Towards Optimal Control of Amyloid Fibrillation

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Abstract
Epigallocatechin-3-gallate, as a representative amyloid inhibitors, has shown a promising ability against Aβ fibrillation by directly degrading the mature fibrils. Most previous studies have been focusing on its functional mechanisms, meanwhile its optimal dosage has been seldom considered. To solve this critical issue, we refer to the generalized Logistic model for amyloid fibrillation and inhibition and adopt the optimal control theory to balance the effectiveness and cost (or toxicity) of inhibitors. The optimal control trajectory of inhibitors is analytically solved, based on which the influence of model parameters, the difference between the optimal control strategy and several other traditional drug dosing strategies are systematically compared and validated through experiments. It is found that the strategy of multiple-times adding is more suitable for a long-term disease treatment, while single high-dose therapy is preferred for a short-term treatment. We hope our findings can shed light on the rational usage of amyloid inhibitors in clinic.

Keywords Optimal control · Amyloid fibrillation · Inhibition · Precision dosing · Pontryagin’s maximum principle

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1 Introduction

Many human neurodegenerative diseases, including Alzheimer’s disease and Parkinson’s disease, are closely related with amyloid fibrillation (Goedert and Spillantini 2006; Geschwind 2003; Ueda et al. 1993). For example, the amyloid cascade hypothesis believes that the aggregation of amyloid-β (Aβ) is a major causative reagent for Alzheimer’s disease, and any effective reduction on the amount of amyloid aggregates will be beneficial to human bodies. However, due to the complexity of amyloid fibrillation processes, especially when considering the variety of amyloid inhibitors, the development of efficient therapeutics for amyloid related diseases is still a difficult task. Until now, all efforts along this direction failed in clinic, except for Aducanumab, a first drug approved by FDA for Alzheimer’s disease in twenty years though full of controversy (Alexander et al. 2021).

To solve this critical issue, in recent years more and more studies have been designed to elucidate the inhibitory mechanisms of different inhibitors. Meanwhile, the potential toxicity or other negative effects of amyloid inhibitors have not received enough attention. Furthermore, some amyloid inhibitors are difficult to synthesize or extract, which makes them quite expensive. Therefore, the exploration on the optimal strategies for the usage of amyloid inhibitors is of great importance in clinic.

In contrast to tremendous applications of optimal control in economics (Kamien and Schwartz 1992; Weber and Kryazhimskiy 2011), epidemics (Agusto et al. 2012; Sharomi and Malik 2017; Shen et al. 2021; Lemecha Obsu and Feyissa Balcha 2020), cancer (Murray 1990; Schättler and Ledzewicz 2015; Jarrett et al. 2020; Cunningham et al. 2018; Cunningham et al. 2020), and eye diseases (Camacho et al. 2014) etc., there are quite few related studies in the current field. Thomas Michaels et al. applied the optimal control theory to analyze the relation between the molecular basis of amyloid fibrillation and optimal regions for inhibition (Michaels et al. 2019). Taking the variability of reaction kinetics into account, Alexander Dear et al. used stochastic optimal control theory to determine the optimal dosage of inhibitors that act on several key steps of amyloid fibrillation (Dear et al. 2021).

In the current study, we refer to the optimal control theory to design the optimal strategy for the usage of amyloid inhibitors, in particular epigallocatechin-3-gallate (EGCG)—a small molecule extracted from green tea which shows a strong ability to eliminate mature fibrils (Ehrnhoefer et al. 2008). Based on the Pontryagin’s Maximum Principle (PMP), the optimal strategy governed by a group of ordinary differential equations is derived, which can be explicitly solved when few fibrils are presented in the system. For general situations, phase diagrams revealing the dependence of optimal control strategy on typical dimensionless parameters are numerically explored. The optimal control strategy is further compared with several other traditional strategies, like lump-sum adding, multiple-times adding, etc. Their difference is revealed and verified through carefully designed in-vitro experiments.

The whole paper is organized as follows. Section 1 contains the introduction. The basic kinetic model for amyloid fibrillation and inhibition, the optimal control strategy derived from the PMP, as well as its analytical solution are presented in Sect. 2. The parameter dependence of the optimal control strategy and its comparison with other traditional dosing strategies are numerically explored and summarized in Sect. 3. The
last section is a conclusion. The details of mathematical derivation and experimental setup are left in the appendix.

2 Optimal Control of Amyloid Fibrillation

2.1 General Formulation

To describe the time-dependent processes of amyloid fibrillation, we denote the interested macroscopic quantities for characterizing the amount of amyloid aggregates by a scalar $X(t) \in \mathbb{R}$. Among extensive candidates of $X(t)$, the number concentration and mass concentration of total aggregates are two most popular ones. Without loss of generality, the procedure of amyloid fibrillation in the presence of inhibitors is characterized by the following ordinary differential equations (ODEs),

$$\frac{dX}{dt} = f(X(t), u(t), t), \quad t \in [0, T], \quad X(t = 0) = x_0,$$

(1)

where the initial time is set to be 0, $T$ is the terminal time, and $x_0$ stands for the initial state. Here the concentration of inhibitors $u(t)$ is adopted to describe the regulatory effect of inhibitors. A concrete form of $f$ specifies the detailed kinetic model for amyloid fibrillation and inhibition, e.g. the Logistic model, the NES (short for primary nucleation, elongation, and secondary nucleation) model, etc. Interested readers are referred to Lim et al. (2019), Yuan and Zhou (2017) for further details.

In what follows, we will first consider situations when the terminal time $T$ is fixed while the terminal state $X(T)$ is free from restrictions. We will then consider the fixed terminal state $X(T) = 0$. By taking the amount of both fibrils and inhibitors into account, our central aim is to minimize the following objective functional $J$ by controlling the time profile of $u(t)$, i.e.

$$\inf_{u(t)} J[u(t)] = \Phi[X(T)] + \int_0^T L[X(t), u(t), t]dt,$$

(2)

where $\Phi$ is the terminal cost, $L$ is the running cost. In the filed of optimal control, a model incorporating Eqs. (1) and (2) is known as the Bolza problem, whose solution gives the optimal control strategy.

As an illustration, here we give two particular examples of the above objective functional. When neglecting the running cost and solely trying to minimizing the amount of amyloid aggregates at time $T$, we choose $\Phi = \|X(T)\|^2, L = 0$. Here and in what follows we denote the $L^2$-norm by $\|\cdot\|$. Contrarily, if neglecting the terminal cost and considering the accumulative effects of amyloid aggregates and inhibitors during the whole process instead, we can set $\Phi = 0, L = \|X(t)\|^2 + \|u(t)\|^2$.

Besides the objective functional, there are also constraints needed to be considered. For example, the concentrations of fibrils and inhibitors can not be negative ($X(t) \geq 0, u(t) \geq 0$). If we put further restrictions on the total amount of inhibitors added during the whole procedure, an integral inequality emerges, i.e. $\int_0^T u(t)dt \leq u_{tot}$. 
Therefore, in general we will have two kinds of constraints,

\[ C(X(t), u(t), t) = a, \quad S(X(t), u(t), t) \leq b, \]

where both functionals \( C \) and \( S \) are assumed to be continuous with respect to \( X(t), u(t) \) and \( t \).

As a summary, a general optimal control problem of amyloid fibrillation includes three major parts: the kinetic model, the objective functional and possible constraints. Once they are specified, the optimal control strategy can be derived by referring to the classical optimal control theory.

### 2.2 Model for Amyloid Fibrillation and Inhibition

In the above section, we illustrate a general picture for the optimal control problem. Now we proceed to more concrete applications with explicit models for amyloid fibrillation and inhibition.

