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Mathematical Decision of Optimal Drug Concentration with State-Space Computational Approach

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Abstract: Drug concentration is pivotal in treating a disease. However, applying unsuitable drug concentrations to treatment will not cure patients and may delay their recovery. This research describes a drug concentration problem through a mathematical model that is a system of nonlinear ordinary differential equations. In solving this model, a simplified model is proposed to characterize the actual drug concentration problem. Then, a loss function, which measures the differences between the simplified model and the real problem, is defined. A state space representation showing the linear relation between drug circulation and metabolism is expressed. Using a gradient method, parameters in the simplified model are updated iteratively until convergence is achieved. With these optimal parameters, the analytical solution of the simplified model, which approximates the result of the actual drug concentration, is obtained. In addition, by adding a control input to the simplified model, the optimal decision of drug concentration is suggested to speed up the process of drug circulation and metabolism. Hence, the time taken decreased for the drug to beat its target site and fasten the recovery. In conclusion, the efficiency of the simplified model with control input for handling the drug concentration problem is highly demonstrated.

Keywords: Pharmacokinetics, Drug Concentration, State-Space Approach, Least-Square Optimization, Optimal Control

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1. Introduction

Pharmacology is a branch of medicine, biology and pharmaceutical sciences that concerns drug or medication action, where it is defined as the science of how drugs act on biological systems and how the body responds to the drug [1]. There are two primary branches in pharmacology that are pharmacodynamics and pharmacokinetics. Basically, pharmacodynamics is the study of how a drug affects an organism, and concerns the interactions of chemicals with biological receptors. While, pharmacokinetics is the study of how the organism affects the drug, and refers to the absorption, distribution, metabolism and excretion (ADME) of chemicals from biological systems [2].

A drug is a chemical substance with a known structure that has a biological effect and can alter the physiology or psychology of an organism when consumed [3], whereas the concentration of a drug is defined as the amount of the drug divided by the volume, where the drug is distributed [4]. The drug can exert its effect when the drug concentration in the blood is higher than a certain concentration, but it should not exceed the maximum drug concentration or else it will produce a toxic effect. The drug concentration in the blood will gradually decrease over time until it cannot be detected. So, the term half-life is generally used to describe the half-period of the circulation process of a drug in the body from the highest drug concentration. For example, the half-life of a drug concentration is three hours indicating that the time the drug concentration drops to half of the highest concentration is three hours. Hence, the optimal drug concentration is the lowest dose that will control symptoms, where long-term side effects are monitored and treated.

The proper dosage of the drug concentration cannot be determined since every patient has different responses to the drug concentration. Therefore, it is always based on the medication record in the past and the experiences of a doctor to give the drug concentration. The dosage of the medication for therapy purposes can be adjusted to a suitable level to achieve the therapeutic goal through mathematical models. However, the formulation of a mathematical model for drug concentration is a complex process. The rate of changes in the drug concentration to the body responses is presented in a nonlinear relation, and the parameters in drug concentration are unknown exactly. Moreover, solving nonlinear models will take a long time to obtain the model solution and approximating the result of a nonlinear model is costly. Due to these reasons, a simplified model is necessarily required for handling the nonlinear model of the concentration of a drug. Hence, in this research, the state space computational approach is proposed to solve the simplified model for which the solution of the nonlinear model for drug concentration can be approximated iteratively. So, the optimal decision on the drug concentration can be made.

Therefore, three objectives of the study are established. First, to describe a mathematical model for the drug concentration problem in nonlinear ordinary differential equations. Second, to suggest a simplified model for solving the drug concentration problem through the state space computational approach. Third, to provide an optimal decision for using the suitable dosage of the drug concentration in treatment. For illustration, a mathematical model of the anticancer drug, namely tirapazamine, is studied. The simulation results show the tractability of the simplified model used in this study, and the efficiency of the state-space computational approach is proven.

2. Materials and Methods

Consider a general model of drug concentration [5],

$$\dot{x}(t) = f(x(t), t) \qquad Eq.1$$

where $x \in \Re^n$ is a state vector and t is time; while $\dot{x}$ is the rate of change of the state with respect to time, and $f : \Re^n \times \Re \to \Re^n$ is the function dynamics. Suppose the initial value of the state is

$x(0) = x_0$, the solution of the model *Eq*.1 can be obtained numerically. However, because model *Eq*.1 is nonlinear and complex, obtaining the solution of the model *Eq*.1 is difficult and costly.

