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*Research article*

## Mathematical analysis of nonlinear combination drug delivery

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**Abstract:** This study examined a single-compartment pharmacokinetic model with intravenous and oral administration. It investigated the trends in steady-state drug exposure and average steady-state plasma drug concentration under multiple dosing regimens. First, the combined drug administration model was a non-autonomous system, and we approximated the solution of the model by estimating the exact upper and lower bounds in conjunction with the comparison theorem for differential equations. We also demonstrated the existence, uniqueness, and stability of the solution. Second, we derived the steady-state drug exposure and compared it with the solution of the intravenous drug delivery model alone. The results indicate that the combined drug delivery scheme offers superior performance. Finally, we theoretically proved the change rule of average steady-state blood drug concentration under different dosing regimens, and verified its feasibility and rationality by combining the numerical simulation results of Phenytoin sodium.

**Keywords:** pharmacokinetic model; combined drug administration; steady-state drug exposure; average steady-state concentration

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### 1. Introduction

Pharmacokinetics (PK) focuses on the absorption, distribution, metabolism, and processes of drugs in the organism. By monitoring changes in the concentration of a drug in the plasma, researchers are able to describe these dynamic processes with the help of mathematical models, which allow them to make predictions about the disposition of the drug [1, 2]. The use of mathematical models is particularly important in drugs because it provides a scientific tool to speculate on the in vivo behavior of a drug candidate based on a small amount of experimental data. The compartmental Model (CM) is one of the most commonly used PK models in drug studies and processes, and linear atrial models are the most common [3, 4]. Many nonlinear and physiologically based pharmacokinetic models have also been derived in recent years, and the elimination pathways may include both first-order and Michaelis-Menten elimination [5–7]. They enable more accurate prediction of complex pharmacoki-

netic behaviors and assessment of the therapeutic effects of drugs. The emergence of these models provides a more accurate tool for drug discovery and development, helping to screen potential drug candidates at the preclinical stage and to predict their pharmacokinetic performance in humans.

In order to better understand the qualitative and quantitative behavior of drugs in vivo, the study of analytical solutions of pharmacokinetic models has received academic attention [8,9]. Tang and Xiao developed a one-compartment model with Michaelis-Menten elimination and a therapeutic window. They used the *Lambert W* transcendental function to derive the analytical solution of the model under three different input conditions, designing a dosing regimen to ensure that the drug concentration remains within the therapeutic window [10]. Single-compartment and two-compartment fractional-order pharmacokinetic models have been studied by Dokoumetzidis and Sopasakis et al. They allowed the formulation of multicompartment models with consistent mixing of different fractional orders, and also provided a numerical inverse Laplace transform algorithm-based solution [11]. Wu et al. introduced a new *X* transcendental function and provided the solution for a single-compartment pharmacokinetic model with parallel first-order and Michaelis-Menten elimination pathways. They also analyzed the dominant roles of the two elimination pathways under specific conditions. Building on this model, Wu further incorporated a constant endogenous production and investigated the case of multiple intravenous administrations, discussing the area under the curve and the average concentration at steady state [12,13]. Daryakenari et al. proposed the AI-Aristotle frameworks and CMINNs, which combine pharmacokinetic compartment models with gray-box identification and neural network methods. The aim is to leverage the strengths of both biophysical models and data-driven approaches to enhance the accuracy and predictive power of pharmacokinetic models [14,15].

With the biomedical technology, co-administration of drugs has gradually become an important strategy to improve therapeutic effects. In co-administration, two or more drugs are usually used in combination in the hope that, through drug-drug interactions, therapeutic effects that are difficult to achieve with a single drug can be achieved. Panaccione et al. compared the efficacy and safety of infliximab alone, azathioprine alone, and their combination in treating ulcerative colitis in a study involving 239 patients [16]. They concluded that combination therapy led to significantly better mucosal healing than azathioprine monotherapy. Maruthur N. M. evaluated the comparative effectiveness and safety of monotherapy versus selected metformin-based combination therapies in adults with type 2 diabetes [17]. Given metformin's beneficial effects on hemoglobin A<sub>1c</sub>, weight, and cardiovascular mortality (compared to sulfonylureas), along with its relative safety, metformin is recommended as the first-line therapy for managing type 2 diabetes in adults. Apatinib and gefitinib were proposed as a co-administration regimen for the treatment of non-small-cell lung cancer (NSCLC) [18], and their pharmacokinetics and drug-drug interactions were investigated in the context of intravenous and oral administration. The results showed that co-administration can alter drug levels and metabolic pathways, which is important for optimizing treatment regimens. Hanum and colleagues studied glioma growth models using chemotherapy and anti-angiogenesis therapy [19]. Chemotherapy can lead to the emergence of resistant cells, while anti-angiogenesis therapy mitigates mutations by blocking nutrient delivery to tumor cells through the blood vessels. As a result, the combination of these two therapies achieves the best therapeutic outcomes.

However, the complexity of combining different drugs may pose problems such as drug-drug interactions and difficulty in dosage adjustment, prompting researchers to explore more simplified and precise treatment strategies [20,21]. Combining the same drug with several delivery methods has

drawn interest recently as a cutting-edge therapeutic strategy. This approach is usually applied in the transition between acute and long-term treatment, where optimization of drug efficacy and minimization of toxic side effects are achieved by combining the pharmacokinetic characteristics of drugs under different modes of administration. Common modes of administration are intravenous, oral, intramuscular, and subcutaneous. With an intravenous injection (IV), the drug can enter the bloodstream directly, quickly reach the therapeutic concentration, avoid the liver and gastrointestinal tract's first-pass effect, and have a high bioavailability [22]. On the other hand, prolonged IV is prone to local circulatory disorders that lead to tissue hypoxia, resulting in side effects such as edema and phlebitis. The benefit of oral administration (PO) is that it is less expensive and allows patients to self-administer the drug at home without the need for specialized handling or equipment [23]. However, oral drug delivery have low bioavailability and variable absorption and efficacy. Additionally, patients may use drugs incorrectly or forget to take them, which would reduce the effectiveness of treatment. Compared to subcutaneous injections, intramuscular injections absorb the drug more quickly and are suitable for administering relatively large doses [24]. Nevertheless, this method of drug delivery may cause more pain. Subcutaneous injections are more appropriate for long-term treatments such as insulin injections and vaccinations. But its limitations include a restriction on the injection volume and a slower absorption rate. In this paper, we combine intravenous injection and oral administration, which can enhance one another's strengths. Despite the potential advantages, there is not much research on this dosing strategy. Kerin et al. compared amiodarone combined intravenous and oral dosing regimens with oral dosing alone and found that the combined regimen decreased the cumulative dose needed and shortened the time to achieve optimal ventricular arrhythmia control [25]. However, this literature was based on specific experimental studies and did not address the discussion of mathematical modeling. Therefore, using the previously stated mathematical model, we propose a new co-administration treatment regimen to explain the pharmacokinetic process.

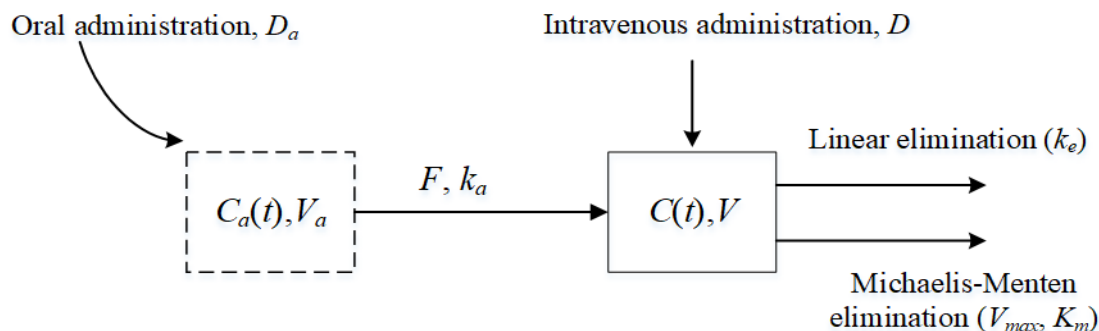
This paper is organized as follows. In Section 2, we present a single-compartment PK model for intravenous combined oral administration. In Section 3, we give an exact approximate solution of the model, as well as proving the existence uniqueness and local stability of the solution. In Section 4, the steady-state drug exposure is calculated. Numerical simulations are used to compare the changes in plasma drug concentration and drug exposure between combination therapy and monotherapy, thereby evaluating the advantages of combination therapy. Section 5 derives the average steady-state concentration of the model and reveals the variation patterns of this key pharmacokinetic parameter under different dosing regimens. Section 6 demonstrates the practical application of the above patterns of change in conjunction with an example of a real drug. The final section discusses the limitations and prospects of the current work.