Let us denote \( M(t) \) and \( u(t) \) as the respective mass concentrations of amyloid aggregates and inhibitors at time \( t \). The typical growth of amyloid fibrils follows a sigmoidal curve, which means the fibrils grow exponentially at the early stage, then get saturated due to the consumption of free monomers, and finally stop growing. In analogy to population dynamics, this process can be depicted by the Logistic model, i.e.

\[
\frac{d}{dt} M(t) = k_a M(t) \left( 1 - \frac{M(t)}{M_{\text{max}}} \right),
\]

where \( k_a \) is the apparent fibril growth rate, \( M_{\text{max}} \) is the maximal mass concentration of aggregates.

In the presence of inhibitors, the conventional Logistic model requires further modification. For many natural compounds against amyloids, especially those against A\( \beta \) such as sulfated polysaccharides from the sea cucumber (Li et al. 2021) and EGCG from green tea (Ehrnhoefer et al. 2008), they show strong abilities in degrading amyloid aggregates directly, which means the rate of inhibition is proportional to the product of concentrations of inhibitors and fibrils as shown in Fig. 1a. Therefore, we have a...
generalized Logistic model as
\[
\frac{d}{dt} M(t) = k_d M(t) \left( 1 - \frac{M(t)}{M_{\text{max}}} \right) - k_d u(t) M(t),
\]
where \( k_d \) is the rate constant of fibril inhibition.

It is noted that here for simplicity the pharmacokinetics of inhibitors (Hedaya 2012; Sharma et al. 2021), meaning the complex physiological processes of absorption, distribution, metabolism and excretion of inhibitors once they come into the body as drugs, has been totally ignored. As a consequence, our above model in principle would be suitable only for in vitro studies.

### 2.3 Optimal Control Strategy

In order to decrease the mass concentrations of fibrils and inhibitors as much as possible during the whole process (for the purpose of reducing the toxicity and cost), here we choose a commonly adopted quadratic objective functional,
\[
J[u(\cdot)] = \int_0^T \left[ v^2 M(t)^2 + w^2 u(t)^2 \right] dt,
\]
with weight coefficients \( v, w > 0 \). Without loss of generality, we can further set \( v = 1 \), and consequently \( w \) denotes the relative weight between the two terms. The objective functional with a terminal cost can be studied analogously and will not be addressed here.

It is straightforward to see that, with respect to the generalized Logistic model in Eq. (4), the mass concentrations of fibrils and inhibitors cannot be minimized simultaneously, which means the optimal control problem does not admit a trivial solution. Suppose \( v \gg w \), then \( M(t)^2 \) should be minimized as much as possible. Since \( M(0) > 0 \) is fixed, we have \( u(0) > k_a/k_d \frac{1 - M(0)/M_{\text{max}}}{M_{\text{max}}} > 0 \) to meet the requirement \( dM/dt < 0 \). On the other hand, if \( w \gg v \), then \( u(t)^2 \) is required to be minimized as much as possible. And according to Eq. (4), we know that \( M(t) \to M_{\text{max}} \).

Here the \( L^2 \) norm is chosen only for simplicity. Alternative choice, like the \( L^1 \) norm, is given in Appendix D. The distinction and connection between \( L^1 \) and \( L^2 \) norms have been discussed by Schattler et al. during the application of optimal control in oncology (Schättler and Ledzewicz 2015).

The mass concentrations of amyloid aggregates and inhibitors need to be non-negative at any time point, that is to say,
\[
M_{\text{max}} \geq M(t) \geq 0 \quad \text{and} \quad u_{\text{max}} \geq u(t) \geq 0, \quad \forall t \geq 0.
\]
Provided \( u_{\text{max}} > k_d M_{\text{max}}^2 T / w^2 \), the existence of an optimal control strategy subject to above constraints can be proved as follows.
Theorem 1 Consider the optimal control of amyloid fibrillation given by the generalized Logistic model in Eq. (4), the quadratic cost in Eq. (5) and the constraints in Eq. (6). Further suppose the terminal state $X(T)$ to be free. When $u_{\text{max}} > k_d M_{\text{max}}^2 T / w^2$, there exists an optimal control strategy, which is given by

$$
\begin{align*}
\dot{M}^*(t) &= k_a M^*(t) (1 - M^*(t) / M_{\text{max}}) - k_d u^*(t) M^*(t), \\
\dot{u}^*(t) &= \frac{k_a}{M_{\text{max}}} u^*(t) M^*(t) - \frac{k_d}{w^2} M^*(t)^2, \quad t < T, \\
M^*(0) &= m_0, \quad u^*(T) = 0.
\end{align*}
$$

where $u^*(t)$ denotes the optimal control strategy, and $M^*(t)$ is the corresponding optimal state.

Furthermore, $u^*(t)$ and $M^*(t)$ have the following analytic expressions,

$$
\begin{align*}
M^*(t) &= \frac{\phi^2(t) - C_1}{2 \sqrt{A} \phi(t) + B}, \\
u^*(t) &= \frac{1}{k_d} \left[ (\sqrt{A} - \frac{k_a}{M_{\text{max}}} M^*(t) - \phi(t) + k_a \right],
\end{align*}
$$

where $A = \frac{k_d^2}{w^2} + \frac{k_a^2}{M_{\text{max}}^2}$, $B = -\frac{2k_a^2}{M_{\text{max}}^2}$, $\phi(t) = \frac{2\sqrt{C_1}}{1 - \exp(\sqrt{C_1} t + C_2)} - \sqrt{C_1}$. $C_1$ and $C_2$ are two constants determined by $M^*(0) = m_0$, $u^*(T) = 0$.

We put the proof in Appendix A.2.

2.4 Analytical Solutions When Fibrils are Few

Generally speaking, the optimal control strategy given in Eq. (7) has to be solved numerically, e.g. by using the shooting method. However, when the mass concentration of fibrils is relatively low, it can be solved analytically under proper approximations.

Notice that Eq. (4) can be linearized around its unstable fixed point $M = 0$, which corresponds to a low concentration of fibrils. This situation is practically significant when considering the suppressing effect of inhibitors. Given $M(t) / M_{\text{max}} \ll 1$, the right-hand side of Eq. (4) becomes

$$
\dot{M}(t) = k_a M(t) - k_d u(t) M(t), \quad M(0) = m_0, \quad t \in (0, T],
$$

where $m_0$ is a small initial value. Meanwhile, $u^*(t)$ satisfies a second-order ODE (see Appendix B), which reads

$$
\begin{align*}
\ddot{u}^*(t) &= 2k_a \dot{u}^*(t) - 2k_d u^* \dot{u}^*(t), \\
\dot{u}^*(T) &= 0, \quad \dot{u}^*(0) = -k_d m_0^2 / w^2.
\end{align*}
$$
Fig. 2  Comparison of the approximate solutions (black lines) with numerical solutions (red dots) on both the optimal fibril concentration $M^*(t)$ (upper panels) and inhibitor concentration $u^*(t)$ (lower panels) for upper unbounded cases. From left to right, the dimensionless parameter $m_0 k_d / k_a$ varies as 0.01, 1, 10, while the rest parameters are kept as $m_0 = 2.7 \times 10^{-3} \mu M$, $M_{max} = 1 \mu M$, $k_a = 5.5 \times 10^{-2} \text{min}^{-1}$, $T = 200 \text{min}$ and $w^2 = 1$ (Color figure online)

In this case, the optimal trajectory $M^*(t)$ and the optimal control strategy $u^*(t)$ can be analytically solved,

$$u^*(t) = C_1 \tan(-k_a C_1 t + C_2) + \frac{k_a}{k_d}, \quad M^*(t) = wC_1 \sec(-k_d C_1 t + C_2), \quad (12)$$

where constants $C_1$ and $C_2$ are given through the equations $m_0^2 = w^2 C_1^2 \sec^2(C_2)$ and $k_a^2 / k_d^2 = C_2^2 \tan^2(-k_d C_1 T + C_2)$. Furthermore, by utilizing the formula $u^*(0) = C_1 \tan(C_2) + \frac{k_a}{k_d}$, Eq. (11) is converted into an initial value problem. Details of calculation are given in Appendix B.