Therefore, we propose a simplified model, which is a set of linear differential equations [6], given as follows,

$$\dot{x}(t) = Ax(t), \qquad Eq.2$$

with $A \in \Re^{n \times n}$ is a transition matrix that has unknown elements. Here, our aim is to solve the simplified model *Eq*.2 iteratively so that the state trajectory $x(t)$ can be determined by estimating the transition matrix *A*, in turn, to approximate the solution of the nonlinear system *Eq*.1. This problem is known as the parameter estimation problem of a nonlinear system based on state error and is referred to as Problem (*A*).

2.1 State Space Computational Approach

Referring to model *Eq*.2, the linear state equation is written as

$$\dot{x}(t) - Ax(t) = 0. \qquad Eq.3$$

Multiplying the exponential term e^{-At} to *Eq*.3 for both sides giving

$$\frac{d}{dt}\left(e^{-At}x(t)\right) = 0. \qquad Eq.4$$

Then, integrating both sides of *Eq*. 4 to obtain

$$e^{-At}x(t) - x(0) = 0. \qquad Eq.5$$

Hence, the solution to *Eq*.2 is given by

$$x(t) = e^{At}x_0. \qquad Eq.6$$

Here, *Eq*.6 is the analytical solution to the state equation *Eq*.2 and is known as the state space approach.

In addition, we verify that the analytical solution *Eq*. 6 is the solution to *Eq*. 2 through the following result,

$$\dot{x}(t) = \frac{d}{dt}x(t) = \frac{d}{dt}(e^{At}x_0) = Ae^{At}x_0 = Ax(t). \qquad Eq.7$$

By the way, the exponential term e^{At} is called the matrix exponential and is represented by the sum of the infinite matrix power series

$$e^{At} = \sum_{k=0}^{\infty}\frac{t^k}{k!}A^k = I + \frac{t}{1!}A + \frac{t^2}{2!}A^2 + \frac{t^3}{3!}A^3 + \cdots + \frac{t^k}{k!}A^k + \cdots \qquad Eq.8$$

The matrix exponential has some properties [5] as given below.

(a) If *A* is a zero matrix, then $e^{At} = e^0 = I$; *I* is the identity matrix.

(b) If *A* = *I*, then $e^{It} = e^t I$.

(c) If *A* has an inverse matrix A^{-1}, then $e^A e^{-A} = I$.

(d) $e^{mA}e^{nA} = e^{(m+n)A}$, where *m*, *n* are arbitrary real or complex numbers.

(e) The derivative of the matrix exponential is given by

$$\frac{d}{dt}(e^{At}) = Ae^{At}.$$

(f) Let *B* be a nonsingular linear transformation. If $A = BMB^{-1}$, then

$$e^{At} = Be^{Mt}B^{-1}.$$

2.2 Transition Matrix Estimation

To solve Problem (*A*), let us define an optimization problem [7] given as follows,

$$\text{Minimize} \quad J_{se}(A) = \frac{1}{2}(f(x) - Ax)^{\mathrm{T}}(f(x) - Ax) \qquad Eq.9$$

subject to the simplified model *Eq*.2, where J_{se} is the loss function, which represents the sum of square errors. Consider the first-order derivative with respect to the transition matrix *A*, that is,

$$\nabla J_{se}(A) = -(f(x) - Ax)x^{\mathrm{T}}. \qquad Eq.10$$

This derivative is the gradient to the loss function J_{se}. Then, the transition matrix *A* can be updated by

$$A^{(i+1)} = A^{(i)} - a \cdot \nabla J_{se}(A^{(i)}), \qquad Eq.11$$

where $a \in \Re, a > 0$ is a real number, *i* represents the iteration number and the initial transition matrix $A^{(0)}$ is given as Jacobian matrix at the initial x_0. Note that *Eq*.9 is known as the least-squares optimization problem and *Eq*.11 is named the gradient descent method.

