

Supporting Information:

Sensitivity analysis of the variability of amyloid aggregation profiles

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I. PROTOCOLS OF PURIFICATION AND PREPARATION OF THE PROTEIN SOLUTIONS FOR EXPERIMENTAL AGGREGATION ASSAYS

We expressed the A β 1 – 42 peptide recombinantly, and we performed the aggregation experiments following the procedure outlined in Ref^{1,2}. Aliquots of lyophilized A β 1 – 42 were dissolved in 6 M guanidinium chloride (GuHCl). The monomeric peptide was isolated by two consecutive rounds of gel filtration performed on a Superdex 75 column (GE Healthcare) using as eluent a 20 mM sodium phosphate buffer at pH 8 with 200 μ M EDTA. In the first round, fractions corresponding to the elution absorbance signal were collected on ice within glass vials. In the second round, the fraction associated with the center of the monomeric peak was further subjected to gel filtration following the same procedure as described above. Only the fraction corresponding to the center of this second monomeric peak was employed in the kinetic experiments. The monomer isolated with this two-steps protocol was then diluted with the same buffer as before to reach the desired nominal concentration, and supplemented with 20 μ M thioflavin T (ThT) from a 2 mM stock to prepare a single stock solution of A β 1 – 42. All of these preparation steps were performed on ice to avoid the formation of aggregates. Aliquots of the stock solution were pipetted into the multiple wells of a 96- half area or 384-well plate of black polystyrene with clear bottom and PEG coating (Corning 3881 and 3766, respectively). The whole plate loading phase also took place on ice, and particular care was taken not to introduce air bubbles when pipetting the aliquots within the different wells. The kinetic assays were then initiated by placing the 96- or 384-well plate at 37 °C in a plate reader (ClarioStar, BMG Labtech, DE).

The formation of fibrils from human insulin was observed under conventional acidic conditions following the protocol adopted in Ref³. Lyophilized human insulin was kindly donated by NovoNordisk (Copenhagen, DN). The powder was freshly dissolved before each experiment in 25 mM HCl at pH 1.6. The solution was filtered with a 200 nm cutoff syringe filter (Millex LG Syringe Driven Filter Unit) to remove the presence of any potential seeds for aggregation. The monomeric state and the concentration of human insulin were checked by size exclusion chromatography (Superdex Peptide 10/300 GL column, GE Healthcare) coupled with in line multiangle light scattering (Wyatt, DE, data not shown). Aliquots of 150 μ l of insulin solution at the desired nominal concentration were incubated with 20 μ M ThT at 60 °C and in presence of shaking (400 rpm) in a 96-well plate (nonbinding μ clear

Greiner bio-one microplate, PS, FBottom, Chimney wells) and the kinetics of aggregation were recorded in a plate reader (ClarioStar, BMG Labtech, DE).

II. VARIABILITY OF AGGREGATION KINETICS ESTIMATED BY MEASUREMENT OF THE SOLUBLE MONOMER

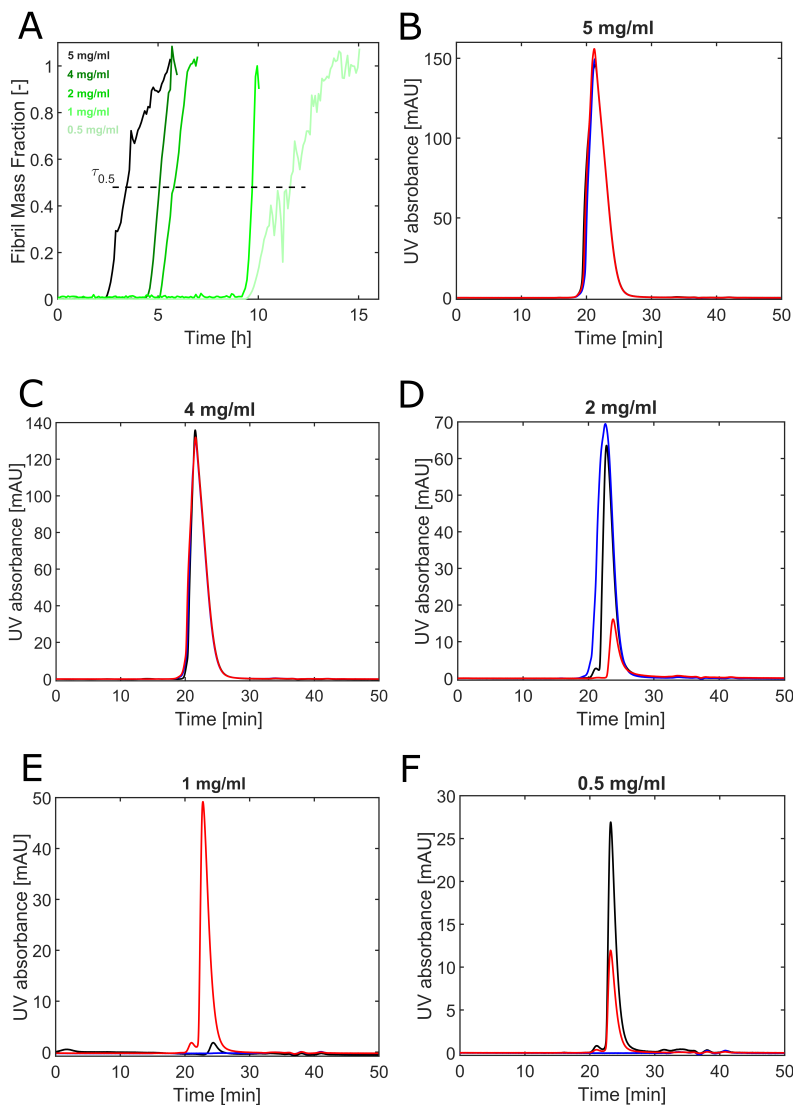


Figure S1: Variability in the aggregation kinetics of human insulin estimated by measuring the concentration of soluble monomer by size exclusion chromatography (SEC). (A): Aggregation profiles of human insulin solutions at 5, 4, 2, 1 and 0.5 mg/mL in 20 mM HCl buffer at pH 2.0; (B-F) SEC chromatograms of the soluble fraction of samples taken at the half-times in the profiles shown in A. For each condition three triplicates were measured.

Aggregation assays were prepared and performed as described in the previous section. For each insulin concentration, four replicates were prepared by aliquoting insulin solutions into

four wells. 20 μ M ThT was added into one well to monitor the aggregation profile. When the half-time was reached (Fig.S1A), we interrupted the aggregation reaction and analyzed the three ThT-free replicates by size exclusion chromatography (SEC). To this aim, we centrifuged the samples at 13500 rpm (17136 rcf) for 30 minutes at 20 °C (Labnet Prism™ R Refrigerated Microcentrifuge, Labnet International, Inc.). 40 μ l of the supernatant of each replicate were then injected in an Agilent 1100 series HPLC unit (Santa Clara, CA, U.S.A.) consisting of a quaternary pump, a column thermostat, an autosampler and a UV detector, using as eluent a 25 mM potassium phosphate buffer at pH 7.4. We calculated the concentration of soluble monomer by integrating the area under the corresponding peak in the chromatograms.

The results show that the variability of the replicates is proportional to the duration of the aggregation process and inversely proportional to the protein concentration (Fig. 2 of the main text)

III. PARAMETRIC SENSITIVITY EQUATIONS

For the analytical expressions of the aggregation lag time τ_{lag} and the maximal growth rate r_{max} in the different aggregation regimes, the results obtained in Ref.⁴ have been adopted.