With respect to the above analytical solutions, the following conclusions can be reached.

(i) If both $w$ and $m_0$ are proportionally enlarged by $k$ times, then $u^*(t)$ remains invariant, while $M^*(t)$ is also proportionally enlarged by $k$ times.

(ii) If both $w$ and $k_d$ are proportionally enlarged by $k$ times, then $M^*(t)$ remains unchanged, while $u^*(t) - \frac{k_a}{k_d}$ is reduced by $k$ times.

(iii) If both $k_a$ and $k_d$ are proportionally enlarged by $k$ times and $T$ is reduced by $k$ times, then $M^*(T)$ remains invariant.

Intuitively, above linear approximation holds as long as the mass concentration of fibril remains low. To further test the validity of this hypothesis, we compare the approximate optimal trajectory of state $M^*(t)$ and the optimal strategy of inhibitors $u^*(t)$ in Eq. (12) with the corresponding exact solutions in Eq. (7). In Fig. 2, it is observed that with the increment of $m_0 k_d / k_a$, a dimensionless parameter representing the degradation effect of inhibitors against amyloid fibrillation, the approximate
solutions converge to the exact values rapidly. And its validity holds in a region even far beyond the original hypothesis that the fibrils should be kept relatively few.

2.5 Solutions for Upper Bounded Case

In the previous discussion, we have analyzed the case when the control constraint satisfies \( u_{\text{max}} > k_d M_{\text{max}}^2 T/w^2 \), which is essentially equivalent to an unbounded control problem. In this section, we will explore the optimal control problem with an effective upper-bound constraints. The linear approximation on the generalized Logistic model is still adopted.

In this case, the optimal trajectory \( M^*(t) \) and the optimal control strategy \( u^*(t) \) still can be solved explicitly, i.e.

\[
\begin{align*}
  u^*(t) &= \begin{cases} 
    u_{\text{max}}, & 0 \leq t < t_1, \\
    C_1 \tan(-k_d C_1 t + C_2) + \frac{k_a}{k_d}, & t_1 \leq t \leq T,
  \end{cases} \\
  M^*(t) &= \begin{cases} 
    m_0 e^{(k_a - k_d u_{\text{max}}) t}, & 0 \leq t < t_1, \\
    w C_1 \sec(-k_d C_1 t + C_2), & t_1 \leq t \leq T,
  \end{cases}
\end{align*}
\]

(13)

and

\[
\begin{align*}
  u_{\text{max}} &= C_1 \tan(-k_d C_1 t_1 + C_2) + \frac{k_a}{k_d}, \\
  m_0 e^{(k_a - k_d u_{\text{max}}) t_1} &= w C_1 \sec(-k_d C_1 t_1 + C_2)
\end{align*}
\]

and

\[
C_1 \tan(-k_d C_1 T + C_2) + \frac{k_a}{k_d} = 0.
\]

Details of calculation can be found in Appendix C.

The influence of upper bound constraints on the solutions of optimal control is illustrated in Fig. 3. Once the upper bound comes into play, the optimal control trajectory follows the upper bound \( u_{\text{max}} \) until the switching time \( t_1 \), and then it starts to decrease to zero. Furthermore, as the upper bound \( u_{\text{max}} \) decreases, the switching time \( t_1 \) approaches the terminal time.

3 Phase Diagram and Strategy Comparison

In this section, we proceed to make a more thorough exploration on the optimal control strategy based on numerical solutions. A major difficulty is the optimal control strategy
Fig. 3 Numerical results for optimal control with upper bound constraints. a, b The optimal state and optimal control trajectories under different upper bound constraints $u_{\text{max}} = \infty, 4 \times 10^{-3}, 3 \times 10^{-3}, 2 \times 10^{-3} \mu\text{M}$, respectively. In subplots (c1–c4), optimal control trajectories under different upper bound constraints are compared to the quantity $-k_d u^*(t)M^*(t)/2w^2$. The parameters are set as $m_0 = 2.7 \times 10^{-3} \mu\text{M}$, $M_{\text{max}} = 1\mu\text{M}$, $k_a = 5.5 \times 10^{-2} \text{min}^{-1}$, $k_d = k_a/m_0$, $T = 200 \text{ min}$ and $w^2 = 1$.

$u^*(t)$ follows a backward equation, which has to be solved from time $t = T$ to $t = 0$. Here we adopt the shooting method, which is a standard approach to find the correct starting point of $u^*(t)$ at time $t = 0$. Thanks to the fact that the terminal state $u^*(T)$ is monotonous with respect to the initial state $u(0)$, so that we can use the method of dichotomy to make an efficient guess.

### 3.1 Phase Diagram for the Optimal Control Strategy

To be specific, we focus on the optimal control problem of using EGCG against Aβ aggregation. The apparent fibril growth rate $k_a$ in the Logistic model is determined with respect to the fibrillation data of Aβ (see Fig. 1b), which gives $k_a = 5.5 \times 10^{-2} \text{min}^{-1}$ under the condition $M_{\text{max}} = 1 \mu\text{M}$, $m_0 = 2.7 \times 10^{-3} \mu\text{M}$. During the fitting procedure, the nonlinear regression tool “nlinfit” in MATLAB is utilized.

To elucidate the inhibitory strength of inhibitors on fibril growth and the toxicity of inhibitors during the medical treatment, two dimensionless parameters, $M_{\text{max}} k_d/k_a$ and $w^2$, are found to play a key role in the optimal control problem. It is good to note that for fixed $u$, $M_{\text{max}} k_d/k_a$ is the negative derivative of the nonzero steady state of Eq. (4) with respect to $u$. Hence, it provides a measure of the effectiveness of the control at reducing the fibril mass. As shown in Fig. 4a, b, by fixing the inhibitor strength $M_{\text{max}} k_d/k_a$, as the toxicity of inhibitors (indicated by $w^2$) increases, less control is applied which in turn leads to the formation of more fibrils. In contrast, the amount of totally added inhibitors shows a non-monotonic dependence on the inhibitor’s strength when $w^2$ is fixed. Therefore, a trade-off between the inhibitory strength and the amount of added inhibitors is presented in the optimal control.
Fig. 4 Phase diagrams for the accumulative mass concentrations of fibrils \( \int_0^T M^*(t) \, dt \) and inhibitors \( \int_0^T u^*(t) \, dt \), as a function of the relative weight \( w^2 \) and \( M_{\text{max}} k_d / k_a \). For clearance, here \( \int_0^T M^*(t) \, dt \) and \( \int_0^T u^*(t) \, dt \) are normalized by their respective maximal values in the simulated region. The optimal trajectories of fibrils and inhibitors are shown respectively, under the conditions of c, d \( M_{\text{max}} k_d / k_a = 1 \), \( w^2 = 0.1 \), 1, 10 and e, f \( M_{\text{max}} k_d / k_a = 0.1, 0.5, 1, 5, 10 \), \( w^2 = 1 \)

Next, we look into the kinetic trajectories of \( M^*(t) \) and \( u^*(t) \) to explore the influence of parameters on the details of optimal control. As shown in Fig. 4C, d, as the contribution of inhibitor cost becomes more and more significant to the objective functional (meaning larger \( w^2 \)), the fibril mass concentration gets higher and higher in the optimal state, meanwhile the inhibitor concentration shows an opposite tendency as expected. The influence of \( M_{\text{max}} k_d / k_a \) on the optimal control is a bit complicated. Overall, by increasing \( M_{\text{max}} k_d / k_a \), the fibril mass concentration drops quickly, demonstrating the improvement of inhibitory effect against the aggregation processes. Similar to the phase diagram in Fig. 4b, the inhibitor concentration shows a non-monotonic dependence on \( M_{\text{max}} k_d / k_a \). And the highest inhibitor concentration is achieved when the fibrillation and inhibition processes are of the same amplitude \( M_{\text{max}} k_d / k_a = 1 \). These typical behaviors of the optimal control trajectories are found in Fig. 4e, f.