Assume that A^* is the optimal transition matrix, which minimizes the loss function J_{se} in *Eq*.9. When the convergence is achieved, we have $A^* = A^{(i+1)} = A^{(i)}$, where the elements in the optimal transition matrix A^* are estimated satisfactorily. Thus, the simplified model *Eq*.2 becomes

$$\dot{x}(t) = A^*x(t). \qquad Eq.12$$

So, the analytical solution *Eq*.12 shall give the solution to the nonlinear system *Eq*.1, and *Eq*.12 is known as the linear state space representation [8] to the general model *Eq*.1.

2.3 Linear Optimal Control Design

Now, for proposing the optimal drug concentration in *Eq*.1, the control input $u \in \Re^m$ is considered in the state equation *Eq*.12

$$\dot{x}(t) = A^*x(t) + Bu(t) \qquad Eq.13$$

where $B \in \Re^{n \times m}$ is a control coefficient matrix. Hence, a set of the control u^* shall be determined on time [0, *T*] so that the performance index in the quadratic criterion

$$J = \frac{1}{2}x(T)^{\mathrm{T}}S(T)x(T) + \frac{1}{2}\int_0^T x^{\mathrm{T}}Qx + u^{\mathrm{T}}Ru \; dt \qquad Eq.14$$

is minimized over the linear dynamic system *Eq*.13. Here, *S, Q, R* are weighting matrices and *T* is the terminal time. The superscript T is the transpose operator for a matrix. This problem is a linear optimal control problem [9], [10].

Define the Hamiltonian function

$$H(t) = \frac{1}{2}(x^{\mathrm{T}}Qx + u^{\mathrm{T}}Ru) + \lambda^{\mathrm{T}}(Ax + Bu) \qquad Eq.15$$

where $\lambda \in \Re^n$ is the multiplier to be determined. Then, the necessary conditions [10], [11] are provided as follows,

(a) Stationary condition

$$0 = \frac{\partial H}{\partial u} = Ru + B^{\mathrm{T}}\lambda\,. \qquad Eq.16$$

(b) State equation

$$\dot{x} = \frac{\partial H}{\partial \lambda} = Ax + Bu\,. \qquad Eq.17$$

(c) Costate equation

$$-\dot{\lambda} = \frac{\partial H}{\partial x} = Qx + A^{\mathrm{T}}\lambda\,. \qquad Eq.18$$

From *Eq*.16, the control input is given by

$$u = -R^{-1}B^{\mathrm{T}}\lambda\,. \qquad Eq.19$$

Then, applying the sweep method [10], [12]

$$\lambda(t) = S(t)x(t), \qquad Eq.20$$

and taking the derivative to have

$$\dot{\lambda} = \dot{S}x + S\dot{x}. \qquad Eq.21$$

Substitute *Eq*.17 into *Eq*.21 to yield

$$\dot{\lambda} = \dot{S}x + S(Ax + Bu), \qquad Eq.22$$

and consider the control input *Eq*.19, the derivative of the costate in *Eq*.22 can be written as

$$\dot{\lambda} = (\dot{S} + SA - SBR^{-1}B^{\mathrm{T}}S)x\,. \qquad Eq.23$$

Notice that *Eq*.18 and *Eq*.23 are equivalent, which gives

$$-Qx - A^{\mathrm{T}}Sx = (\dot{S} + SA - SBR^{-1}B^{\mathrm{T}}S)x\,. \qquad Eq.24$$

As such, a matrix Riccati differential equation

$$-\dot{S} = SA + A^{\mathrm{T}}S - SBR^{-1}B^{\mathrm{T}}S + Q \qquad Eq.25$$

with the final condition $S(T)$ is obtained. Therefore, the control input *Eq*.19 becomes

$$u = -Kx \qquad Eq.26$$

where

$$K = -R^{-1}B^{\mathrm{T}}S \qquad Eq.27$$

is the Kalman feedback gain. Follow from this, the state equation *Eq*.13 can be written as

$$\dot{x}(t) = (A^{*} - BK)x(t) \qquad Eq.28$$

and its analytical solution is

$$x(t) = e^{(A^{*}-BK)t}x_0 . \qquad Eq.29$$

3. Results and Discussion

Consider a mathematical model for the drug concentration of tirapazamine [13], which is an anticancer drug, given by

