \text{(S61c)}$$

$$\varepsilon = \frac{k_n m_{\text{tot}}^{n_c}}{2k_2 m_{\text{tot}}^{n_2+1}}\frac{1 + (m_{\text{tot}}/K_S)^{n_2}}{1 + (m_{\text{tot}}/K_P)^{n_c}} \quad \text{(S61d)}$$

$$n_2' = \frac{n_2}{1 + (m_{\text{tot}}/K_S)^{n_2}} - \frac{2m_{\text{tot}}/K_E}{1 + m_{\text{tot}}/K_E}. \quad \text{(S61e)}$$

This is none other than the general solution of ref. [18]. Its calculation here using our formula Eq. (16) involved considerably less difficulty than the original approach in ref. [18].

S6. FIRST-ORDER PERTURBATION SERIES FOR μ_b AND ITS SIMPLIFICATION

The differential equations to be solved are Eqs. (S51):

$$\begin{aligned}\frac{d\Pi_b}{d\tau_b} &= 2\varepsilon_b\mu_b(\tau_b)^{n_c(b)} + 2\varepsilon_{1,ba}\mu_a(\tau_a)^{n_c(ba)}\mu_b(\tau_b)^{n_c(bb)} + 2\varepsilon_{2,ba}\mu_a(\tau_a)^{n_2(ba)}\mu_b(\tau_b)^{n_2(bb)}(1 - \mu_a(\tau_a)) \\ &\quad + \frac{1 + \mathcal{K}_S(b)^{n_2(b)}}{\mu_b(\tau_b)^{n_2(b)} + \mathcal{K}_S(b)^{n_2(b)}}\mu_b(\tau_b)^{n_2(b)}\big[1 - \mu_b(\tau_b)\big], && \text{(S62a)} \\ \frac{d\mu_b}{d\tau_b} &= -\mu_b(\tau_b)\Pi_b(\tau_b), && \text{(S62b)}\end{aligned}$$

subject to initial conditions $\mu_b(0) = 1,\ \Pi_b(0) = 0$. We pre-multiply the small terms proportional to $\varepsilon_b,\ \varepsilon_{1,ba}$ and $\varepsilon_{2,ba}$ by perturbation indexing parameter s (to be later set to 1), as before. Substituting in $\mu_b = 1 + s\mu_b^{(1)}$ and $\Pi_b = s\Pi_b^{(1)}$ then gives the following equations at first order in s:

$$\frac{d\Pi_b^{(1)}}{d\tau_b} = 2\varepsilon_b + 2\varepsilon_{1,ba}\mu_a(\tau_a)^{n_c(ba)} + 2\varepsilon_{2,ba}\mu_a(\tau_a)^{n_2(ba)}(1-\mu_a(\tau_a)) - \mu_b^{(1)}(\tau_b), \tag{S63a}$$

$$\frac{d\mu_b^{(1)}}{d\tau_b} = -\Pi_b^{(1)}(\tau_b). \tag{S63b}$$

In the limits $e^{\kappa_a t} \gg 1$ and $\delta \ll 1$, the low-seed solution for μ_a (Eq. (22)) becomes: $\mu_a \to (1 + Ae^{\kappa_a t}/c_a)^{-c_a}$, where $A = \varepsilon_a + \delta/2 + p/2$. At this point, Eqs. (S63) may be solved for $\mu_b^{(1)}$ as:

$$\begin{aligned}
\mu_b^{(1)}(t) = -\varepsilon_{1,ba}\Bigg(& e^{\kappa_b t}{}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, c_a n_c(ba), 1-\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}\right] - {}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, c_a n_c(ba), 1-\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right] \\
& + e^{-\kappa_b t}{}_2F_1\left[\frac{\kappa_b}{\kappa_a}, c_a n_c(ba), 1+\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}\right] - {}_2F_1\left[\frac{\kappa_b}{\kappa_a}, c_a n_c(ba), 1+\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right]\Bigg) \\
- \varepsilon_{2,ba}\Bigg(& e^{\kappa_b t}{}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, c_a n_2(ba), 1-\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}\right] - e^{\kappa_b t}{}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, c_a(1+n_2(ba)), 1-\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}\right] \\
& + e^{-\kappa_b t}{}_2F_1\left[\frac{\kappa_b}{\kappa_a}, c_a n_2(ba), 1+\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}\right] - e^{-\kappa_b t}{}_2F_1\left[\frac{\kappa_b}{\kappa_a}, c_a(1+n_2(ba)), 1+\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}\right] \\
& + {}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, c_a(1+n_2(ba)), 1-\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right] - {}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, c_a n_2(ba), 1-\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right] \\
& + {}_2F_1\left[\frac{\kappa_b}{\kappa_a}, c_a(1+n_2(ba)), 1+\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right] - {}_2F_1\left[\frac{\kappa_b}{\kappa_a}, c_a n_2(ba), 1+\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right]\Bigg) \\
& - \varepsilon_b\left(e^{\kappa_b t} + e^{-\kappa_b t} - 2\right),
\end{aligned} \tag{S64}$$