In most cases, we are interested in the efficient inhibitors, which means \( M_{\text{max}} k_d / k_a \gg 1 \). Under this condition, it is found that with the increase of the apparent fibril growth rate \( k_a \) or the toxicity of inhibitors \( w^2 \), more inhibitors are applied from the early time to reach an optimal control. Meanwhile, opposite tendency is observed for the inhibition rate \( k_d \) and the initial monomer concentration \( m_0 \) as shown.
Fig. 5 Influence of model parameters on the optimal trajectories of inhibitors and fibrils. In each subplot, only the remarked parameter is changed by $r$ times ($r = 0.1, 0.5, 1, 2, 4$), while the rest parameters are kept unchanged. Default parameters are set as $m_0 = 2.7 \times 10^{-3} \mu M$, $M_{\text{max}} = 1 \mu M$, $k_a = 5.5 \times 10^{-2} \text{min}^{-1}$, $k_d = k_a/m_0$ and $w^2 = 1$ in Fig. 5a–d. The corresponding optimal trajectories for fibrils and their dependence on model parameters are presented in Fig. 5e–h.

3.2 Comparison with Traditional Control Strategies

Referring to the PMP, the optimal control strategy is undoubtedly the one which leads to the minimal objective functional. However, the optimal control strategy usually follows a complicated trajectory, which may bring great troubles in real applications. In this section, we aim to compare the performance of the optimal control strategy with several other traditional strategies and seek for alternative simple control strategies with acceptable performance.

Several commonly adopted drug dosing strategies are summarized here, including the lump-sum adding, meaning adding drugs all at once; constant adding, meaning continuously adding drugs at a constant speed; multiple-times adding, meaning adding drugs instantly with equal amount for multiple times; and periodic adding, meaning adding drugs for several time periods and for each period drugs are added constantly. Details are listed in Appendix E.

Intuitively, when restricted to the fibril growth stage, the lump-sum adding is a good strategy because it inhibits fibril growth from the beginning. In contrast, the multiple-times adding is preferred once the equilibrium state is reached, since it can effectively reduce the running cost of inhibitors. As demonstrated through the relative difference between the lump-sum adding and multiple-times adding (including twice adding and four times adding) to the optimal strategy in Fig. 6a, b, we can clearly see that the lump-sum adding is better as long as $T \leq 1.4t_{1/2}$, where $t_{1/2}$ represents the moment when $M(t)$ reaches half of its maximal value, i.e. $M(t_{1/2}) = M_{\text{max}}/2$. Figure 6e, f
Fig. 6  Dependence of a, b the relative objective functional (the difference between two objective functionals divided by the optimal one) on the terminal time for the lump-sum adding and multiple-times adding (including twice adding and four times adding) strategies. Representative optimal trajectories for c and d fibril mass concentration and e, f inhibitor mass concentration with the corresponding terminal time, as marked by yellow arrows, are illustrated (Color figure online).

further verify our idea that the multiple-times adding becomes better than the lump-sum adding after reaching the equilibrium state. However, there is no significant difference in the fibril mass concentration between the two cases as shown in Fig. 6c, d.

For the purpose of validation, Aβ40 control experiments are carefully designed. EGCG, a small molecule extracted from green tea and showing a strong ability in eliminating mature fibrils (Ehrnhoefer et al. 2008), is adopted for Aβ40 inhibition. Five controlled groups, including one lump-sum adding, two twice adding and two four-times adding, have been illustrated in Fig. 7a and recorded in Fig. 7c.

4 Conclusion

In this paper, a general theory for the optimal control problem of amyloid aggregation is formulated. With respect to the modified Logistic model with degradation caused by
inhibitors, and a general quadratic objective functional including contributions from both fibrils and inhibitors, the optimal control problem is transformed into a group of backward ordinary differential equations by the PMP. It is then solved either analytically under linear approximation or numerically by the shooting method. The influence of non-dimensional parameters, $M_{max} k_d/k_a$ representing the strength of inhibitors against fibrillation and $w^2$ representing the toxicity of inhibitors, on the optimal control trajectories is explored in detail. Finally, several commonly used drug dosing strategies are numerically compared with the theoretically predicted optimal control strategy. We find that for a long-term disease treatment, the strategy of multiple-times adding is more suitable, while for a short-term treatment, single high-dose treatment is preferred. Our conclusion is further validated through carefully designed experiments of EGCG against Aβ fibrillation.

It should be noted that our current model is an over simplification of the real biochemical kinetics, not only for the amyloid fibrillation but also for the inhibitor acting processes. More detailed kinetic models, especially those based on microscopic mechanisms, need to be further considered in order to provide a more reasonable physical picture. Besides, other combinations of amyloid proteins and inhibitors with different mechanisms are worthy of a systematic examination. It would help to answer the general problem that how the optimal control strategy varies with the system setup which is crucial for clinic practice. We hope our work can raise further interest on the optimal usage of amyloid inhibitors.

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Appendix A: Proof of Main Theorems

A.1 Some Related Lemmas on Optimal Control

The Bolza problem of optimal control reads

$$\inf_{u(t)} J[u(t)] = \Phi[X(T)] + \int_0^T L[X(t), u(t), t] dt$$
subject to

$$\dot{X}(t) = f(X(t), u(t), t), \quad t \in [0, T], \quad X(0) = x_0.$$  \hspace{1cm} (15)

The Pontryagin’s Maximum Principle (PMP) provides a necessary condition, whose concrete form is stated as follows.

**Lemma 1** (Pontryagin 1987) (PMP) Let $u^*(t) \in \Theta \subset \mathbb{R}^m$ be a bounded, measurable and admissible control that optimizes Eq. (15), with $\Theta$ be the control set, and $X^*$ be its corresponding state trajectory. Define a Hamiltonian

$$H(X, u, \lambda, t) = \lambda^T f(X, u, t) - L(X, u, t),$$

where $\lambda \in \mathbb{R}^d$. Then there exists an absolutely continuous process $\lambda(t)$ such that

$$\dot{X}^*(t) = \frac{\partial H(X^*(t), u^*(t), \lambda^*(t), t)}{\partial \lambda}, \quad X^*(0) = x_0$$ \hspace{1cm} (16)

$$\dot{\lambda}^*(t) = -\frac{\partial H(X^*(t), u^*(t), \lambda^*(t), t)}{\partial X}, \quad \lambda^*(T) = -\frac{\partial \Phi(X^*(T))}{\partial X},$$

$$H(X^*(t), u^*(t), \lambda^*(t), t) \geq H(X^*(t), u(t), \lambda^*(t), t), \quad \forall u \in \Theta \quad \text{and a.e.} \ t \in [0, T]$$  \hspace{1cm} (17)

Here Eq. (16) reduces to the state equation under the optimal control, while the co-state $\lambda^*$ evolves backward according to Eq. (17) with a fixed terminal state $\lambda^*(T)$.