A. Primary nucleation regime

The aggregation lag time is given by:

$$\tau_{\text{lag}} = \mu^{-1} \beta^{\frac{1}{2}} \left[\operatorname{arctanh} \left(\frac{1}{\sqrt{1+\beta}} \right) - \operatorname{arcsinh}(\gamma) - \sqrt{\frac{2+n_c}{2\beta}} \left(\frac{2\mu^2}{2+n_c} \right)^{-\frac{1}{n_c}} \left(\frac{m_{\text{tot}}}{m(0)} - \mu^{\frac{2}{n_c}} \left(\frac{2}{2+n_c} \right)^{\frac{1}{n_c}} \right) \right] \lambda^{-1} \quad (1)$$

while the maximal growth rate reads as:

$$r_{\text{max}} = \frac{2m(0)}{\sqrt{2(2+n_c)}} \left(\frac{2\mu^2}{2+n_c} \right)^{\frac{1}{n_c}} \mu \lambda \quad (2)$$

with $\lambda = \sqrt{2k_+k_n m(0)^{n_c}}$, $\beta = 2/n_c$, $\gamma = \frac{\beta^{\frac{1}{2}} k_+ n_c}{\lambda} P(0)$ and $\mu = \sqrt{1+\gamma^2}$. For the primary nucleation regime, all the sensitivities —but those with respect to the initial fibril number $P(0)$ — have been computed for unseeded ($P(0) = M(0) = 0$) conditions; under this hypothesis, $\gamma = 0$, $\mu = 1$ and $m_{\text{tot}} = m(0)$.

•

$$\begin{aligned} \frac{\partial \tau_{\text{lag}}}{\partial k_n} &= -\tau_{\text{lag}} \cdot \frac{1}{\lambda} \frac{\partial \lambda}{\partial k_n} \\ &= -\frac{\tau_{\text{lag}}}{\lambda} \cdot \frac{1}{2\lambda} \cdot 2k_+ m(0)^{n_c} \cdot \frac{k_n}{k_n} \\ &= -\frac{\tau_{\text{lag}}}{2k_n} \end{aligned} \quad (3)$$

• The functional dependence of τ_{lag} on k_n and k_+ is the same, and one can derive:

$$\frac{\partial \tau_{\text{lag}}}{\partial k_+} = \frac{\tau_{\text{lag}}}{2k_+} \quad (4)$$

•

$$\begin{aligned} \frac{\partial \tau_{\text{lag}}}{\partial m(0)} &= -\tau_{\text{lag}} \cdot \frac{1}{\lambda} \frac{\partial \lambda}{\partial m(0)} \\ &= -\frac{\tau_{\text{lag}}}{\lambda} \cdot \frac{1}{2\lambda} \cdot 2k_+ k_n n_c m(0)^{n_c-1} \cdot \frac{m(0)}{m(0)} \\ &= -\frac{\tau_{\text{lag}}}{m(0)} \frac{n_c}{2} \quad (n_c \geq 2) \end{aligned} \quad (5)$$

•

$$\begin{aligned}
\frac{\partial \tau_{\text{lag}}}{\partial P(0)} &= -\frac{1}{\mu} \frac{\partial \mu}{\partial P(0)} \tau_{\text{lag}} - \frac{\beta^{\frac{1}{2}}}{\mu^2 \lambda} \left[\frac{\partial \gamma}{\partial P(0)} + \sqrt{\frac{2+n_c}{2\beta}} \frac{m_{\text{tot}}}{m(0)} \left(\frac{2}{2+n_c}\right)^{-\frac{1}{n_c}} \left(-\frac{2}{n_c}\right) \mu^{-\frac{2}{n_c}} \frac{\partial \mu}{\partial P(0)} \right] \\
&= -\frac{\tau_{\text{lag}}}{P(0)} \left(1 - \frac{1}{\mu^2}\right) - \frac{\beta^{\frac{1}{2}}}{\mu^2 \lambda P(0)} \left[\gamma - \sqrt{\frac{2+n_c}{2\beta}} \frac{m_{\text{tot}}}{m(0)} \left(\frac{2}{2+n_c}\right)^{-\frac{1}{n_c}} \left(\frac{2}{n_c}\right) (\mu^{-\frac{2}{n_c}+1} - \mu^{-\frac{2}{n_c}-1}) \right] \\
&\quad (n_c = 2, m_{\text{tot}} \approx m(0)) \\
&\approx -\frac{\tau_{\text{lag}}}{P(0)} \left(1 - \frac{1}{\mu^2}\right)
\end{aligned} \tag{6}$$

•

$$\begin{aligned}
\frac{\partial r_{\text{max}}}{\partial k_n} &= \frac{2m(0)}{\sqrt{2(2+n_c)}} \left(\frac{2}{2+n_c}\right)^{\frac{1}{n_c}} \frac{1}{2\lambda} \cdot 2k_+ m(0)^{n_c} \cdot \frac{k_n}{k_n} \\
&= \frac{r_{\text{max}}}{2k_n}
\end{aligned} \tag{7}$$

• The functional dependence of r_{max} on k_n and k_+ is the same, and one can derive:

$$\frac{\partial r_{\text{max}}}{\partial k_+} = \frac{r_{\text{max}}}{2k_+} \tag{8}$$

•

$$\begin{aligned}
\frac{\partial r_{\text{max}}}{\partial m(0)} &= \frac{2m(0)}{\sqrt{2(2+n_c)}} \left(\frac{2}{2+n_c}\right)^{\frac{1}{n_c}} \lambda + \frac{2m(0)}{\sqrt{2(2+n_c)}} \left(\frac{2}{2+n_c}\right)^{\frac{1}{n_c}} \frac{\partial \lambda}{\partial m(0)} \\
&= \frac{r_{\text{max}}}{m(0)} + \frac{2m(0)}{\sqrt{2(2+n_c)}} \left(\frac{2}{2+n_c}\right)^{\frac{1}{n_c}} \frac{1}{2\lambda} \cdot 2k_n k_+^{n_c} m(0)^{n_c-1} \cdot \frac{m(0)}{m(0)} \\
&= \frac{r_{\text{max}}}{m(0)} + \frac{r_{\text{max}} n_c}{2m(0)} \\
&= \frac{r_{\text{max}}}{m(0)} \left[1 + \frac{n_c}{2}\right]
\end{aligned} \tag{9}$$

•

$$\begin{aligned}
\frac{\partial r_{\text{max}}}{\partial P(0)} &= \frac{2m(0)}{\sqrt{2(2+n_c)}} \left(\frac{2}{2+n_c}\right)^{\frac{1}{n_c}} \lambda \cdot \frac{\partial}{\partial P(0)} \left[\mu^{\frac{2}{n_c}+1} \right] \\
&= \frac{2m(0)}{\sqrt{2(2+n_c)}} \left(\frac{2}{2+n_c}\right)^{\frac{1}{n_c}} \lambda \left(\frac{2}{n_c} + 1\right) \mu^{\frac{2}{n_c}} \cdot \frac{\mu}{\mu} \cdot \frac{\partial \mu}{\partial P(0)} \\
&= r_{\text{max}} \left(\frac{2}{n_c} + 1\right) \frac{1}{\mu} \frac{\partial \mu}{\partial P(0)} \\
&= r_{\text{max}} \left(\frac{2}{n_c} + 1\right) \left(\frac{\mu^2 - 1}{\mu^2}\right) \cdot \frac{1}{P(0)} \\
&= \frac{r_{\text{max}}}{P(0)} \left(\frac{2}{n_c} + 1\right) \left(1 - \frac{1}{\mu^2}\right)
\end{aligned} \tag{10}$$

B. Surface-induced secondary nucleation regime

The aggregation lag time is given by:

$$\tau_{\text{lag}} = \left[\log \left(\frac{1}{C_+} \right) - e + 1 \right] \kappa^{-1} \quad (11)$$

while the maximal growth rate reads as:

$$r_{\text{max}} = \frac{m_{\text{tot}}}{e} \kappa \quad (12)$$

with $C_{\pm} = \frac{k_+ P(0)}{\kappa} \pm \frac{M(0)}{2m(0)} \pm \frac{\lambda^2}{2\kappa^2}$ and $\kappa = \sqrt{2k_+ k_2 m(0)^{n_2+1}}$. For the secondary nucleation regime, all the sensitivities—but those with respect to the initial fibril number $P(0)$ —have been computed for unseeded ($P(0) = M(0) = 0$) conditions; under this hypothesis, $C_{\pm} = \pm \frac{\lambda^2}{2\kappa^2}$.