where ${}_2F_1[a,b,c,z]$ is the Gaussian hypergeometric function. Since $A/c_a \ll 1$ provided seed concentration is low, and since $\lim_{z\to 0}{}_2F_1[a,b,c,z] = 1$, the first four terms proportional to $\varepsilon_{2,ba}$ cancel, and two of the hypergeometrics proportional to $\varepsilon_{1,ba}$ vanish, simplifying Eq. (S64) to:

$$\begin{aligned}
\mu_b^{(1)}(t) = -\varepsilon_{1,ba}\Bigg(& e^{\kappa_b t} - {}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, c_a n_c(ba), 1-\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right] \\
& + e^{-\kappa_b t} - {}_2F_1\left[\frac{\kappa_b}{\kappa_a}, c_a n_c(ba), 1+\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right]\Bigg) \\
- \varepsilon_{2,ba}\Bigg(& {}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, c_a(1+n_2(ba)), 1-\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right] - {}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, c_a n_2(ba), 1-\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right] \\
& + {}_2F_1\left[\frac{\kappa_b}{\kappa_a}, c_a(1+n_2(ba)), 1+\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right] - {}_2F_1\left[\frac{\kappa_b}{\kappa_a}, c_a n_2(ba), 1+\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right]\Bigg) \\
& - \varepsilon_b\left(e^{\kappa_b t} + e^{-\kappa_b t} - 2\right).
\end{aligned} \tag{S65}$$

Bearing in mind the following identity:

$$ {}_2F_1[a,b,c,z] \equiv \frac{1}{(1-z)^a}\,{}_2F_1\left[a, c-b, c, \frac{z}{z-1}\right], \tag{S66}$$

and since $\frac{\varepsilon_a}{c_a}e^{\kappa_a t} \gg 1$ by the time the Aβxx sigmoid is reached, the remaining hypergeometric functions can be simplified using the relations:

$$ {}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, n_x, 1-\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right] \equiv \left(1+\frac{A}{c_a}e^{\kappa_a t}\right)^{\frac{\kappa_b}{\kappa_a}} {}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, 1-\frac{\kappa_b}{\kappa_a}-n_x, 1-\frac{\kappa_b}{\kappa_a}, \frac{\frac{A}{c_a}e^{\kappa_a t}}{1+\frac{A}{c_a}e^{\kappa_a t}}\right] \tag{S67}$$

$$ \simeq e^{\kappa_b t}\left(\frac{A}{c_a}\right)^{\kappa_b/\kappa_a} {}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, 1-\frac{\kappa_b}{\kappa_a}-n_x, 1-\frac{\kappa_b}{\kappa_a}, 1\right] \tag{S68}$$

$$ {}_2F_1\left[\frac{\kappa_b}{\kappa_a}, n_x, 1+\frac{\kappa_b}{\kappa_a}, -\frac{A}{c_a}e^{\kappa_a t}\right] \equiv \left(1+\frac{A}{c_a}e^{\kappa_a t}\right)^{-\frac{\kappa_b}{\kappa_a}} {}_2F_1\left[\frac{\kappa_b}{\kappa_a}, 1+\frac{\kappa_b}{\kappa_a}-n_x, 1+\frac{\kappa_b}{\kappa_a}, \frac{\frac{A}{c_a}e^{\kappa_a t}}{1+\frac{A}{c_a}e^{\kappa_a t}}\right] \tag{S69}$$

$$ \simeq e^{-\kappa_b t}\left(\frac{A}{c_a}\right)^{-\kappa_b/\kappa_a} {}_2F_1\left[\frac{\kappa_b}{\kappa_a}, 1+\frac{\kappa_b}{\kappa_a}-n_x, 1+\frac{\kappa_b}{\kappa_a}, 1\right]. \tag{S70}$$