**Lemma 2** (Lenhart and Workman 2007) Suppose that $-f(X, u, t)$ and $L(X, u, t)$ are both continuously differentiable functions with respect to their three arguments and convex in $X$ and $u$. Define a Hamiltonian

$$H(X, u, \lambda, t) = \lambda^T f(X, u, t) - L(X, u, t),$$

where $\lambda \in \mathbb{R}^d$. Suppose $u^*(t)$ is a control, with associated state $X^*(t)$, and $\lambda^*(t)$, a piecewise differentiable function, such that $u^*(t), X^*(t)$, and $\lambda^*(t)$, together satisfy
on $0 \leq t \leq T$:

\[
\dot{X}^*(t) = \frac{\partial H(X^*(t), u^*(t), \lambda^*(t), t)}{\partial \lambda}, \quad X^*(0) = x_0 \tag{18}
\]

\[
\dot{\lambda}^*(t) = -\frac{\partial H(X^*(t), u^*(t), \lambda^*(t), t)}{\partial X}, \quad \lambda^*(T) = 0 \tag{19}
\]

\[
\lambda^*(t) \leq 0 \tag{20}
\]

\[
H_u(X^*(t), u^*(t), \lambda^*(t), t) = 0, \quad \forall u \in \Theta \quad \text{and} \quad a.e. \ t \in [0, T] \tag{21}
\]

Then for all controls $u$, we have

\[
J(u^*) \leq J(u).
\]

**Lemma 3** (Michel Petrovitch 1901) *(Comparison Theorem)* Let both functions $f(x, y)$ and $F(x, y)$ be continuous in the plane region $G$ and satisfy the inequality

\[
f(x, y) < F(x, y), \quad (x, y) \in G.
\]

Let $y = \phi(x)$ and $y = \Phi(x)$ be solutions to the initial value problems

\[
\frac{dy}{dx} = f(x, y), \quad y(x_0) = y_0
\]

and

\[
\frac{dy}{dx} = F(x, y), \quad y(x_0) = y_0
\]

respectively on the interval $a < x < b$, where $(x_0, y_0) \in G$. Then we have

\[
\begin{cases}
\phi(x) < \Phi(x), & x_0 < x < b, \\
\phi(x) > \Phi(x), & a < x < x_0.
\end{cases}
\]

By utilizing above lemmas, we can prove that the following boundary value problem has a solution.

**Theorem 2** For $t \in [0, T]$, the boundary value problem,

\[
\begin{cases}
\dot{M}(t) = k_d M(t)(1 - \frac{M(t)}{M_{\text{max}}}) - k_d u(t)M(t), \\
\dot{u}(t) = \frac{k_a}{M_{\text{max}}} u(t)M(t) - \frac{k_d}{u^*} M(t)^2, \quad t < T, \\
M(0) = m_0 > 0, \quad u(T) = 0,
\end{cases}
\]

admits a solution.
By utilizing Lemma 3, we can deduce that
\[ 0 \leq M(t) < M_{\text{max}} \text{ and } 0 \leq u(t) < k_d M_{\text{max}}^2 T / w^2. \]

Let \( h_1(x, y) = k_a x (1 - \frac{x}{M_{\text{max}}}) - k_d x y \) and \( h_2(x, y) = \frac{k_a}{M_{\text{max}}} x y - \frac{k_d}{w^2} x^2 \). Clearly, both \( h_1 \) and \( h_2 \) have continuous partial derivatives on \( \mathbb{R}^2 \). By employing the existence and uniqueness theorem for ordinary differential equations and the continuous dependence on initial values, the initial value problem
\[
\begin{align*}
\dot{M}(t) &= k_a M(t) \left(1 - \frac{M(t)}{M_{\text{max}}} \right) - k_d u(t) M(t), \\
\dot{u}(t) &= \frac{k_a}{M_{\text{max}}} u(t) M(t) - \frac{k_d}{w^2} M(t)^2, \\
M(0) &= m_0 > 0, \quad u(0) = u_0,
\end{align*}
\]
has a unique solution on the interval \([0, T]\), and the solution \( u = \phi(t, u_0) \) with respect to \( u_0 \) is continuous.

Based on the comparison theorem, it is evident that \( u = \phi(T, k_d M_{\text{max}}^2 T / w^2) > 0 \) and \( u = \phi(T, 0) < 0 \). Hence, there exists a \( u_0 \in (0, k_d M_{\text{max}}^2 T / w^2) \) such that \( u = \phi(T, u_0) = 0 \). Therefore, the boundary value problem has a solution. \( \square \)

**Theorem 3** The analytical solution to the boundary value problem (22) is given by:

\[ M = \frac{\phi^2(t) - C_1}{2\sqrt{A} \phi(t) + B}, \quad t < T \]

\[ u = \frac{1}{k_d} \left[ \left( \sqrt{A} - \frac{k_a}{M_{\text{max}}} \right) M - \phi(t) + k_a \right], \quad t < T \]

where

\[ \phi(t) = \frac{2\sqrt{C_1}}{1 - e^{\sqrt{C_1} t + C_2}} - \sqrt{C_1}, \]

with \( C_1 \) and \( C_2 \) being constants determined by the conditions \( M(0) = m_0 \) and \( u(T) = 0 \). Furthermore, \( A = \frac{k_a^2}{w^2} + \frac{k_d^2}{M_{\text{max}}^2} \) and \( B = -\frac{2k_a}{M_{\text{max}}^2} \).

**Proof** Introduce function \( s(t) = \ln(M(t)) \). The boundary value problem in (22) can be transformed into:

\[ \dot{s}(t) = k_a \left(1 - \frac{e^{s(t)}}{M_{\text{max}}} \right) - k_d u(t), \]

\[ \dot{u}(t) = \frac{k_a}{M_{\text{max}}} u(t) e^{s(t)} - \frac{k_d}{w^2} e^{2s(t)}, \]

\[ s(0) = \ln(m_0), \quad u(T) = 0. \]

\( \square \) Springer
Next, differentiate equation (27) with respect to $t$ and substitute equations (28) and (27) into it. Now, we obtain

$$\ddot{s}(t) = Ae^{2s} + \frac{B}{2}e^s,$$

where $A = \frac{k_d^2}{w^2} + \frac{k_a^2}{M_{\text{max}}^2}$ and $B = -\frac{2k_a}{M_{\text{max}}}$. Integrating above formula once, we have:

$$\dot{s}^2(t) = Ae^{2s} + Be^s + C_1,$$ (30)

where $C_1$ is a constant.

By performing separation of variables and Euler’s substitution on both sides, we arrive at

$$\dot{s}(t) = \phi(t) - \sqrt{Ae^s},$$ (31)

where

$$\phi(t) = \frac{2\sqrt{C_1}}{1 - e^{\sqrt{C_1}t+C_2}} - \sqrt{C_1},$$

and $C_1$ and $C_2$ are two constants. Considering equation (30), now we have

$$(\phi(t) - \sqrt{Ae^s})^2 = Ae^{2s} + Be^s + C_1.$$ \hfill \Box$

Its solution gives

$$M(t) = \frac{\phi^2(t) - C_1}{2\sqrt{A}\phi(t) + B},$$ (32)

$$u(t) = \frac{1}{k_d} \left[ \left( \sqrt{A} - \frac{k_a}{M_{\text{max}}} \right) M - \phi(t) + k_a \right].$$ (33)

### A.2 Proof of Theorem 1

The optimal control problem satisfying the constraint (6) is given by:

$$\inf_{u(t) \in [0,u_{\text{max}}]} J[u(\cdot)] = \int_0^T \left[ M(t)^2 + w^2u(t)^2 \right] dt$$

subject to

$$\dot{M}(t) = k_d M(t) \left( 1 - \frac{M(t)}{M_{\text{max}}} \right) - k_d u(t) M(t), \quad M^*(0) = m_0 > 0,$$

where $M_{\text{max}} \geq M(t) \geq 0, \forall t \in [0, T]$. 