•

$$\begin{aligned} \frac{\partial \tau_{\text{lag}}}{\partial k_n} &= \frac{C_+}{\kappa} \frac{\partial}{\partial k_n} \left(\frac{1}{C_+} \right) \\ &= -\frac{1}{\kappa C_+} \frac{\partial C_+}{\partial k_n} \\ &= -\frac{1}{\kappa C_+} \frac{m(0)^{n_c - n_2 - 1}}{2k_2} \cdot \frac{k_n}{k_n} = -\frac{1}{\kappa k_n} \end{aligned} \quad (13)$$

•

$$\begin{aligned} \frac{\partial \tau_{\text{lag}}}{\partial k_+} &= -\frac{1}{\kappa} \frac{\partial \kappa}{\partial k_+} \tau_{\text{lag}} \\ &= -\frac{1}{\kappa} \cdot \frac{\kappa}{2k_+} \tau_{\text{lag}} = -\frac{\tau_{\text{lag}}}{2k_+} \end{aligned} \quad (14)$$

•

$$\begin{aligned} \frac{\partial \tau_{\text{lag}}}{\partial k_2} &= -\frac{1}{\kappa^2} \frac{\partial \kappa}{\partial k_2} \left[\log \left(\frac{1}{C_+} \right) - e + 1 \right] + \frac{C_+}{\kappa} \frac{\partial}{\partial k_2} \left(\frac{1}{C_+} \right) \\ &= -\frac{\tau_{\text{lag}}}{\kappa} \frac{\partial \kappa}{\partial k_2} - \frac{1}{\kappa C_+} \frac{\partial C_+}{\partial k_2} \\ &= -\frac{\tau_{\text{lag}}}{2k_2} + \frac{1}{\kappa k_2} \approx -\frac{\tau_{\text{lag}}}{2k_2} \end{aligned} \quad (15)$$

•

$$\begin{aligned} \frac{\partial \tau_{\text{lag}}}{\partial m(0)} &= -\frac{\tau_{\text{lag}}}{\kappa} \frac{\partial \kappa}{\partial m(0)} - \frac{1}{\kappa C_+} \frac{\partial C_+}{\partial m(0)} \\ &= -\frac{(n_2 + 1)}{2} \frac{\tau_{\text{lag}}}{m(0)} - \frac{(n_c - n_2 - 1)}{\kappa m(0)} \\ &\approx -\frac{(n_2 + 1)}{2} \frac{\tau_{\text{lag}}}{m(0)} \quad (n_2 \geq 2) \end{aligned} \quad (16)$$

- $$\begin{aligned}
\frac{\partial \tau_{\text{lag}}}{\partial P(0)} &= -\frac{1}{\kappa C_+} \frac{\partial C_+}{\partial P(0)} \\
&= -\frac{1}{\kappa C_+} \sqrt{\frac{k_+}{2k_2 m(0)^{n_2+1}}} \cdot \frac{P(0)}{P(0)} \\
&\approx -\frac{1}{\kappa P(0)}
\end{aligned}
\tag{17}$$

- $$\begin{aligned}
\frac{\partial r_{\text{max}}}{\partial k_2} &= \frac{m_{\text{tot}}}{2e} \frac{2k_+ m(0)^{n_2+1}}{\sqrt{2k_+ k_2 m(0)^{n_2+1}}} \\
&= \frac{m_{\text{tot}}}{2e} \sqrt{\frac{2k_+ m(0)^{n_2+1}}{k_2}} \cdot \frac{k_2}{k_2} \\
&= \frac{r_{\text{max}}}{2k_2}
\end{aligned}
\tag{18}$$

- The functional dependence of r_{max} on k_2 and k_+ is the same, and one can derive:

$$\frac{\partial r_{\text{max}}}{\partial k_+} = \frac{r_{\text{max}}}{2k_+}
\tag{19}$$

- $$\begin{aligned}
\frac{\partial r_{\text{max}}}{\partial m(0)} &= (n_2 + 1) \frac{m_{\text{tot}}}{2e} \frac{2k_+ k_2 m(0)^{n_2}}{\sqrt{2k_+ k_2 m(0)^{n_2+1}}} \cdot \frac{m(0)}{m(0)} \\
&= \frac{(n_2 + 1)}{2m(0)} \frac{m_{\text{tot}}}{e} \sqrt{2k_+ k_2 m(0)^{n_2+1}} \\
&= \frac{(n_2 + 1)}{2} \frac{r_{\text{max}}}{m(0)}
\end{aligned}
\tag{20}$$

C. Fragmentation regime

The aggregation lag time is given by:

$$\tau_{\text{lag}} = \left[\log \left(\frac{1}{C_+} \right) - e + 1 \right] \kappa^{-1}
\tag{21}$$

while the maximal growth rate reads as:

$$r_{\text{max}} = \frac{m_{\text{tot}}}{e} \kappa
\tag{22}$$

with $C_{\pm} = \frac{k_+ P(0)}{\kappa} \pm \frac{M(0)}{2m(0)} \pm \frac{\lambda^2}{2\kappa^2}$ and $\kappa = \sqrt{2k_+ k_- m(0)}$. For the fragmentation regime, all the sensitivities—but those with respect to the initial fibril number $P(0)$ —have been computed for unseeded ($P(0) = M(0) = 0$) conditions; under this hypothesis, $C_{\pm} = \pm \frac{\lambda^2}{2\kappa^2}$.

$$\begin{aligned}
\frac{\partial \tau_{\text{lag}}}{\partial k_n} &= -\frac{1}{\kappa C_+} \frac{\partial C_+}{\partial k_n} \\
&= -\frac{1}{\kappa C_+} \frac{m(0)^{n_c-1}}{2k_-} \cdot \frac{k_n}{k_n} \\
&= -\frac{1}{\kappa k_n}
\end{aligned} \tag{23}$$

$$\begin{aligned}
\frac{\partial \tau_{\text{lag}}}{\partial k_+} &= -\frac{1}{\kappa} \frac{\partial \kappa}{\partial k_+} \tau_{\text{lag}} \\
&= -\frac{1}{\kappa} \cdot \frac{\kappa}{2k_+} \tau_{\text{lag}} = -\frac{\tau_{\text{lag}}}{2k_+}
\end{aligned} \tag{24}$$

$$\begin{aligned}
\frac{\partial \tau_{\text{lag}}}{\partial k_-} &= -\frac{\tau_{\text{lag}}}{\kappa} \frac{\partial \kappa}{\partial k_-} - \frac{1}{\kappa C_+} \frac{\partial C_+}{\partial k_-} \\
&= -\frac{\tau_{\text{lag}}}{2k_-} + \frac{1}{\kappa k_-} \approx -\frac{\tau_{\text{lag}}}{2k_-}
\end{aligned} \tag{25}$$

$$\begin{aligned}
\frac{\partial \tau_{\text{lag}}}{\partial m(0)} &= -\frac{\tau_{\text{lag}}}{\kappa} \frac{\partial \kappa}{\partial m(0)} - \frac{1}{\kappa C_+} \frac{\partial C_+}{\partial m(0)} \\
&= -\frac{\tau_{\text{lag}}}{2m(0)} - \frac{1}{\kappa C_+} \frac{(n_c-1)k_n}{2k_-} m(0)^{n_c-2} \cdot \frac{m(0)}{m(0)} \\
&= -\frac{\tau_{\text{lag}}}{2m(0)} - \frac{(n_c-1)}{\kappa m(0)} \approx -\frac{\tau_{\text{lag}}}{2m(0)}
\end{aligned} \tag{26}$$

$$\begin{aligned}
\frac{\partial \tau_{\text{lag}}}{\partial P(0)} &= -\frac{1}{\kappa C_+} \frac{\partial C_+}{\partial P(0)} \\
&= -\frac{1}{\kappa C_+} \sqrt{\frac{k_+}{2k_2 m(0)^{n_2+1}}} \cdot \frac{P(0)}{P(0)} \\
&\approx -\frac{1}{\kappa P(0)}
\end{aligned} \tag{27}$$

$$\begin{aligned}
\frac{\partial r_{\text{max}}}{\partial k_-} &= \frac{m_{\text{tot}}}{2e} \frac{2k_+ m(0)}{\sqrt{2k_+ k_- m(0)}} \\
&= \frac{m_{\text{tot}}}{2e} \sqrt{\frac{2k_+ m(0)}{k_-}} \cdot \frac{k_-}{k_-} \\
&= \frac{r_{\text{max}}}{2k_-}
\end{aligned} \tag{28}$$