## 2. PK model of combined administration

Intravenous injection allows the drug to enter the systemic circulation directly, whereas oral administration requires an absorption phase before entering systemic circulation. The schematic diagram is shown in Figure 1. Therefore, we focus only on their actions within the central compartment. Initially, an intravenous dose of  $D$  is administered to achieve a specific blood concentration level, followed by an oral dose of  $D_a$ . After an interval  $\tau$ , another dose is administered. A single-compartment model for

nonlinear oral combined IV drug administration is established based on this process as follows:

$$\begin{cases} \frac{dC_a(t)}{dt} = -k_a C_a(t), & t \neq n\tau, \\ C_a(t^+) = C_a(t) + \frac{D_a}{V_a}, & t = n\tau, \\ \frac{dC(t)}{dt} = Fk_a C_a(t) - k_e C(t) - \frac{V_{\max} C(t)}{K_m + C(t)}, & t \neq n\tau, \\ C(t^+) = C(t) + \frac{D}{V}, & t = n\tau, n = 0, 1, 2, \dots \end{cases} \quad (2.1)$$



**Figure 1.** Single-compartment model for nonlinear combined oral and intravenous administration.  $C_a(t)$  is the drug concentration in the peripheral compartment;  $C(t)$  is the drug concentration in the central compartment;  $k_a$  is the elimination rate of the drug in the peripheral compartment;  $k_e$  is the elimination rate in the central compartment;  $V_{\max}$  is the theoretical maximum rate of the process;  $K_m$  is the Michaelis-Menten constant;  $F$  denotes the bioavailability of the drug transferring from the peripheral compartment to the central compartment; and  $V_a$  and  $V$  are the apparent volumes of distribution in the peripheral and central compartments, respectively.

### 3. Model solution

Model (2.1) can be viewed as the coupling of two PK systems: the peripheral compartment and the central compartment. The change in drug concentration in the peripheral compartment can be described as follows:

$$\begin{cases} \frac{dC_a(t)}{dt} = -k_a C_a(t), & t \neq n\tau, \\ C_a(t^+) = C_a(t) + \frac{D_a}{V_a}, & t = n\tau. \end{cases} \quad (3.1)$$

To find the solution of model (3.1) over the interval  $t \in (n\tau, (n+1)\tau]$ , we proceed as follows:

$$C_a(t) = C_a(n\tau^+) e^{-k_a(t-n\tau)}.$$

When  $t = (n+1)\tau$ , the concentration at this time is

$$C_a((n+1)\tau) = C_a(n\tau^+) e^{-k_a\tau}.$$

Moreover, we have

$$C_a((n+1)\tau^+) = C_a((n+1)\tau) + \frac{D_a}{V_a} = C_a(n\tau^+) e^{-k_a\tau} + \frac{D_a}{V_a}.$$

Since  $e^{-k_a\tau} < 1$ , the equation has a stable fixed point given by

$$x_a^* = \frac{D_a}{V_a(1 - e^{-k_a\tau})}.$$

Substituting the fixed point into the solution of Eq (3.1), we obtain a stable periodic solution as

$$\tilde{C}_a(t) = x_a^* e^{-k_a(t-n\tau)} = \frac{D_a}{V_a(1-e^{-k_a\tau})} e^{-k_a(t-n\tau)}, t \in (n\tau, (n+1)\tau].$$

The following discusses the changes in drug concentration in the central compartment when the absorption compartment is in a steady state.

$$\begin{cases} \frac{dC(t)}{dt} = Fk_a C_a(t) - k_e C(t) - \frac{V_{\max} C(t)}{K_m + C(t)}, & t \neq n\tau, \\ C(t^+) = C(t) + \frac{D}{V}, & t = n\tau. \end{cases} \quad (3.2)$$

By directly substituting the steady-state solution of the peripheral compartment into the model, the first equation of model (3.2) becomes

$$\begin{aligned} \frac{dC(t)}{dt} &= Fk_a \frac{D_a}{V_a(1-e^{-k_a\tau})} e^{-k_a(t-n\tau)} - k_e C(t) - \frac{V_{\max} C(t)}{K_m + C(t)} \\ &= f(\tau) \cdot e^{-k_a t} - k_e C(t) - \frac{V_{\max} C(t)}{K_m + C(t)}, \end{aligned}$$

where  $f(\tau) = \frac{Fk_a D_a}{V_a(1-e^{-k_a\tau})} e^{k_a n\tau}$ . Then the model is transformed into

$$\begin{cases} \frac{dC(t)}{dt} = f(\tau) e^{-k_a t} - k_e C(t) - \frac{V_{\max} C(t)}{K_m + C(t)}, & t \neq n\tau, \\ C(t^+) = C(t) + \frac{D}{V}, & t = n\tau. \end{cases} \quad (3.3)$$

This is a non-autonomous first-order differential equation that cannot be directly solved analytically. Therefore, we seek the upper and lower bounds of model (3.3) on each interval, and then extend these bounds across the entire interval. By finding bounds in each sub-interval, we can approximate the behavior of the solution over  $[n\tau, (n+1)\tau]$ , allowing us to construct an understanding of the solution's range and stability across the entire interval. This approach provides a framework for analyzing the solution behavior even when an explicit solution is unattainable.

### 3.1. Exact upper and lower bounds on the solution

We are primarily interested in the steady-state situation following the periodic administration of the drug, with the system's changes occurring mainly at the moments of administration and cessation. To simplify the problem, we can focus solely on the states at the beginning and end of each cycle. Specifically, we consider the two endpoints of the interval, construct two subsystems, and label the corresponding solutions. This approach effectively simplifies the non-autonomous system by discretizing time [26]. Therefore, we apply the comparison theorem for differential equations, a mathematical tool used to analyze upper and lower bounds on solutions. It is often employed to study the growth, convergence, and uniqueness of solutions to differential equations. If a function satisfies a certain differential inequality, its solution can be governed by another known function. We denote  $C_{low}(t)$  and  $C_{up}(t)$  as the solutions of the following two models:

$$\begin{aligned} \frac{dC_{low}(t)}{dt} &= f(\tau) e^{-k_a(n+1)\tau} - k_e C_{low}(t) - \frac{V_{\max} C_{low}(t)}{K_m + C_{low}(t)}, \\ \frac{dC_{up}(t)}{dt} &= f(\tau) e^{-k_a n\tau} - k_e C_{up}(t) - \frac{V_{\max} C_{up}(t)}{K_m + C_{up}(t)}. \end{aligned}$$

For model (3.3), it can be observed that

$$f(\tau) e^{-k_a(n+1)\tau} \leq f(\tau) e^{-k_a t} \leq f(\tau) e^{-k_a n\tau} \quad (3.4)$$

for  $t \in [n\tau, (n+1)\tau]$ . According to the comparison theorem for differential equations, the solution  $C(t)$  of model (3.3) satisfies  $C_{low}(t) \leq C(t) \leq C_{up}(t)$ .

First, we have to find the exact upper bound. If  $t = n\tau$ , then Eq (3.3) becomes

$$\begin{cases} \frac{dC_{up}(t)}{dt} = \sigma - k_e C_{up}(t) - \frac{V_{max} C_{up}(t)}{K_m + C_{up}(t)}, & t \neq n\tau, \\ C_{up}(t^+) = C_{up}(t) + \frac{D}{V}, & t = n\tau, \end{cases} \quad (3.5)$$

where  $\sigma = f(\tau) e^{-k_a n\tau} = F k_a x_a^*$ . Divide both sides of the first equation by  $k_e C_{up}(t)$ :

$$\frac{(1/k_e)(K_m + C_{up}(t))}{C_{up}^2(t) + (K_m + V_{max}/k_e - \sigma/k_e) C_{up}(t) - K_m \sigma/k_e} dC_{up}(t) = -dt.$$

Rearrange the above equation as

$$\left( \frac{p}{C_{up}(t) - \alpha} + \frac{q}{C_{up}(t) + \beta} \right) dC_{up}(t) = -dt, \quad (3.6)$$

where  $p = \frac{K_m + \alpha}{k_e(\alpha + \beta)}$ ,  $q = \frac{\beta - K_m}{k_e(\alpha + \beta)}$ ,

$$\alpha = \frac{2K_m \sigma}{K_m k_e + V_{max} - \sigma + \sqrt{(K_m k_e + V_{max} - \sigma)^2 + 4K_m k_e \sigma}},$$

$$\beta = \frac{K_m k_e + V_{max} - \sigma + \sqrt{(K_m k_e + V_{max} - \sigma)^2 + 4K_m \sigma}}{2k_e}.$$

At the same time,  $p$ ,  $q$ ,  $\alpha$ , and  $\beta$  are positive. Integrating Eq (3.6) yields

$$(C_{up}(t) - \alpha)^p (C_{up}(t) + \beta)^q = (C_{up}(n\tau^+) - \alpha)^p (C_{up}(n\tau^+) + \beta)^q e^{-(t-n\tau)}.$$

Divide both sides by  $(\alpha + \beta)^{p+q}$  and further write it as

$$\left( \frac{C_{up}(t) - \alpha}{\alpha + \beta} \right)^p \left( \frac{C_{up}(t) - \alpha}{\alpha + \beta} + 1 \right)^q = \left( \frac{C_{up}(n\tau^+) - \alpha}{\alpha + \beta} \right)^p \left( \frac{C_{up}(n\tau^+) + \beta}{\alpha + \beta} \right)^q e^{-(t-n\tau)}.$$

**Definition 1** (See [12]) We define  $X$  as the solution of the following equation:

$$X(z, p, q)^p (X(z, p, q) + 1)^q = z,$$

where  $p, q \in \mathbb{R}^+$ , and  $z$  is a complex number.