$$\frac{dx_1}{dt} = -k_1 x_1 \qquad Eq.30$$

$$\frac{dx_2}{dt} = k_1 x_1 - \frac{V_{\max} x_2}{K_m + x_2} \qquad Eq.31$$

$$\frac{dx_3}{dt} = \frac{V_{\max} x_2}{K_m + x_2} \qquad Eq.32$$

where x_1, x_2 and x_3 are the patch, circulation and metabolism compartments, respectively, whereas k_1 is the diffusion constant from patch to the circulation, and $V_{\max}$ is the maximal rate of metabolism and K_m is the Michaelis constant that is the substrate concentration at which the rate of metabolism is 50 percent of the $V_{\max}$. Here, $V_{\max}$ and K_m are the standard Michaelis-Menten parameters.

The values of parameters are $k_1 = 0.05$, $V_{\max} = 1.5\times10^{-6} M/s$ and $K_m = 74.8\times10^{-6} M$ [14], [15]. The initial conditions are $x_1(0) = 100$, $x_2(0) = 0$ and $x_3(0) = 0$, while the initial time is $t_0 = 0$ and the final time is $t_f = 200$.

3.1 The Simplified Model

Now, introduce a simplified model for the drug concentration mathematical model in *Eq*.30-*Eq*.32 as follows,

$$\frac{dx_1}{dt} = -k_1 x_1 \qquad Eq.33$$

$$\frac{dx_2}{dt} = k_1 x_1 - k_2 x_2 \qquad Eq.34$$

$$\frac{dx_3}{dt} = k_2 x_2 \qquad Eq.35$$

with $k_2 = V_{\max}/K_m$ at $x_2(0) = 0$. This simplified model is the initial model before the method discussed in Section 2.2 is applied and this model will only provide the linear approximation solution to the model in *Eq*.30-*Eq*.32. Consider the following final simplified model

$$\frac{dx_1}{dt} = -0.05x_1 \qquad Eq.36$$

$$\frac{dx_2}{dt} = 0.049046x_1 - 0.010682x_2 - 0.001158x_3 \qquad Eq.37$$

$$\frac{dx_3}{dt} = 0.000954x_1 + 0.010682x_2 + 0.001158x_3 \qquad Eq.38$$

that has resulted after the iterative procedure is implemented. Therefore, solving the final simplified model in *Eq*.36-*Eq*.38 will approximate the actual solution of the model in *Eq*.30-*Eq*.32.

Table 1 shows the simulation results for the performance of the algorithm used. The mean square errors, which present the differences between the solutions from the actual model and the final simplified model, have a very small value. This reveals that the solution of the final simplified model can be applied to fit the solution of the actual model.