- The functional dependence of r_{max} on k_- , k_+ and $m(0)$ is the same, and one can derive:

$$\frac{\partial r_{\text{max}}}{\partial k_+} = \frac{r_{\text{max}}}{2k_+}, \quad \frac{\partial r_{\text{max}}}{\partial m(0)} = \frac{r_{\text{max}}}{2m(0)} \tag{29}$$

IV. KINETIC PARAMETERS VARIATIONS FOR TUNING TRANSITION BETWEEN DIFFERENT AGGREGATION REGIMES

In the following tables we report the kinetic parameters of the simulations shown in Fig.4, 5 of the Main Text. Percentage values represent the ratio of the number of fibrils generated by the corresponding mechanism over the total number of fibrils. In this case, τ_{lag} has been defined as the intersection point of the tangent to $M(t)$ in t_{max} with the time axis (crf. Main Text).

Primary to surface-induced secondary nucleation regime		
Primary:100%	Primary:44%	Primary:3%
Secondary:0%	Secondary:56%	Secondary:97%
$m(0) = 1 \mu\text{M}$	$m(0) = 1 \mu\text{M}$	$m(0) = 1 \mu\text{M}$
$k_n = 0.36 \text{ M}^{-1} \text{ h}^{-1}$	$k_n = 0.36 \text{ M}^{-1} \text{ h}^{-1}$	$k_n = 0.36 \text{ M}^{-1} \text{ h}^{-1}$
$k_+ = 1.08 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_+ = 1.08 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_+ = 1.08 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$
$k_2 = 10 \times 10^{-20} \text{ M}^{-2} \text{ h}^{-1}$	$k_2 = 2.88 \times 10^6 \text{ M}^{-2} \text{ h}^{-1}$	$k_2 = 1.08 \times 10^8 \text{ M}^{-2} \text{ h}^{-1}$

Table I

Primary nucleation to fragmentation regime		
Primary:100%	Primary:43%	Primary:5%
Fragmentation:0%	Fragmentation:57%	Fragmentation:95%
$m(0) = 1 \mu\text{M}$	$m(0) = 1 \mu\text{M}$	$m(0) = 1 \mu\text{M}$
$k_n = 0.036 \text{ M}^{-1} \text{ h}^{-1}$	$k_n = 0.036 \text{ M}^{-1} \text{ h}^{-1}$	$k_n = 0.036 \text{ M}^{-1} \text{ h}^{-1}$
$k_+ = 1.08 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_+ = 1.08 \times 10^9 \text{ M}^{-1} \text{ h}^{-1}$	$k_+ = 1.8 \times 10^8 \text{ M}^{-1} \text{ h}^{-1}$
$k_- = 10 \times 10^{-20} \text{ h}^{-1}$	$k_- = 2.88 \times 10^{-5} \text{ h}^{-1}$	$k_- = 7.20 \times 10^{-5} \text{ h}^{-1}$

Table II

V. OVERVIEW OF THE LAG TIME AND KINETIC PROFILES PARAMETER-INDUCED VARIATIONS

Simulated variations of τ_{lag} as a function of different kinetic parameters. The variations have been normalised with respect to τ_{lag}^* , which represents the lag time corresponding to a fixed reference set of kinetic parameters.

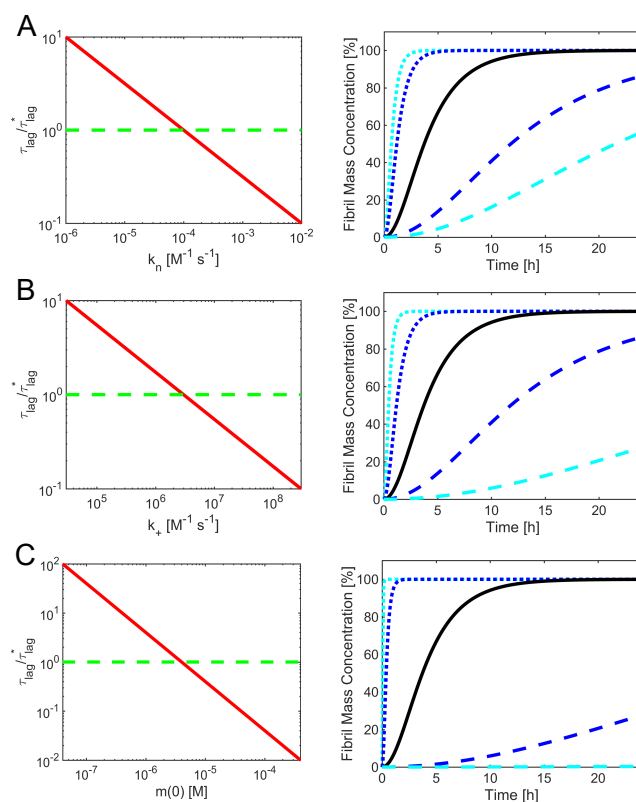


Figure S2: Simulated variations of the lag time (left panels) and of the kinetic profiles (right panels) for the primary nucleation regime upon changes of the kinetic parameters k_n (**A**), k_+ (**B**) and $m(0)$

(**C**) around the reference set. The reference set is: $k_n = 1.0 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$,

$$k_+ = 3.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}, m(0) = 4 \mu\text{M}.$$

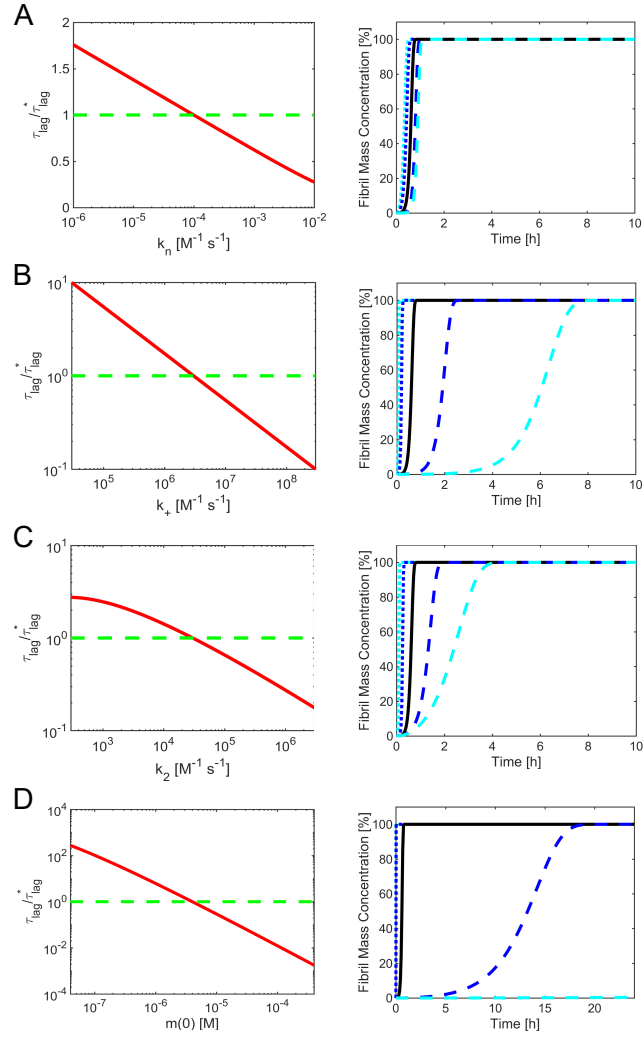


Figure S3: Simulated variations of the lag time (left panels) and of the kinetic profiles (right panels) for the secondary nucleation regime upon changes of the kinetic parameters k_n (A), k_+ (B), k_2 (C) and $m(0)$ (D) around the reference set. The reference set is: $k_n = 1.0 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$,

$$k_+ = 3.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}, k_2 = 3.0 \times 10^4 \text{ M}^{-2} \text{ s}^{-1}, m(0) = 4 \mu\text{M}.$$