This gives:

$$ \begin{aligned} \mu_b^{(1)}(t) = &-\varepsilon_b\left(e^{\kappa_b t}+e^{-\kappa_b t}-2\right) \\ &-\varepsilon_{1,ba}\left(e^{\kappa_b t}\left(1-\left(\frac{A}{c_a}\right)^{\kappa_b/\kappa_a} {}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, 1-\frac{\kappa_b}{\kappa_a}-c_a n_c(ba), 1-\frac{\kappa_b}{\kappa_a}, 1\right]\right)\right. \\ &\left.+e^{-\kappa_b t}\left(1-\left(\frac{A}{c_a}\right)^{-\kappa_b/\kappa_a} {}_2F_1\left[\frac{\kappa_b}{\kappa_a}, 1+\frac{\kappa_b}{\kappa_a}-c_a n_c(ba), 1+\frac{\kappa_b}{\kappa_a}, 1\right]\right)\right) \\ &-\varepsilon_{2,ba}\left(e^{\kappa_b t}\left(\frac{\varepsilon_a}{c_a}\right)^{\kappa_b/\kappa_a}\sum_{i=0}^{1}(-1)^{i+1}\,{}_2F_1\left[-\frac{\kappa_b}{\kappa_a}, 1-\frac{\kappa_b}{\kappa_a}-c_a(n_2(ba)+i), 1-\frac{\kappa_b}{\kappa_a}, 1\right]\right. \\ &\left.+e^{-\kappa_b t}\left(\frac{\varepsilon_a}{c_a}\right)^{-\kappa_b/\kappa_a}\sum_{i=0}^{1}(-1)^{i+1}\,{}_2F_1\left[\frac{\kappa_b}{\kappa_a}, 1+\frac{\kappa_b}{\kappa_a}-c_a(n_2(ba)+i), 1+\frac{\kappa_b}{\kappa_a}, 1\right]\right). \end{aligned} \tag{S71}$$

These simplifications mean the solution no longer satisfies the initial condition $\mu_b^{(1)}(0) = -\delta$. We can restore this limiting behaviour by adding and subtracting constant terms and terms proportional to $e^{-\kappa_b t}$, yielding finally Eq. (23) of the main text. Because the added and subtracted terms vanish in front of the leading-order terms proportional to $e^{\kappa_b t}$, this does not appreciably reduce accuracy of the final expression.

S7. SUPPORTING KINETIC DATA FITTING

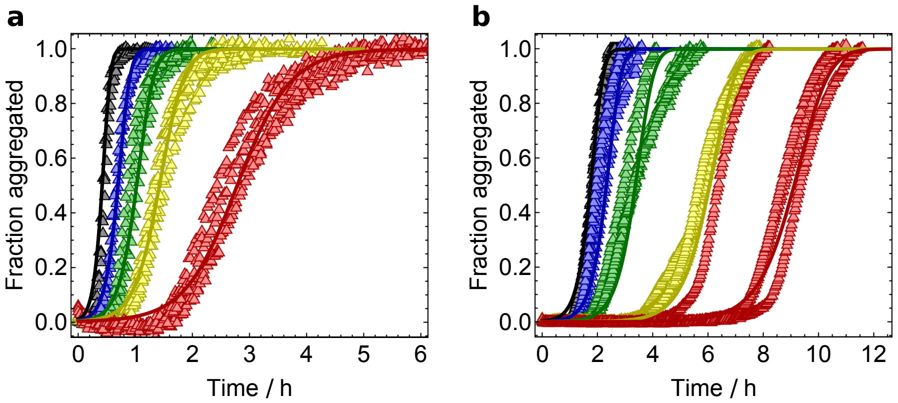

FIG. S3: Data on Aβxx and Aβ42 aggregation in isolation were collected in refs. [20, 21] alongside the coaggregation data. The catalytic secondary nucleation model, Eq. (10), yields good fits to these data. **a**: Aβ42 at pH 7.4; initial monomer concentrations are $m(0) = 10, 5, 3, 2$ and 1 μM. Rate parameters are $K_S = 1.1$ μM, $n_c = n_2 = 2$. **b**: Aβ40 at pH 7.4; initial monomer concentrations are $m(0) = 20, 15, 10, 5$ and 3 μM. Since $K_S \ll 3$ μM, secondary nucleation is completely saturated at these concentrations and we can only provide this bound on K_S rather than a precise value. Other rate parameters are $n_c = 3$ and $n_2 = 2$.