\[ \square \] Springer
According to Lemma 1, an optimal solution to (34) should satisfy the following equations,

\[ \dot{M}^*(t) = k_a M^* - k_d (M^*)^2 / M_{\text{max}} - k_d u^* M^*, \]  

(35)

\[ \dot{\lambda}^*(t) = -k_a \lambda^* + 2k_a \lambda^* M^*/M_{\text{max}} + k_d u^* \lambda^* + 2M^*, \quad t < T, \]  

(36)

\[ u^*(t) \in \arg \max_{u \in [0, +\infty]} \left[ \lambda \left( k_a M^* - k_d (M^*)^2 / M_{\text{max}} - k_d u M^* \right) - (M^*)^2 - w^2 u^2 \right], \]  

(37)

\[ M^*(0) = m_0, \quad \lambda^*(T) = 0. \]  

(38)

We get \( u^*(t) = -k_d \lambda^* M^* / 2w^2 \) by Eq. (37). Further, we can get

\[
\begin{cases}
\dot{M}^*(t) = k_a M^*(t) (1 - \frac{M^*(t)}{M_{\text{max}}}) - k_d u^*(t) M^*(t), \\
\dot{u}^*(t) = \frac{k_d}{M_{\text{max}}} u^*(t) M^*(t) - \frac{k_d}{w^2} M^*(t)^2, \quad t < T, \\
M^*(0) = m_0, \quad u^*(T) = 0.
\end{cases}
\]  

(39)

From Eq. (39), it can be asserted that \( u^* \geq 0 \), otherwise it contradicts with \( u^*(T) = 0 \). By Lemma 3, we can further get \( u^*(t) < k_d M_{\text{max}}^2 T / w^2 \). To sum up, \( 0 \leq u^* < k_d M_{\text{max}}^2 T / w^2 \). We have demonstrated that if the optimal control problem has a solution, it must satisfy Eq. (39).

**Theorem 4** The solution to problem (34) exists and satisfies the system of equations in (39).

**Proof** From the above, we only need to show the existence of a solution for the problem (34).

Introduce the function \( s(t) = \ln(M(t)) \) and consider the equivalent problem obtained by the variable substitution, which will be referred as OC’ problem. The OC’ problem consists of three main components:

(i) The control constraint set is the same as the problem (34).

(ii) The control equation is:

\[
\frac{d}{dt} s(t) = k_a (1 - \frac{e^s}{M_{\text{max}}}) - k_d u, \quad s(0) = \ln(m_0).
\]

(iii) The objective functional is:

\[
J[u(\cdot)] = \int_0^T e^{2s} + w^2 u(t)^2 dt.
\]

The OC’ problem aims to minimize the above objective functional, and its equivalence to the problem (34) is evident.
Next, we verify the conditions of Lemma 2 for the existence of the OC’ problem. By Theorem 2, the boundary value problem for \( t \in [0, T] \) is given by:

\[
\begin{align*}
\dot{s}(t) &= k_a \left( 1 - \frac{e^s(t)}{M_{\text{max}}} \right) - k_d u(t), \\
\dot{u}(t) &= \frac{k_a}{M_{\text{max}}} u(t) e^s(t) - \frac{k_d}{w^2} e^{2s(t)}, \quad t < T, \\
s(0) &= \ln(m_0), \quad u(T) = 0,
\end{align*}
\]

and its solution exists.

By setting \( p = -\frac{2w^2}{k_d} u \), we have:

\[
-k_d p - 2w^2 u = 0,
\]

and

\[
\dot{p}(t) = \frac{k_a}{M_{\text{max}}} e^s(t) p(t) + 2e^{2s(t)}, \quad p(T) = 0,
\]

which implies

\[
p(t) \leq 0,
\]

otherwise, it contradicts \( p(T) = 0 \).

Now, we only need to check that \(- f(x, u) = -k_a \left( 1 - \frac{e^x}{M_{\text{max}}} \right) + k_d u \) and \( L(x, u) = e^{2x} + w^2 u(t) \) are both convex functions. This can be done by directly computing the Hessian matrix. By using Lemma 2, the existence of solutions to the OC’ problem is verified, which implies the solution to the problem (34) exists too.

\[\square\]

### A.3 A Feedback Control

Equation (7) can be transformed into a feedback control given by

\[
\begin{align*}
\dot{M}^*(t) &= k_a M^*(t) \left( 1 - \frac{M^*(t)}{M_{\text{max}}} \right) - k_d M^*(t) u^*(t), \\
u^*(t) &= \frac{k_a (M_{\text{max}} - M^*(t))}{M_{\text{max}} k_d} \pm \sqrt{\frac{M^*(T)^2 - M^*(t)^2}{w^2} + \left( \frac{k_a (M_{\text{max}} - M^*(t))}{M_{\text{max}} k_d} \right)^2}, \quad t < T, \\
M^*(0) &= m_0.
\end{align*}
\]

First, we can derive from Eq. (7) that

\[
\begin{align*}
\left[ k_a M^*(t) \left( 1 - \frac{M^*(t)}{M_{\text{max}}} \right) - k_d u^*(t) M^*(t) \right] du^* + \\
\left[ \frac{k_d}{w^2} M^*(t)^2 - \frac{k_a}{M_{\text{max}}} u^*(t) M^*(t) \right] dM^* = 0,
\end{align*}
\]
\[
\begin{align*}
\left[ k_a \left( 1 - \frac{M^*(t)}{M_{\text{max}}} \right) - k_d u^*(t) \right] d\bar{u}^* + \left[ \frac{k_d}{w^2} M^*(t) - \frac{k_a}{M_{\text{max}}} u^*(t) \right] dM^* &= 0, \\
\left[ \frac{k_d}{M^*_{\text{max}}} - k_d u^*(t) \right] dM^* &= 0,
\end{align*}
\]

As \( M^*(T)^2 = \text{const} \) by \( u^*(T) = 0 \), we have

\[
\begin{align*}
\left[ k_a \left( M_{\text{max}} - M^* \right) \right] u^* + \frac{M^*(T)^2 - M^*^2}{w^2} = 0, \\
\end{align*}
\]

and

\[
\begin{align*}
u^*(t) = \frac{k_a (M_{\text{max}} - M^*(t))}{M_{\text{max}}^2 k_d} \pm \sqrt{\frac{M^*(T)^2 - M^*^2}{w^2} + \left( \frac{k_a (M_{\text{max}} - M^*(t))}{M_{\text{max}}^2 k_d} \right)^2}.
\end{align*}
\]

It is found that, when \( M^*(t) \ll M_{\text{max}} \) is satisfied, the positive sign is initially chosen; and then at the intermediate time \( t_1 \) which satisfies \( M^*(T)^2 - M^*^2 + \left( \frac{k_a (M_{\text{max}} - M^*(t_1))}{M_{\text{max}}^2 k_d} \right)^2 = 0 \), it changes to the minus sign until \( T \). This choice will cause mass concentration of aggregates to decrease first and then increase. Otherwise, we just choose the minus sign for the entire control process. This choice results in a monotonous increase in the mass concentration of aggregates.