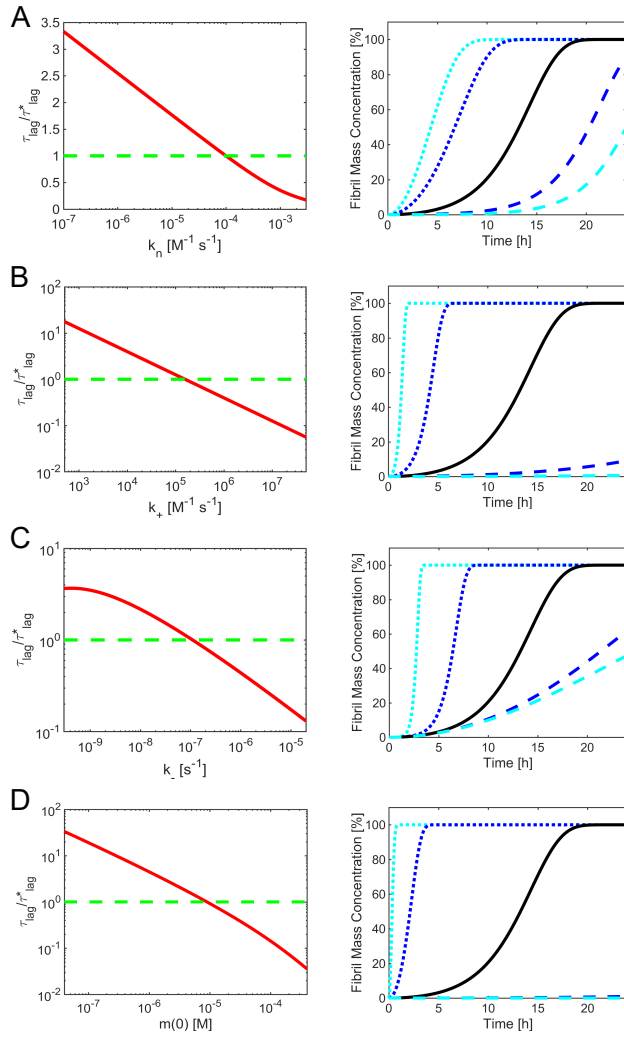


Figure S4: Simulated variations of the lag time (left panels) and of the kinetic profiles (right panels) for the fragmentation-dominated regime upon changes of the kinetic parameters k_n (**A**), k_+ (**B**), k_- (**C**) and $m(0)$ (**D**) around the reference set. The reference set is: $k_n = 1.0 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$,

$$k_+ = 2.0 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}, k_- = 1.0 \times 10^{-7} \text{ s}^{-1}, m(0) = 10 \mu\text{M}.$$

VI. SUMMARY OF THE KINETIC PARAMETERS FOR THE $A\beta 1 - 42$ FITTINGS

The following tables summarise the kinetic parameters corresponding to the simulations of the aggregation profiles of $A\beta - 42$ shown in Fig.6A of the Main Text.

Fitting parameter: $m(0)$		
$k_+k_n = 1.17 \times 10^{10} \text{ M}^{-2}\text{h}^{-2}$ $k_+k_2 = 3.88 \times 10^{17} \text{ M}^{-3}\text{h}^{-2}$		
$m(0)_1 = 1.62 \text{ }\mu\text{M}$	$m(0)_1 = 2.54 \text{ }\mu\text{M}$	$m(0)_1 = 3.04 \text{ }\mu\text{M}$
$m(0)_2 = 1.86 \text{ }\mu\text{M}$	$m(0)_2 = 2.68 \text{ }\mu\text{M}$	$m(0)_2 = 3.30 \text{ }\mu\text{M}$
$m(0)_3 = 1.74 \text{ }\mu\text{M}$	$m(0)_3 = 2.86 \text{ }\mu\text{M}$	$m(0)_3 = 3.26 \text{ }\mu\text{M}$
$m(0)_1 = 3.77 \text{ }\mu\text{M}$	$m(0)_1 = 3.88 \text{ }\mu\text{M}$	$m(0)_1 = 4.72 \text{ }\mu\text{M}$
$m(0)_2 = 3.78 \text{ }\mu\text{M}$	$m(0)_2 = 3.79 \text{ }\mu\text{M}$	$m(0)_2 = 4.50 \text{ }\mu\text{M}$
$m(0)_3 = 3.82 \text{ }\mu\text{M}$	$m(0)_3 = 3.85 \text{ }\mu\text{M}$	$m(0)_3 = 4.56 \text{ }\mu\text{M}$

Table III

Fitting parameter: k_+		
$k_n = 1.08 \text{ M}^{-1} \text{ h}^{-1} \quad k_2 = 3.6 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$		
$m(0) = 1.73 \text{ } \mu\text{M}$	$m(0) = 2.69 \text{ } \mu\text{M}$	$m(0) = 3.20 \text{ } \mu\text{M}$
$k_{+,1} = 9.07 \times 10^9 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 9.23 \times 10^9 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 9.4 \times 10^9 \text{ M}^{-1} \text{ h}^{-1}$
$k_{+,2} = 1.3 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 1.06 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 1.17 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$
$k_{+,3} = 1.09 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 1.26 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 1.13 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$
$m(0) = 3.79 \text{ } \mu\text{M}$	$m(0) = 3.84 \text{ } \mu\text{M}$	$m(0) = 4.59 \text{ } \mu\text{M}$
$k_{+,1} = 1.06 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 1.11 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 1.16 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$
$k_{+,2} = 1.07 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 1.04 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 1.02 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$
$k_{+,3} = 1.11 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 1.09 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 1.06 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$

Table IV

Fitting parameter: k_2		
$k_n = 1.08 \text{ M}^{-1} \text{ h}^{-1} \quad k_+ = 1.08 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$		
$m(0) = 1.73 \text{ } \mu\text{M}$	$m(0) = 2.69 \text{ } \mu\text{M}$	$m(0) = 3.20 \text{ } \mu\text{M}$
$k_{2,1} = 2.87 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$	$k_{2,1} = 2.91 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$	$k_{2,1} = 3.02 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$
$k_{2,2} = 4.95 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$	$k_{2,2} = 3.63 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$	$k_{2,2} = 4.12 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$
$k_{2,3} = 3.81 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$	$k_{2,3} = 4.65 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$	$k_{2,3} = 3.95 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$
$m(0) = 3.79 \text{ } \mu\text{M}$	$m(0) = 3.84 \text{ } \mu\text{M}$	$m(0) = 4.59 \text{ } \mu\text{M}$
$k_{2,1} = 3.52 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$	$k_{2,1} = 3.79 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$	$k_{2,1} = 4.04 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$
$k_{2,2} = 3.54 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$	$k_{2,2} = 3.46 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$	$k_{2,2} = 3.36 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$
$k_{2,3} = 3.72 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$	$k_{2,3} = 3.68 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$	$k_{2,3} = 3.55 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$

Table V

Fitting parameter: k_n		
$k_2 = 3.6 \times 10^7 \text{ M}^{-2} \text{ h}^{-1}$ $k_+ = 1.08 \times 10^{10} \text{ M}^{-1} \text{ h}^{-1}$		
$m(0) = 1.73 \text{ } \mu\text{M}$	$m(0) = 2.69 \text{ } \mu\text{M}$	$m(0) = 3.20 \text{ } \mu\text{M}$
$k_{n,1} = 0.60 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 0.63 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 0.63 \text{ M}^{-1} \text{ h}^{-1}$
$k_{n,2} = 1.54 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 0.93 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 1.23 \text{ M}^{-1} \text{ h}^{-1}$
$k_{n,3} = 0.97 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 1.49 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 1.08 \text{ M}^{-1} \text{ h}^{-1}$
$m(0) = 3.79 \text{ } \mu\text{M}$	$m(0) = 3.84 \text{ } \mu\text{M}$	$m(0) = 4.59 \text{ } \mu\text{M}$
$k_{n,1} = 1.03 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 1.07 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 1.30 \text{ M}^{-1} \text{ h}^{-1}$
$k_{n,2} = 1.07 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 0.89 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 0.85 \text{ M}^{-1} \text{ h}^{-1}$
$k_{n,3} = 1.18 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 1.04 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 0.96 \text{ M}^{-1} \text{ h}^{-1}$

Table VI

VII. SUMMARY OF THE KINETIC PARAMETERS FOR THE β_2 -MICROGLOBULIN FITTINGS

The following tables summarise the kinetic parameters corresponding to the simulations of the aggregation profiles of β_2 -microglobulin shown in Fig.6F of the Main Text.