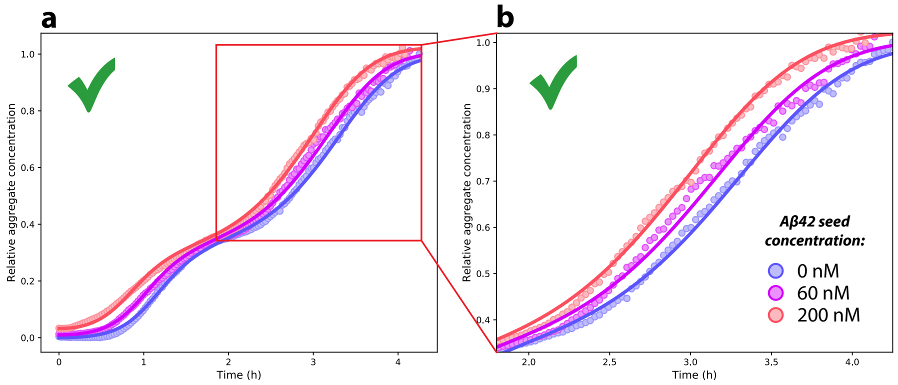

FIG. S4: Full time course for seeded coaggregation reaction displayed in Fig. 3**iii**. Both kinetic data and global fits to Eq. (10) displayed.

S8. SUMMARY OF PARAMETERS

In all subsequent tables, an asterisk "*" means "chosen to be arbitrarily small".

TABLE S1: Parameter values for Aβ42 + Aβ40 aggregation in Fig. 2 and Fig. 8

	Values (units of μM, h)
Parameter	Aβ42
k_+k_2	10.7
k_+k_n	0.0203
n_2	2
n_c	2
K_S	1.1
$K_S(ba)$	0.845
$n_2(aa)$	1
$n_2(ab)$	1

TABLE S2: Parameter values for Fig. 5**b** and for Aβ42 + Aβ38 aggregation in Fig. 2

<table>
<tr><th></th><th colspan="2">Values (units of μM, h)</th></tr>
<tr><th>Parameter</th><th>Aβ42</th><th>Aβ38</th></tr>
<tr><td>k_+k_2</td><td>19</td><td>50</td></tr>
<tr><td>k_+k_n</td><td>0.015</td><td>$10^{-16}*$</td></tr>
<tr><td>n_2</td><td>2</td><td>2</td></tr>
<tr><td>n_c</td><td>2</td><td>3</td></tr>
<tr><td>K_S</td><td>1.1</td><td>0.099</td></tr>
<tr><td>$n_2(ba)$</td><td colspan="2">0.14</td></tr>
<tr><td>$n_2(bb)$</td><td colspan="2">1.5</td></tr>
<tr><td>$k_2(ba)$</td><td colspan="2">1.2×10^{-4}</td></tr>
<tr><td>$n_2(aa)$</td><td>1</td><td></td></tr>
<tr><td>$n_2(ab)$</td><td>1</td><td></td></tr>
<tr><td>$K_S(ba)$</td><td colspan="2">1.38</td></tr>
</table>

TABLE S3: Parameter values for Aβ42 + Aβ37 aggregation in Fig. 2

	Values (units of μM, h)
Parameter	Aβ42
k_+k_2	110
k_+k_n	0.015
n_2	2
n_c	2
K_S	1.1
$n_2(aa)$	1
$n_2(ab)$	1
$K_S(ba)$	0.82

TABLE S4: Parameter values for Fig. 3**b(i)-(ii)**

<table>
<tr><th></th><th colspan="2">Values (units of μM, h)</th></tr>
<tr><th>Parameter</th><th>Aβ42</th><th>Aβ40</th></tr>
<tr><td>k_+k_2</td><td>17.2</td><td>48.8</td></tr>
<tr><td>k_+k_n</td><td>0.012</td><td>$8.5 \times 10^{-12}*$</td></tr>
<tr><td>n_2</td><td>2</td><td>2</td></tr>
<tr><td>n_c</td><td>2</td><td>3</td></tr>
<tr><td>K_S</td><td>1.1</td><td>0.081</td></tr>
<tr><td>$n_2(ba)$</td><td colspan="2">1</td></tr>
<tr><td>$n_2(bb)$</td><td colspan="2">1</td></tr>
<tr><td>$k_2(ba)$</td><td colspan="2">1.9×10^{-4}</td></tr>
<tr><td>$n_2(aa)$</td><td>1</td><td></td></tr>
<tr><td>$n_2(ab)$</td><td>1</td><td></td></tr>
<tr><td>$K_S(ba)$</td><td colspan="2">0.845</td></tr>
</table>

TABLE S5: Parameter values for Fig. 3**b(iii)**

	Values (units of µM, h)	
Parameter	Aβ42	Aβ40
k_+k_2	19.2	69.4
k_+k_n	0.025	$8.5 \times 10^{-12}*$
n_2	2	2
n_c	2	3
K_S	1.1	0.081
$n_2(ba)$	1	
$n_2(bb)$	1	
$k_2(ba)$	1.4×10^{-2}	
$n_2(aa)$	1	
$n_2(ab)$	1	
$K_S(ba)$	0.845	

TABLE S6: Parameter values for Fig. 5**a**

	Values (units of µM, h)	
Parameter	Aβ42	Aβ40
k_+k_2	20	9.2
k_+k_n	0.0097	$8.5 \times 10^{-12}*$
n_2	2	2
n_c	2	3
K_S	1.1	0.081
$n_2(ba)$	2.3	
$n_2(bb)$	0.0	
$k_2(ba)$	3.7×10^{-3}	
$n_2(aa)$	1	
$n_2(ab)$	1	
$K_S(ba)$	0.845	

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[1] H. Stephani, *Differential Equations: Their Solution Using Symmetries* (Cambridge University Press, 1990).