### Appendix B: Derivation of the Analytical Solution

The optimal control problem under the linear approximation is given by

\[
\begin{align*}
\dot{M}^*(t) &= k_a M^* - k_d u^* M^*, \\
\dot{\lambda}^*(t) &= -k_a \lambda^* + k_d u^* \lambda^* + 2 M^*, \quad t < T, \\
M^*(0) &= m_0, \quad \lambda^*(T) = 0.
\end{align*}
\]

Additionally, based on the optimality condition, \( H(M^*(t), u^*(t), \lambda^*(t), t) \geq H(M^*(t), u(t), \lambda^*(t), t) \) with \( H(M, u, \lambda, t) = \lambda (k_a M - k_d u M) - M^2 - w^2 u^2 \), we have

\[
u^*(t) = \arg \max_{u \in [0, +\infty]} \left[ \lambda^* \left( k_a M^* - k_d u M^* \right) - (M^*)^2 - w^2 u^2 \right],
\]

or equivalently,

\[
0 = \left. \frac{\partial H(M, u, \lambda, t)}{\partial u} \right|_{M^*, u^*, \lambda^*} = -2 w^2 u^*(t) - k_d \lambda^*(t) M^*(t).
\]
It is straightforward to solve above algebraic equation, which leads to \( u^*(t) = -k_d \lambda^*(t) M^*(t) / 2w^2 \) by noticing \( w^2 > 0 \). Combining this with the terminal co-state \( \lambda^*(T) = 0 \) deduces \( u^*(T) = 0 \).

In the next step, by taking the time derivative on both sides of the algebraic equation (49),

\[
- \left( \frac{2w^2}{k_d} \right) \frac{du^*}{dt} = \lambda^* \frac{dM^*}{dt} + M^* \frac{d\lambda^*}{dt},
\]

and substituting the ODEs of \( M^* \) and \( \lambda^* \) in Eq. (47) into the above one, we arrive at

\[
\frac{du^*}{dt} = -\frac{k_d}{w^2} (M^*)^2. \tag{50}
\]

By multiplying \(-2k_d M^*/w^2\) on both sides of the first equation in (47) and substituting Eq. (50), a decoupled equation for the co-state variable \( u^*(t) \) is derived, i.e.

\[
\frac{d^2u^*}{dt^2} = 2k_a \frac{du^*}{dt} - 2k_d u^* \frac{du^*}{dt}, \tag{51}
\]

which is of the second order. Integration once gives

\[
\frac{du^*}{dt} = -k_d u^* + 2k_a u^* - C,
\]

where \( C \) is an undetermined constant. The above equation can be rewritten as

\[
\frac{du^*}{dt} = -k_d \left[ \left( u^* - \frac{k_a}{k_d} \right)^2 + \left( \frac{C}{k_d} - \frac{k_a^2}{k_d^2} \right) \right],
\]

whose solution gives the optimal trajectories of \( u^* \) and \( M^* \),

\[
\begin{align*}
u^*(t) &= C_1 \tan(-k_d C_1 t + C_2) + \frac{k_a}{k_d}, \\
M^*(t) &= wC_1 \sec(-k_d C_1 t + C_2).
\end{align*}
\]

The constants \( C_1 \) and \( C_2 \) are determined by the boundary conditions \( M^*(0) = m_0 \) and \( u^*(T) = 0 \) as

\[
w^2 C_1^2 \sec^2(C_2) = m_0^2, \quad C_1^2 \tan^2(-k_d C_1 T + C_2) = \frac{k_a^2}{k_d^2},
\]

which further gives

\[
\begin{align*}
u^*(0) &= C_1 \tan(C_2) + \frac{k_a}{k_d}, \\
M^*(T) &= wC_1 \sec(-k_d C_1 T + C_2).
\end{align*}
\]
Appendix C: Analytical Solutions for Upper Bounded Cases

The optimal control problem with general upper bound constraints under the linear approximation is given by

\[
\begin{aligned}
\dot{M}^*(t) &= k_a M^* - k_d u^* M^*, \\
\dot{\lambda}^*(t) &= -k_a \lambda^* + k_d u^* \lambda^* + 2M^*, \quad t < T, \\
M^*(0) &= m_0, \quad \lambda^*(T) = 0.
\end{aligned}
\] (52)

Based on the optimality condition, \( H(M^*(t), u^*(t), \lambda^*(t), t) \geq H(M^*(t), u(t), \lambda^*(t), t) \) with \( H(M, u, \lambda, t) = \lambda(k_a M - k_d u M) - M^2 - w^2 u^2 \), we have

\[
\begin{aligned}
u^*(t) &\in \arg\max_{u \in [0, u_{\text{max}}]} \left[ \lambda^* (k_a M^* - k_d u M^*) - (M^*)^2 - w^2 u^2 \right], \\
&\quad \text{or equivalently,} \\
u^*(t) &\in \arg\max_{u \in [0, u_{\text{max}}]} \left[ -k_d M^* \lambda^* u - w^2 u^2 \right].
\end{aligned}
\] (53) (54)

Let \( Q = -k_d M^* \lambda^*/(2w^2) \). Since \( dQ/dt = -k_d/(2w^2)d(M^* \lambda^*)/dt = -k_d(M^*)^2/w^2 < 0 \), the axis of symmetry (also the position of maximal value) of \( A[u] := -k_d M^* \lambda^* u - w^2 u^2 \) decreases from \( -k_d m_0 \lambda^*(0)/(2w^2) \) to 0. Hence, at the initial time, if \( -k_d m_0 \lambda^*(0)/(2w^2) \notin [0, u_{\text{max}}] \), we have \( u^* = u_{\text{max}} \), which persist to time \( t_1 \) satisfying \( u^*(t_1) = -k_d \lambda^*(t_1) M^*(t_1)/2w^2 \). Within the interval \([t_1, T]\), the optimal control problem reduces to the unbounded case, and results in Appendix B apply.

Appendix D: Objective Functional with \( L_1 \) Norm

The quadratic cost in the main text is adopted to illustrate our conclusions, alternative forms of the objective functional are allowed too, such as the \( L_1 \) norm which reads

\[
J[u(\cdot)] = \int_0^T [M(t) + wu(t)]dt.
\] (55)

To keep the non-negativity of \( M(t) \) and \( u(t) \), additional constraints are introduced too, that is

\[
\forall t \geq 0, \quad M_{\text{max}} \geq M(t) \geq 0 \quad \text{and} \quad u_{\text{max}} \geq u(t) \geq 0,
\] (56)
According to the optimality condition, 
\[ H(M^*(t), u^*(t), \lambda^*(t), t) \geq H(M^*(t), u(t), \lambda^*(t), t) \]
with 
\[ H(M, u, \lambda, t) = \lambda (k_a M (1 - M/M_{\text{max}}) - k_d u M) - M - w u, \]
we have 
\[ u^*(t) = \begin{cases} 
  u_{\text{max}}, & - (\lambda^* M^* k_d + w) > 0, \\
  0, & - (\lambda^* M^* k_d + w) < 0. 
\end{cases} \] (57)

The above description actually is a Bang–bang control.