Fitting parameter: $m(0)$				
$k_+k_n = 2.87 \times 10^3 \text{ M}^{-2}\text{h}^{-2}$		$k_+k_- = 4.47 \times 10^3 \text{ M}^{-1}\text{h}^{-2}$		
$m(0)_1 = 218 \mu\text{M}$	$m(0)_1 = 181 \mu\text{M}$	$m(0)_1 = 180 \mu\text{M}$	$m(0)_1 = 39.3 \mu\text{M}$	$m(0)_1 = 112 \mu\text{M}$
$m(0)_2 = 246 \mu\text{M}$	$m(0)_2 = 111 \mu\text{M}$	$m(0)_2 = 136 \mu\text{M}$	$m(0)_2 = 58.5 \mu\text{M}$	$m(0)_2 = 133 \mu\text{M}$
$m(0)_3 = 241 \mu\text{M}$	$m(0)_3 = 155 \mu\text{M}$	$m(0)_3 = 162 \mu\text{M}$	$m(0)_3 = 47.8 \mu\text{M}$	$m(0)_3 = 139 \mu\text{M}$
$m(0)_4 = 280 \mu\text{M}$	$m(0)_4 = 150 \mu\text{M}$	$m(0)_4 = 146 \mu\text{M}$	$m(0)_4 = 67.2 \mu\text{M}$	$m(0)_4 = 181 \mu\text{M}$
$m(0)_1 = 97.1 \mu\text{M}$	$m(0)_1 = 101 \mu\text{M}$	$m(0)_1 = 51.2 \mu\text{M}$	$m(0)_1 = 75.3 \mu\text{M}$	$m(0)_1 = 26.1 \mu\text{M}$
$m(0)_2 = 71 \mu\text{M}$	$m(0)_2 = 98.1 \mu\text{M}$	$m(0)_2 = 58.1 \mu\text{M}$	$m(0)_2 = 68 \mu\text{M}$	$m(0)_2 = 30.5 \mu\text{M}$
$m(0)_3 = 104 \mu\text{M}$	$m(0)_3 = 77 \mu\text{M}$	$m(0)_3 = 65.2 \mu\text{M}$	$m(0)_3 = 57.2 \mu\text{M}$	$m(0)_3 = 30.7 \mu\text{M}$
$m(0)_4 = 119 \mu\text{M}$	$m(0)_4 = 92.2 \mu\text{M}$	$m(0)_4 = 77.6 \mu\text{M}$	$m(0)_4 = 55.1 \mu\text{M}$	$m(0)_4 = 33.8 \mu\text{M}$
$m(0)_1 = 28.5 \mu\text{M}$	$m(0)_1 = 19.1 \mu\text{M}$	$m(0)_1 = 10.2 \mu\text{M}$	$m(0)_1 = 8.04 \mu\text{M}$	
$m(0)_2 = 28.6 \mu\text{M}$	$m(0)_2 = 18.7 \mu\text{M}$	$m(0)_2 = 10.5 \mu\text{M}$	$m(0)_2 = 9.13 \mu\text{M}$	
$m(0)_3 = 34.5 \mu\text{M}$	$m(0)_3 = 20 \mu\text{M}$	$m(0)_3 = 14.8 \mu\text{M}$	$m(0)_3 = 9.98 \mu\text{M}$	
$m(0)_4 = 27.6 \mu\text{M}$	$m(0)_4 = 22.4 \mu\text{M}$	$m(0)_4 = 13.8 \mu\text{M}$	$m(0)_4 = 8.462 \mu\text{M}$	

Table VII

Fitting parameter: k_+

$$k_n = 2.6 \times 10^2 \text{ M}^{-1}\text{h}^{-1} \quad k_- = 1.51 \times 10^3 \text{ M}^{-1}\text{h}^{-1}$$

$m(0) = 243 \mu\text{M}$	$m(0) = 142 \mu\text{M}$	$m(0) = 123 \mu\text{M}$	$m(0) = 122 \mu\text{M}$	$m(0) = 102 \mu\text{M}$
$k_{+,1} = 3.41 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 5.16 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 6.07 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 3.22 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 4.26 \text{ M}^{-1} \text{ h}^{-1}$
$k_{+,2} = 3.96 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 2.84 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 4.32 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 5.11 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 5.24 \text{ M}^{-1} \text{ h}^{-1}$
$k_{+,3} = 3.85 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 4.27 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 5.32 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 4.04 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 5.51 \text{ M}^{-1} \text{ h}^{-1}$
$k_{+,4} = 4.62 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,4} = 4.09 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,4} = 4.71 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,4} = 6.01 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,4} = 7.57 \text{ M}^{-1} \text{ h}^{-1}$
$m(0) = 84 \mu\text{M}$	$m(0) = 61 \mu\text{M}$	$m(0) = 48 \mu\text{M}$	$m(0) = 43 \mu\text{M}$	$m(0) = 30 \mu\text{M}$
$k_{+,1} = 9.51 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 8.30 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 4.02 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 7.24 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 3.14 \text{ M}^{-1} \text{ h}^{-1}$
$k_{+,2} = 4.49 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 6.82 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 4.67 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 6.41 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 3.77 \text{ M}^{-1} \text{ h}^{-1}$
$k_{+,3} = 3.09 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 6.61 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 5.37 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 5.21 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 3.80 \text{ M}^{-1} \text{ h}^{-1}$
$k_{+,4} = 4.90 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,4} = 4.95 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,4} = 6.58 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,4} = 4.99 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,4} = 4.25 \text{ M}^{-1} \text{ h}^{-1}$
$m(0) = 29 \mu\text{M}$	$m(0) = 17 \mu\text{M}$	$m(0) = 14 \mu\text{M}$	$m(0) = 12 \mu\text{M}$	
$k_{+,1} = 3.62 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 4.18 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 2.53 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,1} = 2.29 \text{ M}^{-1} \text{ h}^{-1}$	
$k_{+,2} = 3.63 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 4.07 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 2.62 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,2} = 2.65 \text{ M}^{-1} \text{ h}^{-1}$	
$k_{+,3} = 4.53 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 4.44 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 3.90 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,3} = 2.94 \text{ M}^{-1} \text{ h}^{-1}$	
$k_{+,4} = 3.49 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,4} = 5.03 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,4} = 3.58 \text{ M}^{-1} \text{ h}^{-1}$	$k_{+,4} = 2.42 \text{ M}^{-1} \text{ h}^{-1}$	