[2] P. Olver, *Applications of Lie Groups to Differential Equations*, Graduate Texts in Mathematics (Springer New York, 2000), ISBN 9780387950006, URL `https://books.google.com/books?id=sI2bAxgLMXYC`.

[3] V. A. Baikov, R. K. Gazizov, and N. H. Ibragimov, Matematicheskii Sbornik **178**, 435 (1988).

[4] N. Ibragimov and V. Kovalev, *Approximate and Renormgroup Symmetries*, Nonlinear Physical Science (Springer Berlin Heidelberg, 2009), ISBN 9783642002281.

[5] V. F. Kovalev, V. V. Pustovalov, and D. V. Shirkov, J. Math. Phys. **39**, 1170 (1998).

[6] A. J. Dear and L. Mahadevan, Proc. R. Soc. A. **481**, 20240103 (2025), URL `https://royalsocietypublishing.org/doi/abs/10.1098/rspa.2024.0103`.

[7] T. C. T. Michaels, S. I. A. Cohen, M. Vendruscolo, C. M. Dobson, and T. P. J. Knowles, Phys. Rev. Lett. **116**, 038101 (2016).

[8] S. I. A. Cohen, S. Linse, L. M. Luheshi, E. Hellstrand, D. A. White, L. Rajah, D. E. Otzen, M. Vendruscolo, C. M. Dobson, and T. P. J. Knowles, Proc. Natl. Acad. Sci. U.S.A. **110**, 9758 (2013).

[9] T. C. T. Michaels, A. J. Dear, and T. P. J. Knowles, Phys. Rev. E **99**, 062415 (2019).

[10] G. Gaeta, Journal of Physics A: Mathematical and General **27**, 437 (1994).

[11] D. Levi and M. A. Rodríguez, EPL **80**, 60005 (2007).

[12] T. P. J. Knowles, C. A. Waudby, G. L. Devlin, S. I. A. Cohen, A. Aguzzi, M. Vendruscolo, E. M. Terentjev, M. E. Welland, and C. M. Dobson, Science **326**, 1533 (2009).

[13] S. I. A. Cohen, M. Vendruscolo, M. E. Welland, C. M. Dobson, E. M. Terentjev, and T. P. J. Knowles, J. Chem. Phys. **135**, 065105 (2011).

[14] G. Meisl, J. B. Kirkegaard, P. Arosio, T. C. T. Michaels, M. Vendruscolo, C. M. Dobson, S. Linse, and T. P. J. Knowles, Nat. Protoc. **11**, 252 (2016).

[15] S. I. A. Cohen, M. Vendruscolo, C. M. Dobson, and T. P. J. Knowles, J. Chem. Phys. **135**, 065106 (2011).

[16] A. J. Dear, T. C. T. Michaels, and T. P. J. Knowles, J. Chem. Phys. **145**, 175101 (2016).

[17] G. Meisl, X. Yang, E. Hellstrand, B. Frohm, J. B. Kirkegaard, S. I. A. Cohen, C. M. Dobson,

S. Linse, and T. P. J. Knowles, Proc. Natl. Acad. Sci. U.S.A. **111**, 9384 (2014).

[18] A. J. Dear, G. Meisl, T. C. T. Michaels, M. R. Zimmermann, S. Linse, and T. P. J. Knowles, J. Chem. Phys. **152**, 045101 (2020).

[19] G. Meisl, C. K. Xu, J. D. Taylor, T. C. T. Michaels, A. Levin, D. Otzen, D. Klenerman, S. Matthews, S. Linse, M. Andreasen, et al., Science Advances **8**, eabn6831 (2022).

[20] R. Cukalevski, X. Yang, G. Meisl, U. Weininger, K. Bernfur, B. Frohm, T. P. J. Knowles, and S. Linse, Chem. Sci. **6**, 4215 (2015).

[21] G. A. Braun, A. J. Dear, K. Sanagavarapu, H. Zetterberg, and S. Linse, Chem. Sci. **13**, 2423 (2022).