According to the definition of the  $X$  function,  $\frac{C_{up}(t) - \alpha}{\alpha + \beta}$  can be written as

$$\frac{C_{up}(t) - \alpha}{\alpha + \beta} = X \left( \left( \frac{C_{up}(n\tau^+) - \alpha}{\alpha + \beta} \right)^p \left( \frac{C_{up}(n\tau^+) + \beta}{\alpha + \beta} \right)^q e^{-(t-n\tau)}, p, q \right).$$

Hence any solution of model (3.5) is

$$C_{up}(t) = \alpha + (\alpha + \beta) \cdot X \left( \left( \frac{C_{up}(n\tau) + D/V - \alpha}{\alpha + \beta} \right)^p \left( \frac{C_{up}(n\tau) + D/V + \beta}{\alpha + \beta} \right)^q e^{-(t-n\tau)}, p, q \right). \quad (3.7)$$

In particular,

$$C_{up}((n+1)\tau) = \alpha + (\alpha + \beta) \cdot X \left( \left( \frac{C_{up}(n\tau) + D/V - \alpha}{\alpha + \beta} \right)^p \left( \frac{C_{up}(n\tau) + D/V + \beta}{\alpha + \beta} \right)^q e^{-\tau}, p, q \right), \quad (3.8)$$

$$C_{up}((n+1)^+\tau) = \alpha + (\alpha + \beta) \cdot X \left( \left( \frac{C_{up}(n\tau) + D/V - \alpha}{\alpha + \beta} \right)^p \left( \frac{C_{up}(n\tau) + D/V + \beta}{\alpha + \beta} \right)^q e^{-\tau}, p, q \right) + \frac{D}{V}. \quad (3.9)$$

To determine the steady-state concentration at any given time  $t$ , we define  $C_n = C_{up}(n\tau)$ . Hence Eq (3.8) becomes

$$C_{n+1} = \alpha + (\alpha + \beta) \cdot X \left( \left( \frac{C_n + D/V - \alpha}{\alpha + \beta} \right)^p \left( \frac{C_n + D/V + \beta}{\alpha + \beta} \right)^q e^{-\tau}, p, q \right). \quad (3.10)$$

Using the definition of the  $X$  function, the above equation is rearranged as

$$\left( \frac{C_{n+1} - \alpha}{C_n + D/V - \alpha} \right)^{1-r} \left( \frac{C_{n+1} + \beta}{C_n + D/V + \beta} \right)^r = e^{-k_e \tau}, \quad (3.11)$$

where  $r = \frac{\beta - K_m}{\alpha + \beta} \in (0, 1)$ , i.e.,  $\beta > K_m$ . Let the steady-state solution  $C^* = C_n = C_{n+1}$ , and we obtain

$$\left( \frac{C^* - \alpha}{C^* + D/V - \alpha} \right)^{1-r} \left( \frac{C^* + \beta}{C^* + D/V + \beta} \right)^r = e^{-k_e \tau}. \quad (3.12)$$

We know that  $C^*$  uniquely exists (the proof of the existence and uniqueness is given in the next subsection), and thus we get the unique periodic solution as

$$\tilde{C}_{up}(t) = \alpha + (\alpha + \beta) \cdot X \left( \left( \frac{C^* + D/V - \alpha}{\alpha + \beta} \right)^p \left( \frac{C^* + D/V + \beta}{\alpha + \beta} \right)^q e^{-(t-n\tau)}, p, q \right), \quad t \in (n\tau, (n+1)\tau]. \quad (3.13)$$

Now we seek the lower bound. If  $t = (n+1)\tau$ , then Eq (3.3) becomes

$$\begin{cases} \frac{dC_{low}(t)}{dt} = \sigma e^{-k_a \tau} - k_e C_{low}(t) - \frac{V_{max} C_{low}(t)}{K_m + C_{low}(t)}, & t \neq n\tau, \\ C_{low}(t^+) = C_{low}(t) + \frac{D}{V}, & t = n\tau, \end{cases}$$

where  $\sigma e^{-k_a \tau} = f(\tau) e^{-k_a(n+1)\tau} = F k_a x_a^* e^{-k_a \tau}$ . Similarly, using the same approach, the solution of the model is given by

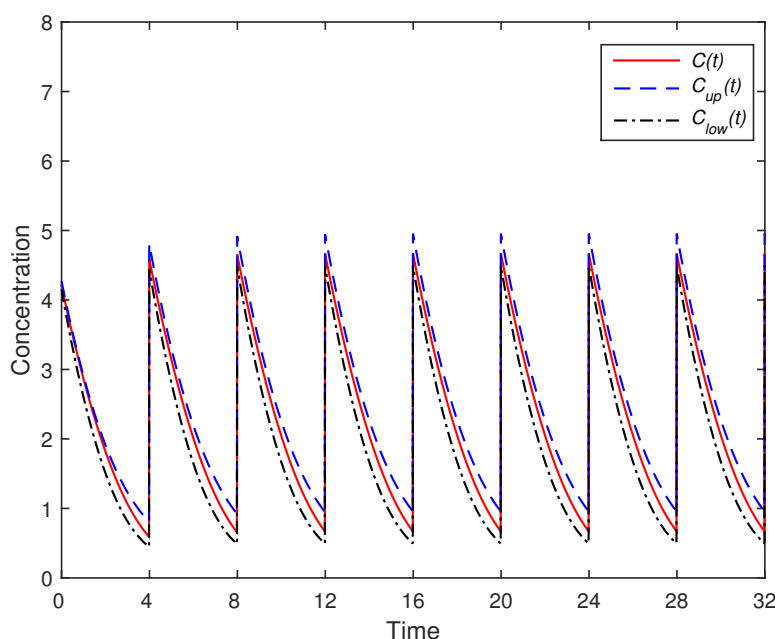
$$\tilde{C}_{low}(t) = \alpha_1 + (\alpha_1 + \beta_1) \cdot X \left( \left( \frac{C^* + D/V - \alpha_1}{\alpha_1 + \beta_1} \right)^{p_1} \left( \frac{C^* + D/V + \beta_1}{\alpha_1 + \beta_1} \right)^{q_1} e^{-(t-n\tau)}, p_1, q_1 \right), \quad t \in (n\tau, (n+1)\tau],$$

where  $p_1 = \frac{K_m + \alpha_1}{k_e(\alpha_1 + \beta_1)}$ ,  $q_1 = \frac{\beta_1 - K_m}{k_e(\alpha_1 + \beta_1)}$ ,

$$\alpha_1 = \frac{2K_m\sigma e^{-k_a\tau}}{K_mk_e + V_{\max} - \sigma e^{-k_a\tau} + \sqrt{(K_mk_e + V_{\max} - \sigma e^{-k_a\tau})^2 + 4K_mk_e\sigma e^{-k_a\tau}}},$$

$$\beta_1 = \frac{K_mk_e + V_{\max} - \sigma e^{-k_a\tau} + \sqrt{(K_mk_e + V_{\max} - \sigma e^{-k_a\tau})^2 + 4K_mk_e\sigma e^{-k_a\tau}}}{2k_e}.$$

The exact upper and lower bounds of model (3.3) in each interval of length  $\tau$  are derived separately according to the above method. Connect each interval by numerical simulation.



**Figure 2.** Approximation between the exact solution and the upper and lower bounds.  $F = 0.8$ ;  $k_a = 0.25/h$ ;  $k_e = 0.21/h$ ;  $K_m = 1.5mM$ ;  $V_{\max} = 1.5mg/\text{min}$ ;  $V_a = 2L$ ;  $V = 2L$ ;  $D_a = 8mg$ ;  $D = 4mg$ ;  $\tau = 4h$ .

The concentrations exhibit periodic changes, as shown in Figure 2, and the upper and lower bounds steadily decrease and are consistent with the trend of the precise solution. In order to simplify the subsequent analysis, we choose upper bounds with very small differences from the exact solution for our study, which ensures accuracy and reduces computational complexity. This approach is commonly used to analyze complex periodic systems and can help us understand the range of up and down fluctuations in drug concentration especially in multiple dosing models.