Table 1: Simulation results for algorithm performance

Iteration Number	Mean Square Errors	Elapsed Time (s)
95	5.9618×10^{-10}	13.3342

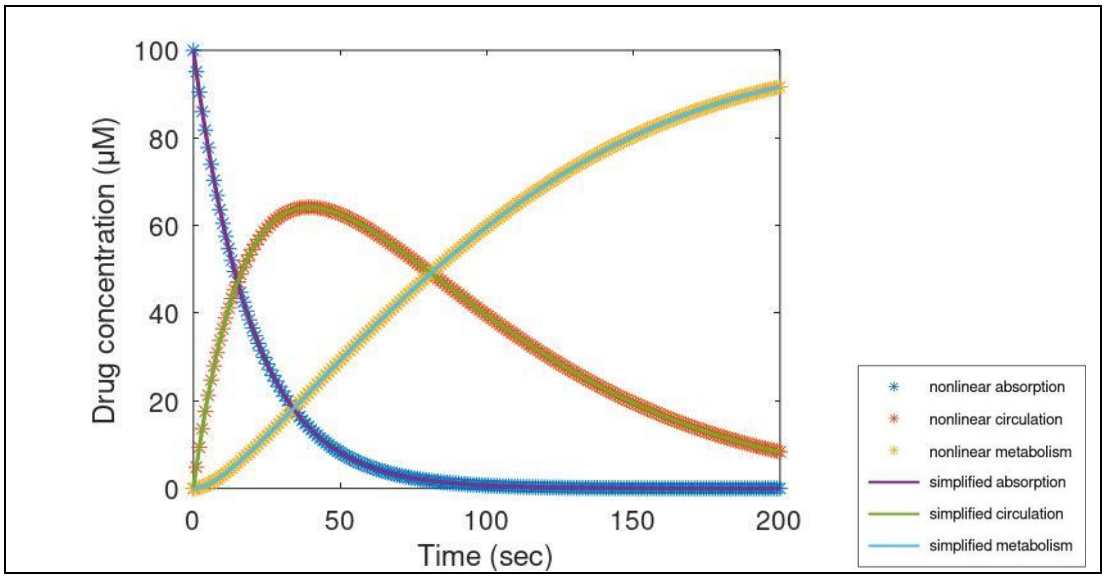

Figure 1: Drug concentration in absorption, circulation and metabolism for the nonlinear and final simplified models

Figure 1 shows the graphical solution of the drug concentration for the nonlinear and final simplified models in *Eq*.36-*Eq*.38. Notice that the solution of the final simplified model overlapped with the result of the actual model in *Eq*.30-*Eq*.32. This indicates that the solution of the final simplified model is identical to the solution of the actual model. The drug concentration is absorbed from the patch to the blood at the concentration of 100 μM and the absorption rate was decreased over time to close to

zero after 100 sec. In the circulation, the drug concentration of the circulation rate increased from zero until reaching the maximum drug concentration of 64.193 μM at 40 sec before turning down as the initial concentration of 100 μM was exhausted and metabolized. After 40 sec, the drug concentration decreased, and a reduction of 50 percent from the maximum drug concentration was observed at 116 sec. At this half-life concentration, prescribers will know when the drug concentration loses its effectiveness and how often repeated dosing should be provided. In addition, the metabolism rate increased with the drug concentration since the therapeutic doses usually used are significantly below the saturation level of the enzymes needed for the metabolic pathway to take place.

As a result, the final simplified model gives an alternative model for handling the nonlinear model of the drug concentration of tirapazamine. It is highlighted that the final simplified model has the patch, circulation and metabolism compartments in observing the drug concentration for the rate of changes for circulation and metabolism. However, in the actual model, only patch and circulation are considered in the drug concentration for the rate of change of circulation, and only circulation is considered in the drug concentration for the rate of change of metabolism.

3.2 The Optimal Control Model

For suggesting an optimal decision to handle the drug concentration, a control input $u \in \Re$, which is a vasodilation drug used to speed up the drug circulation in the human body, is added in the final simplified model in *Eq*.36-*Eq*.38. Hence, the optimal control model is defined as follows.

$$\begin{pmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \\ \frac{dx_3}{dt} \end{pmatrix} = \begin{pmatrix} -0.05 & 0 & 0 \\ 0.049046 & -0.010682 & -0.001158 \\ 0.000954 & 0.010682 & 0.001158 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} + \begin{pmatrix} 0 \\ -0.1 \\ 0 \end{pmatrix} u \qquad Eq.39$$

such that the following performance index in the quadratic criterion

$$J(u) = \frac{1}{2}\int_0^{200} x^{\mathrm{T}} Q x + u^{\mathrm{T}} R u \; dt \qquad Eq.40$$

is minimized, where Q and R are the weighting matrices with

$$Q = diag([0.01, 0.01, 0.01) \text{ and } R = 100.$$

Here, the term *diag* represents the diagonal matrix.

Figure 2 shows the graphical solution of the drug concentration for the optimal control model in *Eq*.39-*Eq*.40. Note that the maximum drug concentration of 60.533 μM occurred at 37 sec and the half-life of the drug concentration was measured at 103 sec. Obviously, the maximum drug concentration and its half-life with adding the control input were reached earlier than the maximum and half-life of drug concentration without the control input. The drug concentration of the metabolism curve breaks down to its active form and exerts its effect on the tumor site so that the drug concentration will be less than the previous model. Hence, the model with the control input can increase the speed of drug circulation and reduce the time for the drug to its target site, in turn, speed up the recovery of a patient.

Figure 3 shows the solution of the control input. In the beginning, the control input of 1.0936 μM was supplied to the drug concentration of the circulation rate, and this control input reduced gradually over time toward the value of 0.9015 μM. With this control solution, the optimal decision for regulating

the drug concentration of tirapazamine can be suggested as shown in Figure 2. Moreover, this optimal decision is guaranteed since the stationary condition was satisfied as shown in Figure 4. The optimal cost was 1.4937×10^4 units when applying this optimal decision.