Table VIII

Fitting parameter: k_-				
$k_n = 1.8 \times 10^{-1} \text{ M}^{-1}\text{h}^{-1}$		$k_+ = 5.83 \times 10^3 \text{ M}^{-1}\text{h}^{-1}$		
$m(0) = 243 \mu\text{M}$	$m(0) = 142 \mu\text{M}$	$m(0) = 123 \mu\text{M}$	$m(0) = 122 \mu\text{M}$	$m(0) = 102 \mu\text{M}$
$k_{-,1} = 0.85 \text{ h}^{-1}$	$k_{-,1} = 1.42 \text{ h}^{-1}$	$k_{-,1} = 1.72 \text{ h}^{-1}$	$k_{-,1} = 0.79 \text{ h}^{-1}$	$k_{-,1} = 1.12 \text{ h}^{-1}$
$k_{-,2} = 1.02 \text{ h}^{-1}$	$k_{-,2} = 0.68 \text{ h}^{-1}$	$k_{-,2} = 1.14 \text{ h}^{-1}$	$k_{-,2} = 1.40 \text{ h}^{-1}$	$k_{-,2} = 1.44 \text{ h}^{-1}$
$k_{-,3} = 0.99 \text{ h}^{-1}$	$k_{-,3} = 1.12 \text{ h}^{-1}$	$k_{-,3} = 1.47 \text{ h}^{-1}$	$k_{-,3} = 1.05 \text{ h}^{-1}$	$k_{-,3} = 1.53 \text{ h}^{-1}$
$k_{-,4} = 1.24 \text{ h}^{-1}$	$k_{-,4} = 1.07 \text{ h}^{-1}$	$k_{-,4} = 1.27 \text{ h}^{-1}$	$k_{-,4} = 1.70 \text{ h}^{-1}$	$k_{-,4} = 2.24 \text{ h}^{-1}$
$m(0) = 84 \mu\text{M}$	$m(0) = 61 \mu\text{M}$	$m(0) = 48 \mu\text{M}$	$m(0) = 43 \mu\text{M}$	$m(0) = 30 \mu\text{M}$
$k_{-,1} = 2.93 \text{ h}^{-1}$	$k_{-,1} = 2.48 \text{ h}^{-1}$	$k_{-,1} = 1.04 \text{ h}^{-1}$	$k_{-,1} = 2.10 \text{ h}^{-1}$	$k_{-,1} = 0.77 \text{ h}^{-1}$
$k_{-,2} = 1.19 \text{ h}^{-1}$	$k_{-,2} = 1.96 \text{ h}^{-1}$	$k_{-,2} = 1.25 \text{ h}^{-1}$	$k_{-,2} = 1.81 \text{ h}^{-1}$	$k_{-,2} = 0.97 \text{ h}^{-1}$
$k_{-,3} = 0.76 \text{ h}^{-1}$	$k_{-,3} = 1.89 \text{ h}^{-1}$	$k_{-,3} = 1.47 \text{ h}^{-1}$	$k_{-,3} = 1.42 \text{ h}^{-1}$	$k_{-,3} = 0.98 \text{ h}^{-1}$
$k_{-,4} = 1.32 \text{ h}^{-1}$	$k_{-,4} = 1.34 \text{ h}^{-1}$	$k_{-,4} = 1.88 \text{ h}^{-1}$	$k_{-,4} = 1.35 \text{ h}^{-1}$	$k_{-,4} = 1.11 \text{ h}^{-1}$
$m(0) = 29 \mu\text{M}$	$m(0) = 17 \mu\text{M}$	$m(0) = 14 \mu\text{M}$	$m(0) = 12 \mu\text{M}$	
$k_{-,1} = 0.92 \text{ h}^{-1}$	$k_{-,1} = 1.09 \text{ h}^{-1}$	$k_{-,1} = 0.61 \text{ h}^{-1}$	$k_{-,1} = 0.54 \text{ h}^{-1}$	
$k_{-,2} = 0.92 \text{ h}^{-1}$	$k_{-,2} = 1.06 \text{ h}^{-1}$	$k_{-,2} = 0.63 \text{ h}^{-1}$	$k_{-,2} = 0.64 \text{ h}^{-1}$	
$k_{-,3} = 1.20 \text{ h}^{-1}$	$k_{-,3} = 1.17 \text{ h}^{-1}$	$k_{-,3} = 1.01 \text{ h}^{-1}$	$k_{-,3} = 0.72 \text{ h}^{-1}$	
$k_{-,4} = 0.88 \text{ h}^{-1}$	$k_{-,4} = 1.36 \text{ h}^{-1}$	$k_{-,4} = 0.91 \text{ h}^{-1}$	$k_{-,4} = 0.57 \text{ h}^{-1}$	

Table IX

Fitting parameter: k_n

$k_+ = 1.54 \times 10^3 \text{ M}^{-1}\text{h}^{-1}$ $k_- = 3.91 \text{ h}^{-1}$				
$m(0) = 243 \text{ }\mu\text{M}$	$m(0) = 142 \text{ }\mu\text{M}$	$m(0) = 123 \text{ }\mu\text{M}$	$m(0) = 122 \text{ }\mu\text{M}$	$m(0) = 102 \text{ }\mu\text{M}$
$k_{n,1} = 0.30 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 2.48 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 5.41 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 0.19 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 0.97 \text{ M}^{-1} \text{ h}^{-1}$
$k_{n,2} = 0.65 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 0.09 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 1.03 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 2.44 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 2.83 \text{ M}^{-1} \text{ h}^{-1}$
$k_{n,3} = 0.57 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 0.95 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 2.90 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 0.71 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 3.60 \text{ M}^{-1} \text{ h}^{-1}$
$k_{n,4} = 1.38 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,4} = 0.77 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,4} = 1.60 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,4} = 5.26 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,4} = 14.8 \text{ M}^{-1} \text{ h}^{-1}$
$m(0) = 84 \text{ }\mu\text{M}$	$m(0) = 61 \text{ }\mu\text{M}$	$m(0) = 48 \text{ }\mu\text{M}$	$m(0) = 43 \text{ }\mu\text{M}$	$m(0) = 30 \text{ }\mu\text{M}$
$k_{n,1} = 1.28 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 11.1 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 0.72 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 15.9 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 0.13 \text{ M}^{-1} \text{ h}^{-1}$
$k_{n,2} = 0.14 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 9.36 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 1.72 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 9.09 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 0.46 \text{ M}^{-1} \text{ h}^{-1}$
$k_{n,3} = 2.03 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 2.23 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 3.61 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 3.09 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 0.49 \text{ M}^{-1} \text{ h}^{-1}$
$k_{n,4} = 4.41 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,4} = 6.71 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,4} = 10.1 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,4} = 2.42 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,4} = 0.99 \text{ M}^{-1} \text{ h}^{-1}$
$m(0) = 29 \text{ }\mu\text{M}$	$m(0) = 17 \text{ }\mu\text{M}$	$m(0) = 14 \text{ }\mu\text{M}$	$m(0) = 12 \text{ }\mu\text{M}$	
$k_{n,1} = 0.36 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 0.93 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 0.02 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,1} = 0.01 \text{ M}^{-1} \text{ h}^{-1}$	
$k_{n,2} = 0.36 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 0.77 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 0.03 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,2} = 0.03 \text{ M}^{-1} \text{ h}^{-1}$	
$k_{n,3} = 1.45 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 1.32 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 0.57 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,3} = 0.07 \text{ M}^{-1} \text{ h}^{-1}$	
$k_{n,4} = 0.28 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,4} = 2.85 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,4} = 0.32 \text{ M}^{-1} \text{ h}^{-1}$	$k_{n,4} = 0.01 \text{ M}^{-1} \text{ h}^{-1}$	