For ease of writing, we replace  $\tilde{C}_{up}(t)$  with  $\tilde{C}(t)$ . According to Eq (3.13), the solution in the interval  $(n\tau, (n+1)\tau]$  is

$$\tilde{C}(t) = \alpha + (\alpha + \beta) \cdot X \left( \left( \frac{C^* + D/V - \alpha}{\alpha + \beta} \right)^p \left( \frac{C^* + D/V + \beta}{\alpha + \beta} \right)^q e^{-(t-n\tau)}, p, q \right). \quad (3.14)$$

The minimum steady-state blood drug concentration is

$$\tilde{C}_{\min} = \alpha + (\alpha + \beta) \cdot X \left( \left( \frac{C^* + D/V - \alpha}{\alpha + \beta} \right)^p \left( \frac{C^* + D/V + \beta}{\alpha + \beta} \right)^q e^{-\tau}, p, q \right),$$



and the maximum steady-state blood drug concentration is

$$\tilde{C}_{\max} = \alpha + (\alpha + \beta) \cdot X \left( \left( \frac{C^* + D/V - \alpha}{\alpha + \beta} \right)^p \left( \frac{C^* + D/V + \beta}{\alpha + \beta} \right)^q e^{-\tau}, p, q \right) + \frac{D}{V}.$$

### 3.2. Existence uniqueness and local stability analysis of the periodic solution

The existence and uniqueness of the periodic solution is the basis for analyzing the periodic behavior of the system, and the local stability further portrays the behavior of the system in response to the perturbation of the periodic solution. The ability of the system to sustain a specific periodic state, such as the preservation of stable fluctuations in drug concentration, is determined by the stability of the periodic solution. As a result, the study of these two properties offers methodological direction for real-world applications in the domains of pharmacokinetics in addition to theoretical significance.

**Theorem 2** *The periodic solution given by Eq (3.14) exists uniquely.*

**Proof.** Define the left-hand side of Eq (3.12) as a function  $F(C^*)$ , i.e.,

$$F(C^*) = \left( \frac{C^* - \alpha}{C^* + D/V - \alpha} \right)^{1-r} \left( \frac{C^* + \beta}{C^* + D/V + \beta} \right)^r.$$

The solution  $C^*$  of  $F(C^*) = e^{-k_e \tau}$  must be shown to be unique in an equivalent way in order to demonstrate the uniqueness of the periodic solution. The derivatives of the following expressions are all greater than 0, namely,

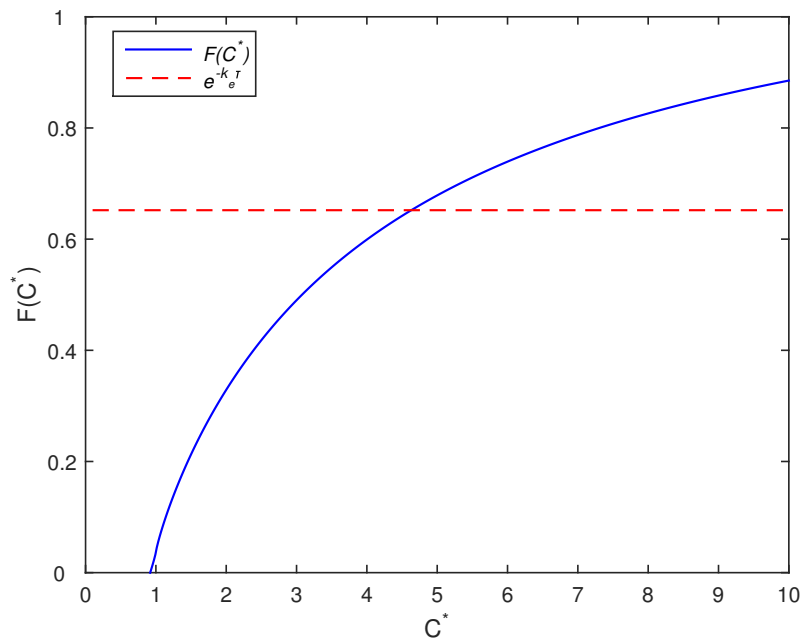
$$\frac{d}{dC^*} \left( \frac{C^* - \alpha}{C^* + D/V - \alpha} \right) = \frac{D/V}{(C^* + D/V - \alpha)^2} > 0,$$

$$\frac{d}{dC^*} \left( \frac{C^* + \beta}{C^* + D/V + \beta} \right) = \frac{D/V}{(C^* + D/V + \beta)^2} > 0.$$

Hence  $F(C^*)$  is globally rising as it is the product of these two partially increasing functions and the powers  $1 - r$  and  $r$  are both positive. This means that  $F(C^*)$  has at most one point of intersection with  $e^{-k_e \tau}$ , as shown in Figure 3. Consequently, there is only one solution to the equation  $F(C^*) = e^{-k_e \tau}$ . At the same time, we deduce that

$$F(0) = \left( \frac{-\alpha}{D/V - \alpha} \right)^{1-r} \left( \frac{\beta}{D/V + \beta} \right)^r < 0, \quad \lim_{C^* \rightarrow +\infty} F(C^*) = 1.$$

Thus the continuity theorem requires that a solution  $C^*$  exists for  $e^{-k_e \tau} \in (0, 1)$ . In conclusion, the solution  $C^*$  to the equation  $F(C^*) = e^{-k_e \tau}$  exists uniquely, i.e., the periodic solution exists uniquely.



**Figure 3.** Schematic representation of the uniqueness of the existence of  $C^*$ .  $k_e = 0.21/h$ ;  $K_m = 0.5mM$ ;  $V = 1L$ ;  $D = 4mg$ ;  $\tau = 2h$ .

**Theorem 3** *The periodic solution given by Eq (3.14) is locally stable if*

$$\left. \frac{\partial \Gamma(C((n+1)\tau^+))}{\partial C((n+1)\tau^+)} \right|_{C((n+1)\tau^+) = \tilde{C}_{\max}} < 1.$$

**Proof.** Define

$$g(C(n+1)\tau^+) = \left( \frac{C(n+1)\tau^+ - \alpha}{\alpha + \beta} \right)^p \left( \frac{C(n+1)\tau^+ + \beta}{\alpha + \beta} \right)^q e^{-\tau}.$$

Equation (3.9) is deformed into

$$C((n+1)\tau^+) = \alpha + (\alpha + \beta) \cdot X(g(C(n+1)\tau^+), p, q) + D/V \\ := \Gamma(C((n+1)\tau^+)).$$

Clearly,  $\tilde{C}_{\max}$  is an equilibrium point in the equation above. The above equation's derivation leads to

$$\frac{\partial \Gamma(C((n+1)\tau^+))}{\partial C((n+1)\tau^+)} = (\alpha + \beta) \frac{\partial X}{\partial z} \cdot \frac{\partial g}{\partial C((n+1)\tau^+)}. \quad (3.15)$$

Here  $X(z, p, q)$  is simply written as  $X$ . We let  $H = X^p(X+1)^q - z$  according to the specification of  $X$ . The following partial derivatives with respect to  $z$  and  $X$  are obtained separately for  $H$ .

$$H_z = -1,$$

$$H_X = X^{p-1}(X+1)^{q-1} (p(X+1) + qX) \\ = X^p(X+1)^q \left( \frac{p}{X} + \frac{q}{X+1} \right) \\ = z \left( \frac{p}{X} + \frac{q}{X+1} \right).$$

This leads to

$$\frac{\partial X}{\partial z} = -\frac{H_z}{H_X} = -\frac{-1}{z\left(\frac{p}{X} + \frac{q}{X+1}\right)} = \frac{1}{z}\left(\frac{p}{X} + \frac{q}{X+1}\right)^{-1}.$$

At steady state,  $X$  satisfies the following equation:

$$X(g(C(n+1)\tau^+), p, q) = \frac{\tilde{C}_{\max} - D/V - \alpha}{\alpha + \beta},$$

and thus

$$\frac{\partial X}{\partial z} = \frac{1}{z} \cdot \frac{1}{\alpha + \beta} \left( \frac{p}{\tilde{C}_{\max} - D/V - \alpha} + \frac{q}{\tilde{C}_{\max} - D/V + \beta} \right)^{-1}.$$

At the same time, we calculate that the partial derivative of the function  $g$  as

$$\begin{aligned} \left. \frac{\partial g}{\partial C((n+1)\tau^+)} \right|_{C((n+1)\tau^+) = \tilde{C}_{\max}} &= \left( \frac{p}{C((n+1)\tau^+) - \alpha} + \frac{q}{C((n+1)\tau^+) + \beta} \right) \cdot z \\ &= \left( \frac{p}{\tilde{C}_{\max} - \alpha} + \frac{q}{\tilde{C}_{\max} + \beta} \right) \cdot z. \end{aligned}$$

From Eq (3.15), we get

$$\left. \frac{\partial \Gamma(C((n+1)\tau^+))}{\partial C((n+1)\tau^+)} \right|_{C((n+1)\tau^+) = \tilde{C}_{\max}} = \frac{\frac{p}{\tilde{C}_{\max} - \alpha} + \frac{q}{\tilde{C}_{\max} + \beta}}{\frac{p}{\tilde{C}_{\max} - D/V - \alpha} + \frac{q}{\tilde{C}_{\max} - D/V + \beta}} < 1,$$

which implies that  $\tilde{C}_{\max}$  is locally stable, and then the periodic solution is locally stable.