So when do we have 
\[ - (\lambda^* M^* k_d + w) = 0? \]
It is found that this happens at only one time point. Based on PMP, we have
\[ \frac{d \lambda^*(t)}{dt} = -k_a \lambda^* + 2k_a \lambda^* M^* / M_{\text{max}} + k_d u^* \lambda^* + 1, \lambda^*(T) = 0 \]
and
\[ \frac{d N(t)}{dt} = (k_a N / M_{\text{max}} + 1) M^*, \] (58)

where \( N(t) = \lambda^*(t) M^*(t) \). Since \( N(T) = 0 \), we assert that \( N(t) > -M_{\text{max}} / k_a \). It tells us an important fact that when \( w/k_d > M_{\text{max}} / k_a \), there must be 
\[ u^*(t) = 0, \quad t \in [0, T]. \]
This states an extreme case when an inhibitor is too toxic and ineffective, we would better not to use it at all. Because of 
\[ (k_a N / M_{\text{max}} + 1) M^*, N(t) \]
increases monotonically to 0, which means 
\[ - (\lambda^* M^* k_d + w) = 0 \]
holds at one time point at most. Solving Eq. (58), we get
\[ N(t) = \frac{M_{\text{max}}}{k_a} \left[ \exp(k_a / M_{\text{max}} \int_{t_1}^{T} M^*(\tau) d\tau) - 1 \right]. \]

If the switch happens at \( t_1 \), it must satisfy the condition 
\[ N(t_1) = -w / k_d. \] We have
\[ \frac{d M^*(t)}{dt} = \begin{cases} 
  k_a M^*(t) \left( 1 - \frac{M^*(t)}{M_{\text{max}}} \right) - k_d u_{\text{max}} M^*(t), & t \in [0, t_1], \\
  k_a M^*(t) \left( 1 - \frac{M^*(t)}{M_{\text{max}}} \right), & t \in (t_1, T]. \end{cases} \] (59)

Through calculations, \( t_1 \) must satisfy
\[ (n_1 - 1)(\exp(k_a(T - t_1)) - 1) + (1/n_2 - M_{\text{max}}/m_0) \exp(-k_a n_2 t_1) - 1/n_2 = 0, \] (60)

where \( n_1 = k_d M_{\text{max}} / (k_a w) \) and \( n_2 = 1 - k_d u_{\text{max}} / k_a \). To sum up, the Bang–bang control is given by
\[ u^*(t) = \begin{cases} 
  u_{\text{max}}, & t \in [0, t_1], \\
  0, & t \in (t_1, T]. \end{cases} \] (61)

where \( t_1 \) satisfies (60).
Influence of model parameters on the Bang–bang control. Subplots in the first row show how the switching time depends on $k_a$, $k_d$, $w$ and $u_{\text{max}}$. The corresponding optimal trajectories for the inhibitor concentration and fibril concentration with parameters at five marked positions are illustrated in second and third rows. Default parameters are set as $m_0 = 2.7 \times 10^{-3} \mu M$, $k_a = 5.5 \times 10^{-2} \text{ min}^{-1}$, $M_{\text{max}} = 1 \mu M$, $k_d = k_a$, $w = 1$ and $u_{\text{max}} = 10m_0$ for subplots (a–c). In subplots (d), $k_d = k_a/m_0$ is taken.

We have known that the optimal control trajectory is uniquely determined by the switching time $t_1$. How the switching time is affected by parameters $k_a$, $k_d$, $w$ and $u_{\text{max}}$ is of great importance. As shown in Fig. 8a1, b1, the switching time remains zero (meaning no inhibitor) when the apparent fibril growth rate $k_a$ is either too large or too small, or when the rate constant for fibril inhibition $k_d$ is very small. In the presence of large fibril inhibition rate $k_d$ or small toxicity of inhibitors $w$, the switching time is close to 1 (meaning using inhibitors at every time), as long as $u_{\text{max}}$ remains small.

Appendix E: Strategies for Drug Dosing

The strategies used for drug dosing in the maintext are summarized as follows:

Lump-sum adding All inhibitors will be added at the initial instant as shown in Fig. 7a, b. The corresponding ODEs for $M(t)$ and $u(t)$ are

$$\begin{cases}
\dot{M}(t) = k_a M (1 - \frac{M}{M_{\text{max}}}) - k_d u M, \\
\dot{u}(t) = -k_d u M, \\ t \leq T, \\
M(0) = m_0, \\ u(0) = u_{\text{tot}}.
\end{cases}$$

(62)
**Constant adding** Inhibitors will be added at a constant rate during the whole procedure from \( t = 0 \) to \( t = T \),

\[
\begin{align*}
\dot{M}(t) &= k_d M \left(1 - \frac{M}{M_{\text{max}}} \right) - k_d u M, \\
\dot{u}(t) &= \frac{u_{\text{tot}}}{T} - k_d u M, \quad t \leq T, \\
M(0) &= m_0, \quad u(0) = \frac{u_{\text{tot}}}{T}. 
\end{align*}
\]

(63)

**Periodic adding**

During the whole procedure, inhibitors are added intermittently. The adjacent adding of inhibitors and non-adding forms a cycle. Assume that there are \( N \) cycles \( \{0, 1, 2, \ldots, N - 1\} \). Each cycle includes a time interval \( (T/N - t_1) \) during which inhibitors are added uniformly, and a time interval \( t_1 \) when no inhibitor is added. Let

\[
u_{\text{per}}(t) = \begin{cases} 
\frac{u_{\text{tot}}}{N} & \frac{kT}{N} \leq t < \frac{(k+1)T}{N} - t_1, \quad k = 0, 1, 2, \ldots N - 1, \\
0 & \frac{(k+1)T}{N} - t_1 \leq t < \frac{(k+1)T}{N}, \quad k = 0, 1, 2, \ldots N - 1.
\end{cases}
\]

The following ODEs are obtained,

\[
\begin{align*}
\dot{M}(t) &= k_d M \left(1 - \frac{M}{M_{\text{max}}} \right) - k_d u M, \\
\dot{u}(t) &= u_{\text{per}} - k_d u M, \\
M(0) &= m_0, \quad u(0) = \frac{u_{\text{per}}}{T - N t_1}.
\end{align*}
\]

(64)

**Multiple-times adding**

In this strategy, inhibitors are equally divided into \( N \) pieces and each piece will be added sequentially into the solution after a constant time interval (see Fig. 7a, b for example). Accordingly, the optimal control is given by

\[
\begin{align*}
\dot{M}(t) &= k_d M \left(1 - \frac{M}{M_{\text{max}}} \right) - k_d u M, \\
\dot{u}(t) &= u_{\text{per}} \sum_{i=1}^{N} \delta(t - i T / N) - k_d u M, \quad t \leq T, \\
M(0) &= m_0, \quad u(0) = \frac{u_{\text{per}}}{N T}.
\end{align*}
\]

(65)

**Appendix F: Experimental Setup**

\( \alpha \beta 40 \) (purity > 98%) was purchased from ChinaPeptides. Other chemical reagents were bought from Aladdin. \( \alpha \beta 40 \) was pre-treated with ammonium hydroxide as previously described (Li et al. 2021). The aqueous solution of \( \alpha \beta 40 \) was prepared by dissolving \( 6 \) mM \( \text{NaOH} \) to \( 100 \mu \text{M} \) while ThT and EGCG were directly solubilized in PBS. For ThT kinetics, the final concentrations of \( \alpha \beta 40 \) and ThT were 5 \( \mu \text{M} \) and 20 \( \mu \text{M} \), respectively. Corning 3603 96-well plates were used and ThT kinetics was monitored at a Tecan Infinite M200 PRO microplate reader with continuously shaking. Fluorescence intensities at ex = 440 nm and em = 480 nm were recorded every 6 min.

For the “Lump-sum” group, 10 \( \mu \text{M} \) EGCG was mixed with \( \alpha \beta 40 \) and ThT at \( t = 0 \) min.
For the “Twice adding” group, 5 \( \mu M \) EGCG was mixed with \( \text{A} \beta 40 \) and ThT at \( t = 0 \) min. Then stock solutions of EGCG (0.5 \( mM \)) was added to the mixture at \( t = 30 \) min or \( t = 60 \) min to increase the concentration of EGCG to 10 \( \mu M \) while minimize the changes of \( \text{A} \beta 40 \) concentration.

For the “Four times adding” group, 2.5 \( \mu M \) EGCG was mixed with \( \text{A} \beta 40 \) and ThT at \( t = 0 \) min. Then stock solutions of EGCG (0.5 \( mM \)) was added to the mixture at \( t = 30, 60, 90 \) min or \( t = 60, 120, 180 \) min to increase the concentration of EGCG to 5, 7.5 and 10 \( \mu M \), respectively.

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