Table X

VIII. KOLMOGOROV-SMIRNOV TEST FOR THE FITTED $A\beta - 42$ AGGREGATION LAG TIMES DISTRIBUTIONS

The quality of the fitting for the distribution of the lag times (Figure 7 in the Main Text) has been quantified by means of a one-sample Kolmogorov-Smirnov (K-S) test. This non-parametric test evaluates the null hypothesis that an empirical cumulative distribution associated with a given data set of cardinality n , $\tilde{F}_n(x)$, is equal to a hypothesised cumulative distribution function (CDF) $F(x)$. The test takes the form:

$$D_n = \sup_x |\tilde{F}_n(x) - F(x)| \quad , \quad (30)$$

where sup denotes the supremum of the set of distances. The one-sample K-S test requires the independence between $\tilde{F}_n(x)$ and $F(x)$. To ensure this condition, the full set of the experimental data of the aggregation lag times ($n = 352$) has been subjected to a bootstrap resampling procedure, according to which $\tilde{n} = 10^5$ different sub-samples have been randomly drawn from the original data set. Each sub-sample has been fitted according to either a Gamma distribution probability density function (PDF) or a log-logistic PDF of the form:

$$f(x) = \frac{1}{2\sigma} \frac{e^z}{(1 + e^z)^2}, \quad \text{with} \quad z = \frac{\ln x - \mu}{\sigma} \quad (31)$$

The hypothesized PDF describing the overall data set was constructed from the average values of the parameters estimated for all the \tilde{n} sub-samples. The parameters for the different functions were the following: the log-logistic PDF had $\mu = (2.312 \pm 0.012)$ and $\sigma = (0.1313 \pm 0.0063)$ (Fig.S5A, red line), while the Gamma PDF had a shape parameter $k = (16.9 \pm 1.8)$ and a scale parameter $\theta = (0.6221 \pm 0.0070)$ (Fig.S5B, blue line). We then applied the K-S test to the CDFs built from the above PDFs at a 5% significance level. This test resulted in the acceptance of the null hypothesis for the hypothesised log-logistic distribution and in its rejection for the other distribution. These results provide robust statistical evidence that the variability observed in the aggregation profiles of the $A\beta - 42$ peptide does not emerge from the stochasticity intrinsic in primary nucleation events.

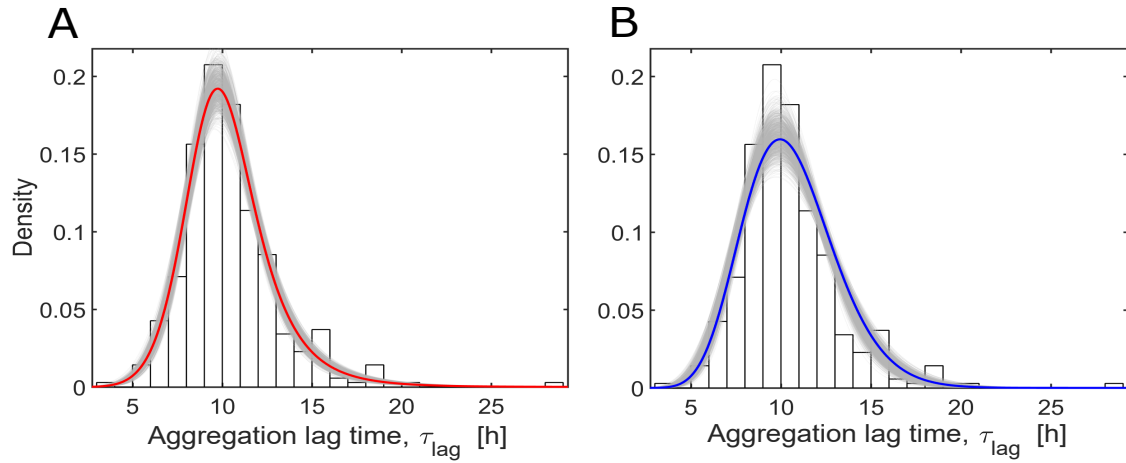


Figure S5: Comparison between the hypothesised PDFs for the $A\beta - 42$ aggregation time, as resulting from a bootstrap resampling procedure applied to the original experimental data set. **A**: Log-logistic distribution (red continuous line), **B**: Gamma distribution (blue continuous line). Gray lines represent only 10^3 out of the $\tilde{n} = 10^5$ distributions fitted for each drawn sub-sample.

IX. DISTRIBUTIONS OF THE FITTED KINETIC PARAMETERS FOR THE 384 $A\beta - 42$ KINETICS TRACES

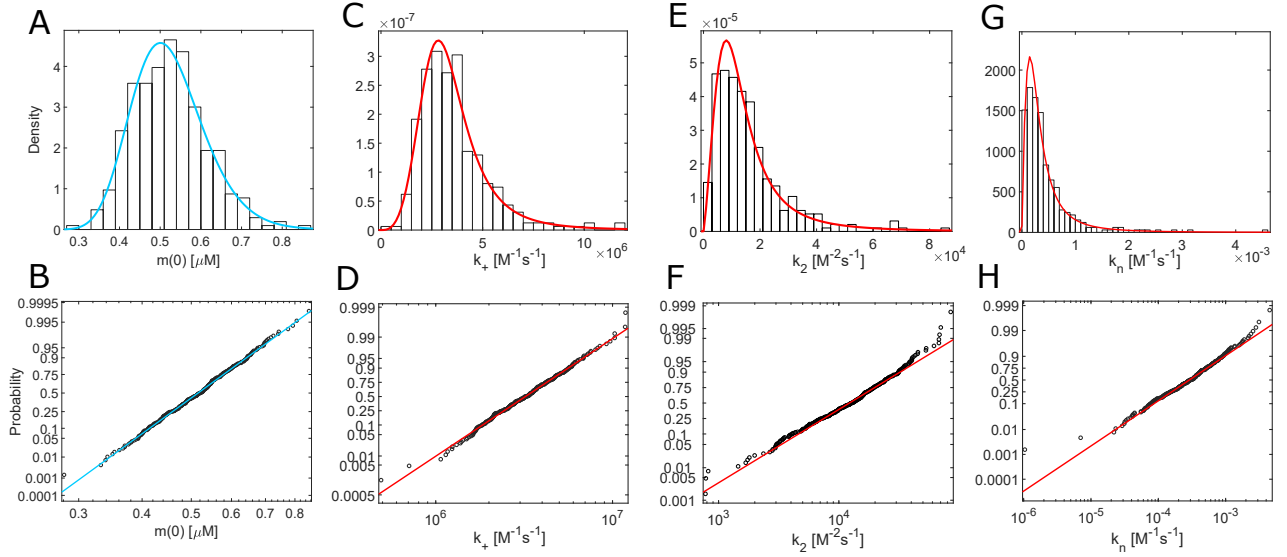


Figure S6: Distributions of the parameters fitting the experimental irreproducibility of the $n = 382$ $0.5 \mu\text{M}$ $A\beta - 42$ kinetic traces. **A**: log-normal distribution of $m(0)$ (**B**: corresponding P-P plot; the axes have been stretched so to represent the fitted lognormal CDF as a straight line). **C**, **E**, **G**: log-logistic distributions of k_+ , k_2 , k_n , respectively (**D**, **F**, **H**: corresponding P-P plots; the axes have been stretched so to represent the fitted log-logistic CDF as a straight line).

Distributions of the kinetic parameters that best fit the experimental irreproducibility of the $0.5 \mu\text{M}$ $A\beta - 42$ aggregation profiles shown in Fig.7A of the Main Text. The distributions result from varying specifically one individual parameter at a time within the reference set of kinetic constants and by keeping fixed all the remaining ones. The reference set consists of $m(0) = 0.5 \mu\text{M}$, $k_+ = 3 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, $k_2 = 1 \times 10^4 \text{ M}^{-2}\text{s}^{-1}$, $k_n = 3 \times 10^{-4} \text{ M}^{-1}\text{s}^{-1}$. The fitted initial monomer concentrations are found to follow a log-normal distribution of parameters $\mu = (-0.6626 \pm 0.0093)$ and $\sigma = (0.1716 \pm 0.0066)$ (Fig.S6A,B). All the other kinetic constants (k_+ , k_2 , k_n) are found to follow instead a log-logistic distribution, with parameters $\mu = (14.984 \pm 0.024)$ and $\sigma = (0.253 \pm 0.012)$, $\mu = (9.411 \pm 0.043)$ and $\sigma = (0.441 \pm 0.021)$, $\mu = (-8.148 \pm 0.053)$ and $\sigma = (0.550 \pm 0.025)$ respectively (Fig.S6C-H).

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