## 4. Co-administration vs. intravenous bolus administration

### 4.1. Comparison of blood concentration

For model (3.3), we consider simultaneous intravenous and oral administration, and then there exists an additional input of drug to the absorption chamber. When the absorption compartment is stable, then we consider the change in drug concentration in the central compartment. If the drug is administered intravenously alone, the drug enters directly into the circulation of the body, and the periodic solution is

$$\tilde{C}_{IV}(t) = \mu \cdot X\left(\left(\frac{C_{IV}^* + D/V}{\mu}\right)^{p_2} \left(\frac{C_{IV}^* + D/V}{\mu} + 1\right)^{q_2} e^{-(t-n\tau)}, p_2, q_2\right), \quad (4.1)$$

where  $p_2 = \frac{K_m}{K_m k_e + V_{\max}}$ ,  $q_2 = \frac{V_{\max}}{k_e(K_m k_e + V_{\max})}$ ,  $\mu = K_m + \frac{V_{\max}}{k_e}$ , and  $C_{IV}^*$  is the steady-state solution for intravenous injection alone. Details are in Appendix A. We compare the pattern of change in blood drug concentration over time between co-administration and intravenous administration alone.

Co-administration is more effective than IV administration alone under the same initial conditions (assuming both are in the effective concentration range) displayed in Figure 4(a). IV alone increased rapidly after administration, with marked fluctuations, but remained at consistently low levels. Co-administration shows a gradual increase in concentration, exhibits flatter periodic fluctuations with a wider range of fluctuations, and reaches a steady state where the concentration fluctuates at a higher level. This may be due to the fact that different drugs can enhance the efficacy or prolong the half-life of the drug in the body through synergistic effects. Overall, co-administration of drugs performed better in this system due to its higher steady-state level and slower cyclic fluctuations which provided better maintenance of the drug concentration.

#### 4.2. Comparison of steady-state AUC

In pharmacokinetics, AUC (area under the curve) refers to the area under the concentration-time curve of a drug and represents an indicator of the degree of exposure of a drug in the body. The AUC is commonly used to assess the absorption, distribution, metabolism, and excretion of a drug, reflecting the total amount of the drug that remains in the body. Generally the AUC is calculated by integrating the curve of drug concentration over time, while model (3.5) involves an additional input from an absorption chamber, and we define the AUC calculation accordingly as follows.

**Theorem 4** *There exists a bounded steady-state AUC for model (3.5) with the analytic expression*

$$AUC = \alpha\tau + \frac{D}{Vk_e} - \frac{\beta - K_m}{k_e} \ln \left( 1 + \frac{D/V}{\tilde{C}_{\min} + \beta} \right). \quad (4.2)$$

**Proof.** Since Eq (3.6) still holds at steady state, we have

$$\left( \frac{p}{\tilde{C}(t) - \alpha} + \frac{q}{\tilde{C}(t) + \beta} \right) d\tilde{C}(t) = -dt.$$

Multiply both sides by  $\tilde{C}(t) - \alpha$ ,

$$(\tilde{C}(t) - \alpha) dt = - \left( p + q - q \frac{\alpha + \beta}{\tilde{C}(t) + \beta} \right) d\tilde{C}(t).$$

Therefore, we define the drug exposure during a cycle  $\tau$  to be

$$\begin{aligned} AUC &= \int_0^\tau \tilde{C}(\tau) dt \\ &= \alpha\tau - \int_0^\tau \left( p + q - q \frac{\alpha + \beta}{\tilde{C}(t) + \beta} \right) d\tilde{C}(t) \\ &= \alpha\tau - (p + q) (\tilde{C}(\tau) - \tilde{C}(0)) + q(\alpha + \beta) \ln \frac{(\tilde{C}(\tau) + \beta)}{(\tilde{C}(0) + \beta)}, \end{aligned}$$

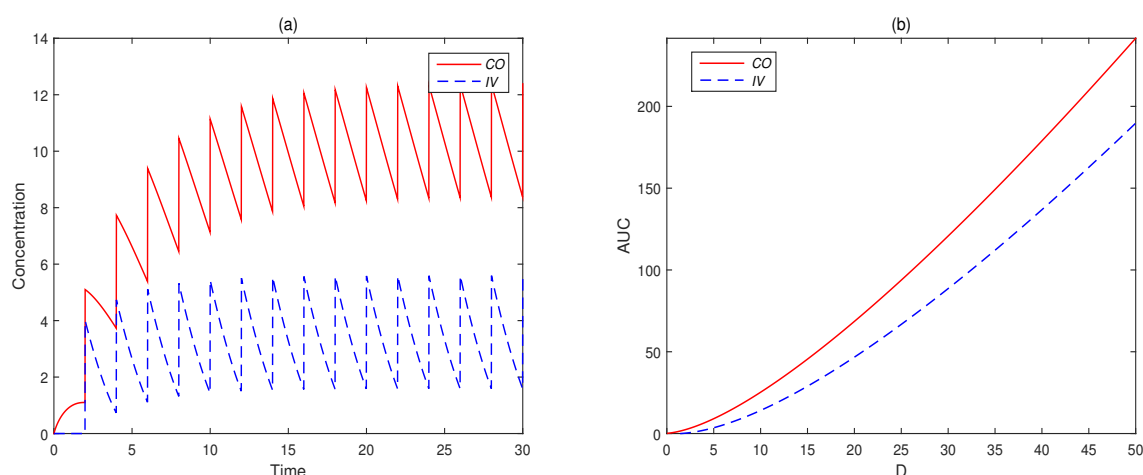
where  $p + q = \frac{1}{k_e}$ ,  $q(\alpha + \beta) = \frac{\beta - K_m}{k_e}$ . Since  $\tilde{C}(t)$  is a periodic solution with period  $\tau$ , it follows that  $\tilde{C}(\tau) - \tilde{C}(0) = -D/V$ . We therefore calculate

$$AUC = \alpha\tau + \frac{D}{Vk_e} - \frac{\beta - K_m}{k_e} \ln \left( 1 + \frac{D/V}{\tilde{C}_{\min} + \beta} \right).$$

Similarly, the drug exposure for IV administration alone is (details are in Appendix A)

$$AUC_{IV} = \frac{D}{Vk_e} - \frac{K_m}{k_e} \ln \left( 1 + \frac{D/V}{\tilde{C}_{\min,IV} + \mu} \right), \quad (4.3)$$

where  $\tilde{C}_{\min,IV}$  is the minimum steady-state blood drug concentration under IV administration.



**Figure 4.** (a) Comparison of the solutions of the two modes of administration. (b) Comparison of drug exposure between two modes of administration.  $F = 0.8$ ;  $k_a = 0.25/h$ ;  $k_e = 0.54/h$ ;  $K_m = 1.5mM$ ;  $V_{\max} = 1.5mg/min$ ;  $V_a = 2L$ ;  $V = 1L$ ;  $D_a = 8mg$ ;  $D = 4mg$ ;  $\tau = 2h$ .

The AUC values all showed a non-linear increasing trend with an increasing drug dose in Figure 4(b).  $AUC_{IV} < AUC < \frac{D}{V k_e}$  always holds and the co-administration regimen is more sensitive to dose  $D$ . It indicates that the concentration and duration of action of the drug in the body is longer and the efficacy of the drug is enhanced when co-administered. Obviously, co-administration is not suitable for all conditions and is typically employed during the transition from acute to long-term treatment. It is important to consider that the dosing regimen must account for factors such as drug cost, treatment duration, and other relevant considerations. As a result, not all co-administration regimens are superior to monotherapy.

## 5. Changes in the average steady-state concentration under different dosing regimens

The study of the effect of dosage and the dosing interval on the average steady-state blood drug concentration ( $C_{av}$ ) is an important topic in pharmacokinetics, which is essential for optimizing therapeutic efficacy and avoiding toxic side effects [27]. After a drug has been administered several times, the rate of absorption and elimination of the drug in the body reaches a state of equilibrium, at which time the blood drug concentration tends to a constant state. For the linear pharmacokinetic model, the absorption, distribution, metabolism, and clearance of a drug follow first-order kinetics, i.e., the rate of change of the drug in the body is proportional to its current concentration. This gives a linear relationship between the steady-state concentration and the dose and dosing interval. However, these rules no longer apply for nonlinear drug delivery. We prove the following lemma before going on to the pattern of nonlinear changes.