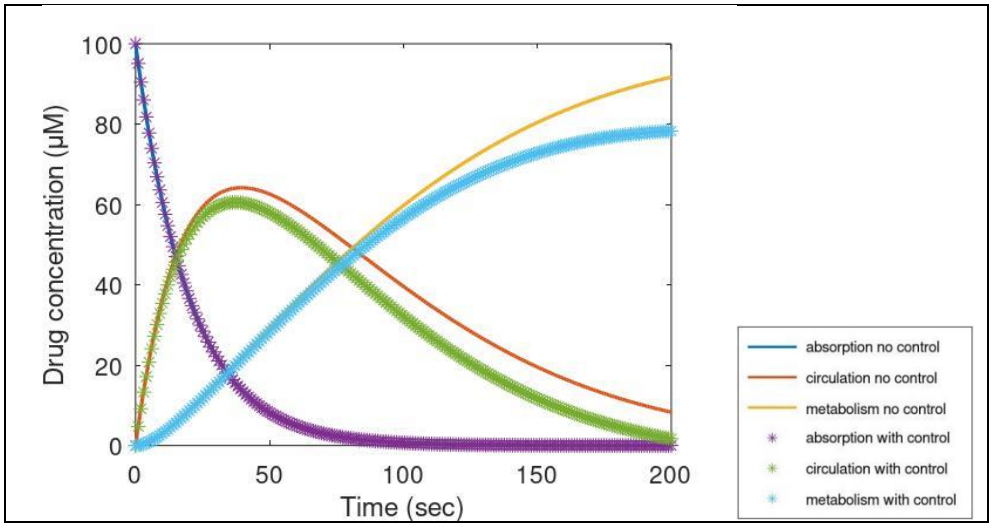

Figure 2: Drug concentration in absorption, circulation and metabolism for the optimal control model

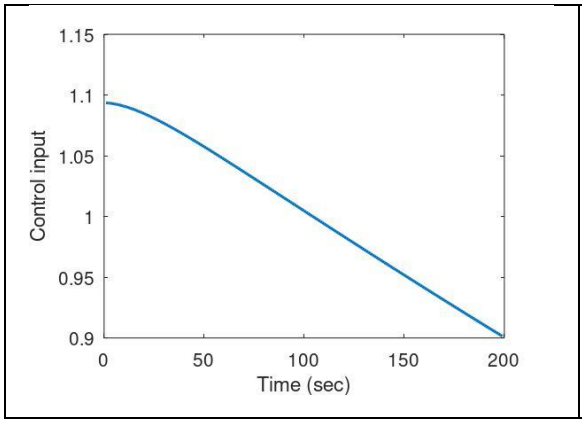

Figure 3: Control input for drug concentration

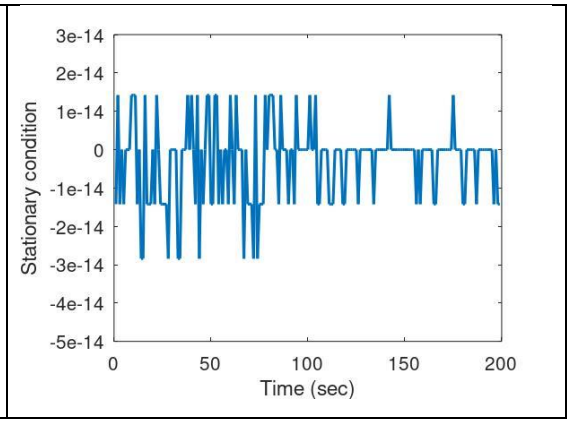

Figure 4: Stationary condition

4. Conclusion

This research discussed the mathematical decision of optimal drug concentration with a state-space computational approach. The actual model is the nonlinear model, and its solution was obtained by solving the simplified model iteratively. When the convergence was achieved, the final simplified model provided the approximate solution to the actual model. Moreover, a control input was added to the final simplified model to form an optimal control model for the drug concentration. After solving this optimal control model, the optimal decision for the drug concentration was suggested to speed up the treatment of a patient. Since this study only focuses on a single drug and a single delivery mechanism, an exploration of complex drug concentration cases is recommended for future studies.

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