**Lemma 5** *For the multiple nonlinear combined dosing model (3.5), the minimum concentration at steady state decreases if the dose  $D$  and the interval  $\tau$  are doubled, i.e.,*

$$\tilde{C}_{\min}(D, \tau) > \tilde{C}_{\min}(2D, 2\tau).$$

*Conversely the drug exposure at steady state increases, i.e.,*

$$2AUC(D, \tau) < AUC(2D, 2\tau).$$

**Proof.** From Eq (3.12), we have

$$\left(\frac{C_{n+1} - \alpha}{C_n + D/V - \alpha}\right)^{1-r} \left(\frac{C_{n+1} + \beta}{C_n + D/V + \beta}\right)^r = e^{-k_e \tau}.$$

It is further written as

$$\left(1 + \frac{D/V}{C_{n+1} - \alpha}\right)^{1-r} \left(1 + \frac{D/V}{C_{n+1} + \beta}\right)^r = e^{k_e \tau}.$$

Subsequently, the following equation holds:

$$\begin{aligned} \left(1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) - \alpha}\right)^{1-r} \left(1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) + \beta}\right)^r &= e^{k_e \tau}, \\ \left(1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) - \alpha}\right)^{1-r} \left(1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) + \beta}\right)^r &= e^{2k_e \tau}. \end{aligned}$$

The following equation,

$$\left(1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) - \alpha}\right)^{1-r} \left(1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) + \beta}\right)^r = \left[\left(1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) - \alpha}\right)^2\right]^{1-r} \left[\left(1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) + \beta}\right)^2\right]^r, \quad (5.1)$$

is derived from the two equations above. Here we assume that  $\tilde{C}_{\min}(D, \tau) \leq \tilde{C}_{\min}(2D, 2\tau)$  holds and that the right side of the above equation is greater than the left side. Therefore, we obtain

$$\tilde{C}_{\min}(D, \tau) > \tilde{C}_{\min}(2D, 2\tau). \quad (5.2)$$

Now we prove that  $2AUC(D, \tau) < AUC(2D, 2\tau)$ .

$$\begin{aligned} AUC(2D, 2\tau) &= 2\alpha\tau + \frac{2D}{Vk_e} - \frac{\beta - K_m}{k_e} \ln(1 + 2M), \\ 2AUC(D, \tau) &= 2\alpha\tau + \frac{2D}{Vk_e} - \frac{\beta - K_m}{k_e} \ln[(1 + N)^2], \end{aligned}$$

where  $M = \frac{D/V}{\tilde{C}_{\min}(2D, 2\tau) + \beta}$ ,  $N = \frac{D/V}{\tilde{C}_{\min}(D, \tau) + \beta}$ . According to Eq (5.2) we have  $M > N$ . To prove that  $AUC(2D, 2\tau) > 2AUC(D, \tau)$ , we need to equivalently prove that  $\ln(1 + 2M) < \ln[(1 + N)^2]$ . Then Eq (5.1) is transformed into

$$\left(1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) - \alpha}\right) (1 + 2M)^{\frac{r}{1-r}} = \left(1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) - \alpha}\right)^2 [(1 + N)^2]^{\frac{r}{1-r}},$$

and reorganize into

$$\left(1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) - \alpha}\right)^2 \left(1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) - \alpha}\right)^{-1} = [(1 + N)^2 (1 + 2M)^{-1}]^{\frac{r}{1-r}}. \quad (5.3)$$

According to the monotonicity of the function, the following inequality holds:

$$\left(1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) - \alpha}\right)^2 \left(1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) - \alpha}\right)^{-1} < (1 + N)^2 (1 + 2M)^{-1}. \quad (5.4)$$

Details are in Appendix B. Combining Eqs (5.3) and (5.4), it can be concluded that

$$\left[(1+N)^2(1+2M)^{-1}\right]^{\frac{-r}{1-r}} < (1+N)^2(1+2M)^{-1}.$$

Multiplying the left and right together by  $\left[(1+N)^2(1+2M)^{-1}\right]^{\frac{r}{1-r}}$ , the above inequality becomes

$$\left[(1+N)^2(1+2M)^{-1}\right]^{\frac{r}{1-r}} > 1,$$

and then

$$(1+N)^2 > 1+2M.$$

It is further written as

$$\ln \left[(1+N)^2\right] > \ln(1+2M).$$

The proof is complete.

**Theorem 6** For the multiple nonlinear combined dosing model (3.5), the average concentration at steady state increases if the dose  $D$  and the interval  $\tau$  are doubled, i.e.,

$$C_{av}(D, \tau) < C_{av}(2D, 2\tau).$$

**Proof.** For dosing regimen  $(D, \tau)$ , the steady state average concentration is

$$C_{av}(D, \tau) = \frac{\int_0^\tau \tilde{C}(t) dt}{\tau} = \frac{AUC(D, \tau)}{\tau},$$

and the average steady-state concentration of  $(2D, 2\tau)$  is

$$C_{av}(2D, 2\tau) = \frac{AUC(2D, 2\tau)}{2\tau}.$$

By Lemma 5, one has that

$$\frac{AUC(D, \tau)}{\tau} < \frac{AUC(2D, 2\tau)}{2\tau}.$$

Hence we obtain

$$C_{av}(D, \tau) < C_{av}(2D, 2\tau).$$

It is reasonable to hypothesize that the following conclusion hold true if the dose and dosing interval are halved, namely,

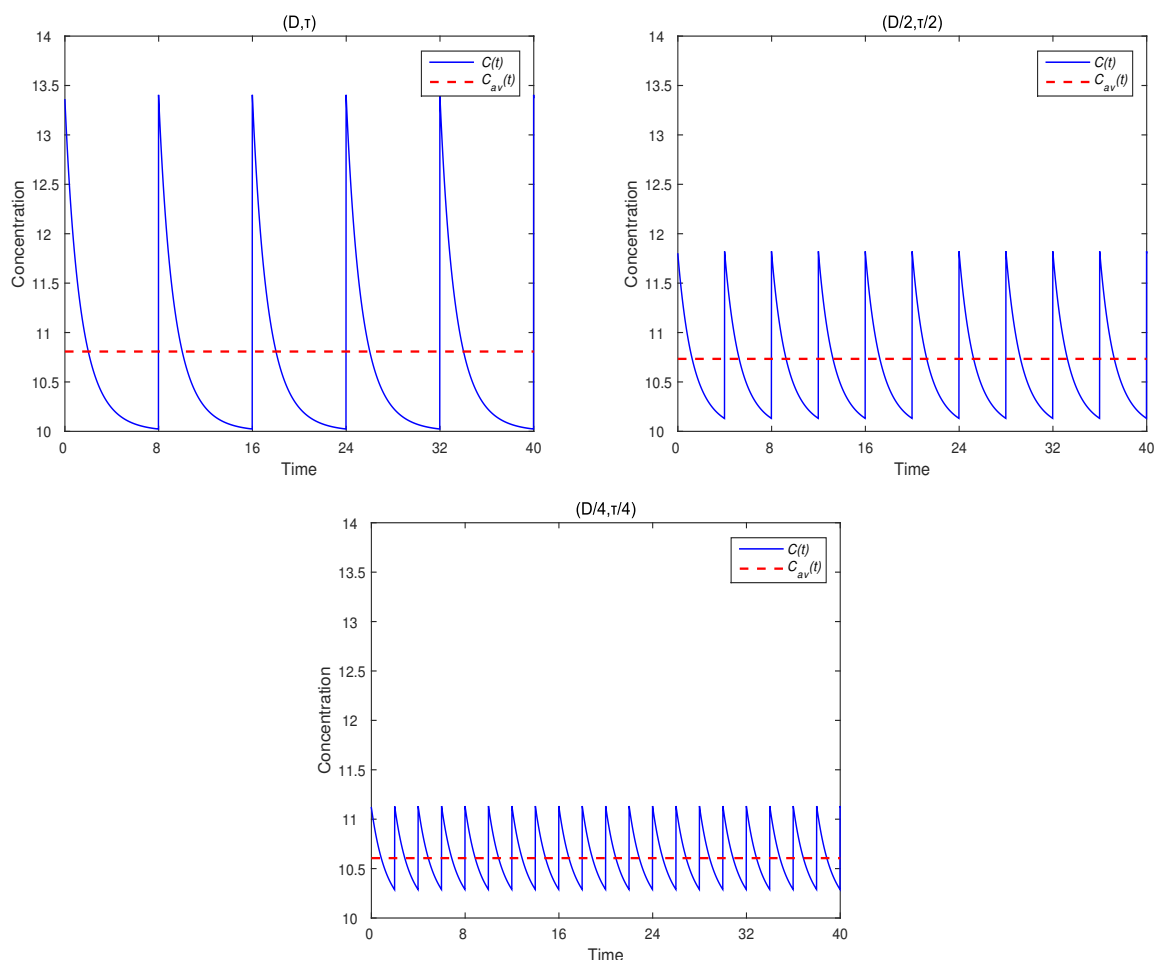
$$C_{av}(D, \tau) > C_{av}\left(\frac{D}{2}, \frac{\tau}{2}\right) > C_{av}\left(\frac{D}{4}, \frac{\tau}{4}\right) > \dots$$

Due to the complexity of nonlinearity, it is difficult to theoretically prove the change rule of different  $C_{av}(D, \tau)$  precisely, so we mainly observe the change rule of the average steady-state concentration under different dosing regimens by numerical simulation.

## 6. Application case

A well-known antiepileptic medication that can be administered intravenously or orally is phenytoin sodium. When treating persistent status epilepticus with injectable phenytoin sodium, the medication is typically administered intravenously as a sodium salt that can be added to an aqueous solution of propylene glycol, particularly if benzodiazepines are not able to provide additional relief. This approach is sometimes also used to treat cardiac arrhythmias or neuropathic discomfort [28–30]. In clinical practice, combinations are utilized mostly for the short-term shift from intravenous acute phase therapy to oral maintenance therapy. Intravenous injection quickly establishes effective blood drug concentration, while oral administration is used to maintain blood drug concentration and reduce the risk of epilepsy recurrence.

To verify the conclusion of the previous section, we extracted data from [31, 32]. A patient weighs 70.4 kg and he is given an intravenous dose of phenytoin sodium at  $D = 300 \text{ mg/day}$  and an oral dose at  $D_a = 2 \text{ mg/kg}$ . The other pharmacokinetic parameters are  $k_a = 0.569 \text{ /h}$ ,  $k_e = 0.022 \text{ /h}$ ,  $V = 0.63 \text{ l /kg}$ ,  $V_{\max} = 5.24 \text{ mg/kg}$ ,  $K_m = 4.20 \text{ mg/l}$ ,  $F = 0.87$ , and the dosing interval  $\tau = 8 \text{ h}$ . We Draw the following images according to the given parameters.

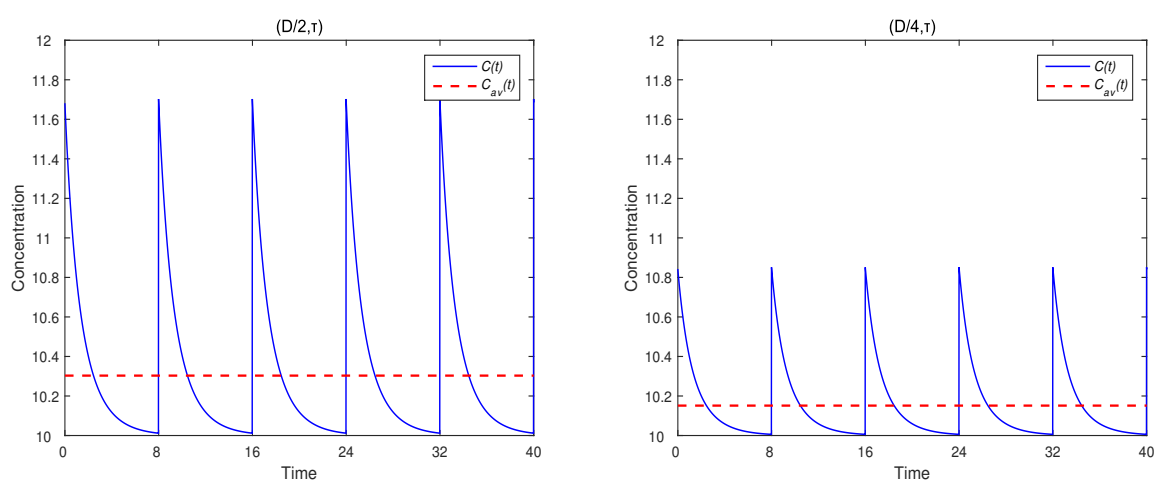


**Figure 5.** Steady-state average concentrations under different dosing regimens. The solid blue line is the blood concentration and the dashed red line is the average steady-state concentration.

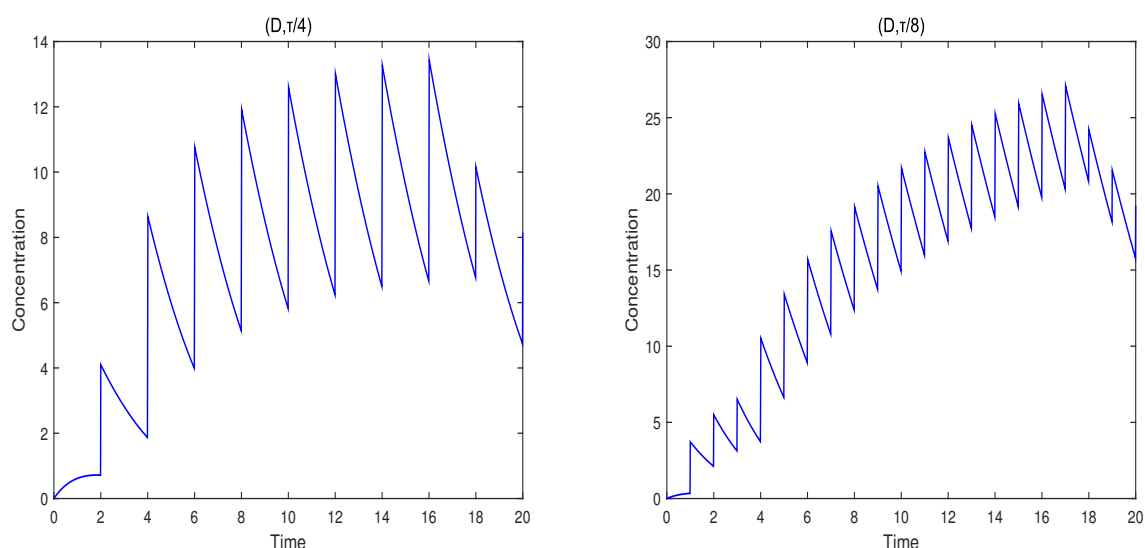


Figure 5 shows that there was no significant difference in the fluctuation of blood concentration of the drug at each dosing interval during the period of attainment of steady-state blood concentration. As the dose  $D$  and dosing interval  $\tau$  were halved, the steady-state concentration decreased, as did the average steady-state concentration, but the minimum steady-state concentration increased. The results of these numerical simulations are consistent with the previous theoretical results. Therefore, it is appropriate to shorten the dosing interval and reduce the dosage at the same time when trying to implement an effective dosing regimen. This approach helps to maintain the efficacy of the drug while reducing the drastic fluctuations in drug concentration and avoiding the toxic effects of excessive concentration.

It is natural to think about how the steady-state concentration would change if only one of the indicators changed. Figures 6 and 7 show the change in steady-state concentration when only the dose administered or the interval between administrations is changed, respectively.



**Figure 6.** Steady-state average concentration with only change in administered dose  $D$ . The solid blue line is the blood concentration and the dashed red line is the average steady-state concentration.



**Figure 7.** Steady-state average concentration with only change in dosing interval  $\tau$ . The solid blue line is the blood concentration.

Both steady-state and average steady-state concentrations were reduced when dose  $D$  was halved as shown in Figure 6. However, the drug concentration may not reach the effective therapeutic range if the dose is too low; Figure 7 shows that as the dosing interval  $\tau$  decreases, the blood drug concentration increases rapidly and the drug is re-administered before it is fully metabolized and cleared, leading to concentration accumulation. The drug concentration tends to increase and eventually loses its steady state. According to this phenomena, a drug may not be completely digested and eliminated from the body if the dose interval is too short. This could result in a cumulative impact that could eventually cause toxicity. Therefore, in order to get the best therapeutic impact and to guarantee drug safety and efficacy, it is vital to balance both the drug dose and the dosing interval. Multiple administrations of small doses is a drug delivery strategy that maintains blood levels in a stable range, avoiding drug concentrations that are too high or too low, thereby improving efficacy or reducing side effects.

## 7. Conclusions

In this paper, we study the nonlinear PK model of intravenous combined oral drug administration in the context of periodic drug administration. We mainly consider the variation of blood drug concentration in the central compartment. Intravenous administration permits the drug to enter the body fluid circulation directly, but oral administration has a process of absorption before it enters the body circulation. Therefore, based on the multiple intravenous injection PK model, we incorporate the oral administration process to establish the model under investigation. The approximate periodic solution of the model is derived from the  $X$  function. When comparing the solution and steady-state AUC of intravenous administration alone and co-administration separately, Figure 4 shows the superiority of co-administration. In addition, the variation rule of  $C_{av}(D, \tau)$  under various dosing regimens for co-administration is also determined by varying the administration dose  $D$  and the administration interval  $\tau$ . The numerical simulations in Figure 5 have demonstrated that stable and effective drug therapy can be achieved by reducing the single dose and reducing the interval between doses. This improves efficacy while decreasing negative effects, lowers concentration fluctuations, and raises steady-state minimum concentrations. These results offer a theoretical foundation for recommended dosage schedules as well as recommendations for developing novel drugs and enhancing existing dosage forms.

There are a few limitations in this study. First, the steady-state AUC and blood drug concentration may contain inaccuracies since model (2.1) is a non-autonomous system, meaning we can only obtain precise upper and lower bounds for the solution rather than the actual solution itself. Second, a time gap between intravenous and oral drug delivery occurs in real life. We disregarded this distinction and assumed that the two drug administration types happened simultaneously for computational and modeling convenience. Furthermore, the steady-state concentration is directly impacted by the patient's drug adherence [33,34]. Good drug adherence can help patients maintain stable blood concentrations and achieve the desired therapeutic effect. Conversely, noncompliance might result in variations in steady-state concentrations, which can impact the effectiveness of treatment and potentially cause unfavorable medication reactions. New mathematical techniques are required to examine each of these in further depth.

Multi-objective optimization, systems biology, nonlinear dynamics, and machine learning are the main areas of future mathematical study in combination medication [35, 36]. These techniques can theoretically facilitate the creation of customized combination medication regimens by integrating in-

tricate biological data and drug interactions. In fact, the distribution, metabolism, and clearance processes of many drugs cannot be adequately modeled by only one or two compartments, especially for lipid-soluble drugs, macromolecules, or multi-tissue-distributed drugs. Hence inspired by model 3 in reference [15], we extended the original model to a three-compartment PK model to more accurately portray the dynamic processes of drugs:

$$\begin{cases} \frac{dC_1(t)}{dt} = g(t) + k_{21}C_2(t) + k_{31}C_3(t) - (k_e + k_{12} + k_{13})C_1(t) - \frac{V_{\max}C_1(t)}{K_m + C_1(t)}, \\ \frac{dC_2(t)}{dt} = k_{12}C_1(t) - (k_{21} + k_{23})C_2(t), \\ \frac{dC_3(t)}{dt} = k_{13}C_1(t) - (k_{31} + k_{32})C_3(t), \end{cases}$$

where  $C_1(t^+) = C_1(t) + D/V$ , and  $C_i(t)$  represents the concentration in the  $i^{th}$  compartment ( $i = 1, 2, 3$ ), respectively. Parameters  $k_{12}$ ,  $k_{21}$ ,  $k_{13}$ ,  $k_{31}$ ,  $k_{23}$ , and  $k_{32}$  are the transfer rates between compartments and  $k_e$  is the elimination rate of the central compartment ( $i = 1$ ), and  $g(t)$  is the drug input. Although the three-compartment model provides greater flexibility and accuracy, it also increases the complexity of the model. The important PK parameters of it are currently unclear and require further research.

### Use of AI tools declaration

The authors declare that no Artificial Intelligence (AI) tools were used in the creation of this article.

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### Conflict of interest

The authors declare no conflict of interest.

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## Appendix A: Periodic solution and $AUC_{IV}$ in a model of intravenous drug administration alone

With only intravenous administration, i.e.,  $D_a = 0$ , then model (2.1) becomes

$$\begin{cases} \frac{dC_{IV}(t)}{dt} = -k_e C_{IV}(t) - \frac{V_{\max} C_{IV}(t)}{K_m + C_{IV}(t)}, & t \neq n\tau, \\ C_{IV}(t^+) = C_{IV}(t) + \frac{D}{V}, & t = n\tau. \end{cases} \quad (\text{A.1})$$

Divide both sides simultaneously by  $k_e C_{IV}(t)$ :

$$\frac{1}{k_e C_{IV}(t)} \frac{dC_{IV}(t)}{dt} = -1 - \frac{V_{\max}}{k_e (K_m + C_{IV}(t))}.$$

Rearrange the above equation as

$$\left( \frac{p_2}{C_{IV}(t)} + \frac{q_2}{C_{IV}(t) + \mu} \right) dC_{IV}(t) = -dt, \quad (\text{A.2})$$

where  $p_2 = \frac{K_m}{K_m k_e + V_{\max}}$ ,  $q_2 = \frac{V_{\max}}{k_e (K_m k_e + V_{\max})}$ ,  $\mu = K_m + \frac{V_{\max}}{k_e}$ . Integrating the above equation, we have

$$(C_{IV}(t))^{p_2} (C_{IV}(t) + \mu)^{q_2} = (C_{IV}(n\tau^+))^{p_2} (C_{IV}(n\tau^+) + \mu)^{q_2} e^{-(t-n\tau)},$$

which can be further rearranged into

$$\left( \frac{C_{IV}(t)}{\mu} \right)^{p_2} \left( \frac{C_{IV}(t)}{\mu} + 1 \right)^{q_2} = \left( \frac{C_{IV}(n\tau^+)}{\mu} \right)^{p_2} \left( \frac{C_{IV}(n\tau^+)}{\mu} + 1 \right)^{q_2} e^{-(t-n\tau)}.$$

Based on the definition of the  $X$  function and Eqs (3.8) and (3.9), the periodic solution for only IV administration is found to be

$$\tilde{C}_{IV}(t) = \mu \cdot X \left( \left( \frac{C_{IV}^* + D/V}{\mu} \right)^{p_2} \left( \frac{C_{IV}^* + D/V}{\mu} + 1 \right)^{q_2} e^{-(t-n\tau)}, p_2, q_2 \right), \quad (\text{A.3})$$

where  $C_{IV}^*$  is the steady-state solution for intravenous injection alone. Since Eq (7.2) still holds in the steady state, we have

$$\left( \frac{p_2}{\tilde{C}_{IV}(t)} + \frac{q_2}{\tilde{C}_{IV}(t) + \mu} \right) d\tilde{C}_{IV}(t) = -dt,$$

and

$$\tilde{C}_{IV}(t) dt = - \left( p_2 + q_2 - q_2 \frac{\mu}{\tilde{C}(t) + \mu} \right) d\tilde{C}_{IV}(t).$$

Therefore, the drug exposure for only IV administration is

$$\begin{aligned} AUC_{IV} &= \int_0^\tau \tilde{C}_{IV}(t) dt \\ &= - \int_0^\tau \left( p_2 + q_2 - q_2 \frac{\mu}{\tilde{C}_{IV}(t) + \mu} \right) d\tilde{C}_{IV}(t) \\ &= \frac{D}{V k_e} - \frac{K_m}{k_e} \ln \left( 1 + \frac{D/V}{\tilde{C}_{\min, IV}(t) + \mu} \right). \end{aligned} \quad (\text{A.4})$$

## Appendix B: The derivation of Eq (5.4)

To prove Eq (5.4), we construct a function as follows:

$$A(x) = \left( 1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) - (\alpha + x)} \right)^2 \left( 1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) - (\alpha + x)} \right)^{-1}, \quad x \in [-(\alpha + \beta), 0].$$

The values of the function at the two endpoints are

$$\begin{aligned} A(-(\alpha + \beta)) &= \left( 1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) + \beta} \right)^2 \left( 1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) + \beta} \right)^{-1}, \\ A(0) &= \left( 1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) - \alpha} \right)^2 \left( 1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) - \alpha} \right)^{-1}. \end{aligned}$$

It is only necessary to prove that  $A(0) < A(-(\alpha + \beta))$ . We take the derivative of the function  $A(x)$  and organize it to get

$$\begin{aligned} A'(x) &= 2 \frac{D}{V} \left( 1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) - (\alpha + x)} \right) \left( 1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) - (\alpha + x)} \right)^{-2} \\ &\quad \left[ \frac{1}{(\tilde{C}_{\min}(D, \tau) - (\alpha + x))^2} \left( 1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) - (\alpha + x)} \right) \right. \\ &\quad \left. - \left( 1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) - (\alpha + x)} \right) \frac{1}{(\tilde{C}_{\min}(2D, 2\tau) - (\alpha + x))^2} \right]. \end{aligned}$$

Generalize and simplify the above equation as

$$A'(x) = 2 \frac{D}{V} \left( 1 + \frac{D/V}{\tilde{C}_{\min}(D, \tau) - (\alpha + x)} \right) \left( 1 + \frac{2D/V}{\tilde{C}_{\min}(2D, 2\tau) - (\alpha + x)} \right)^{-2} \left( \frac{b - c}{a} \right),$$

where

$$\begin{aligned} a &= \left( \tilde{C}_{\min}(D, \tau) - (\alpha + x) \right)^2 \left( \tilde{C}_{\min}(2D, 2\tau) - (\alpha + x) \right)^2, \\ b &= \left( \tilde{C}_{\min}(2D, 2\tau) - (\alpha + x) + 2D/V \right) \left( \tilde{C}_{\min}(2D, 2\tau) - (\alpha + x) \right), \\ c &= \left( \tilde{C}_{\min}(D, \tau) - (\alpha + x) + D/V \right) \left( \tilde{C}_{\min}(D, \tau) - (\alpha + x) \right). \end{aligned}$$

The sign of  $A'(x)$  is consistent with  $b - c$ . Since  $\tilde{C}_{\min}(D, \tau) > \tilde{C}_{\min}(2D, 2\tau)$ , we have  $b - c < 0$ , i.e.,  $A'(x) < 0$ . Hence the function  $A(x)$  is monotonically decreasing on the interval  $x \in [-(\alpha + \beta), 0]$ , so that

$$A(0) < A(-(\alpha + \beta)).$$



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