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MATHEMATICAL SOLUTION OF A PHARMACOKINETIC MODEL WITH SIMULTANEOUS FIRST-ORDER AND HILL-TYPE ELIMINATION*

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Abstract Mathematical studies on pharmacokinetic models are essentially important for drug development and optimal dose design. Considering the interaction between drug molecules and their receptors, the elimination of drug molecules can exhibit Hill-type kinetics. In this paper, motivated by the recombinant human granulocyte colony-stimulating factor (G-CSF) and the transcendent Lambert W function, we have studied the mathematical solutions of a one-compartment nonlinear pharmacokinetic model with simultaneous first-order and Hill-type ($n = 2$) elimination for the case of intravenous bolus administration. By introducing three well-defined transcendental functions depending on three different scenarios, we have established the closed-form precise solutions of time course of drug concentration, which is a method to calculate drug concentrations at any time point. As a result, we also have derived the explicit expressions of some key pharmacokinetic surrogates such as the elimination half-life $t_{1/2}$ and total drug exposure (i.e. area under the concentration curve (AUC)), which are found as dose-dependent. Finally, a case study of a G-CSF drug is quantitatively illustrated to delineate our theoretical results, including the elimination half-life and AUC for different dosages. Our findings can provide an effective guidance for drugs with simultaneous first-order and Hill-type ($n = 2$) elimination in clinical pharmacology.

Keywords Nonlinear pharmacokinetic model, Hill-type elimination, closed-form solution, elimination half-life, area under the concentration curve.

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1. Introduction

In recent years, more and more people have used mathematical models to conduct qualitative and quantitative research on pharmacokinetics. Pharmacokinetics is a scientific discipline to study the change of drug concentration over time in the living organisms. It mainly includes the dynamic change of drugs absorption, distribution, metabolism, and excretion [8,9]. Considering different modes of administration such as oral, intravenous, subcutaneous, intramuscular injections, and different eliminations routes, compartment models are proposed to study the dynamical behavior

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of drug concentration with time, and characterize the corresponding pharmacokinetic surrogates qualitatively and quantitatively, such as elimination half-life ($t_{1/2}$) and drug exposure (AUC) [2]. The resultant findings are beneficial to the drug development and optimal drug designs in clinical pharmacology [19].

The closed-form solution of plasma drug concentration is important and necessary in the field of pharmacometric community for several reasons. Firstly, the closed-form solution of drug concentration over time is a complete solution of the pharmacokinetic model. Secondly, with these closed-form solutions, we are able to derive the mathematical formulas of the key pharmacokinetic indicators, such as elimination half-life in this study. Their pharmacokinetic properties are very useful for the experimental design of new drug development and drug regimen design in the clinical trial. Moreover, closed-form solutions of drug concentration provide the theoretical base which allows pharmacometric modellers for better pharmacokinetic modelling and parameter estimation. These also enable pharmacists to easily calculate the drugs concentration at any time, which is impossible if one only relies on drug measurement because of limited sampling. As such, the closed-form solutions of common known linear pharmacokinetic models were completely solved through direct integration or convolution [25]. However, nonlinear pharmacokinetic models with saturated elimination are observed for more and more drugs, such as biological agents [18]. Their closed-form solutions of drug concentration are still important while very scare in the field of pharmacokinetics. The reason behind is that there is no standard mathematical techniques to deal with the solutions of nonlinear ordinary differential equations [26], which leads to the difficulty for the closed-form solutions of nonlinear pharmacokinetic models.

As we mentioned above, more and more drugs exhibit nonlinear elimination. The reason is the complicated biochemical reaction involved in the interaction between the drug molecules behind and their receptors. Michaelis-Menten kinetics is the most classical elimination [10]. In 2007, Tang and Xiao [21] have studied one compartment PK model with Michaelis-Menten elimination alone. For the case of intravenous blous administration, the model can be described as

$$\begin{cases} \dfrac{dC(t)}{dt} = -\dfrac{V_m C(t)}{K_m + C(t)}, & t > 0, \\ C(0^+) = \frac{D}{V_d} \triangleq C_0, & t = 0, \end{cases} \tag{1.1}$$

where $C(t)$ is the drug concentration (unit: mass/volume) at time t; V_m is the maximum elimination rate of Michaelis-Menten elimination (unit: concentration/time); K_m is the Michaelis-Menten constant (unit: mass/volume); $C_0 = \frac{D}{V_d}$ is the initial blood concentration, here D is the administered dose (unit: mass), V_d is the apparent volume of distribution (unit: volume). Utilizing the well-known Lambert W transcendent function, the closed-form solution of drug concentration over time can be expressed as

$$C(t) = K_m \times \text{Lambert}W\left(\frac{C_0}{K_m}\exp\left(\frac{C_0 - V_m t}{K_m}\right)\right).$$

In 2015, Wu et al. have studied a one-compartment pharmacokinetic model with simultaneous first-order and Michaelis-Menten elimination for the case of intravenous

bolus administration [24]. The model is described by

$$\begin{cases} \dfrac{dC(t)}{dt} = -K_{ren}C(t) - \dfrac{V_m C(t)}{K_m + C(t)}, & t > 0, \\ C(0^+) = \frac{D}{V_d} = C_0, & t = 0, \end{cases} \tag{1.2}$$

where K_{ren} is elimination rate constant of drug molecules from linear elimination pathway. By customizing a new transcendental function X, the closed-form expression of drug concentration over time of model (1.2) can be given

$$C(t) = C_\beta \times X\left(\left(\frac{D}{C_\beta V_d}\right)^{p_1}\left(\frac{D}{C_\beta V_d}+1\right)^{p_2}\exp(-t), p_1, p_2\right), t \geq 0,$$

where $C_\beta = K_m(K_{ren}+K_{int})/K_{ren}$, $p_1 = 1/(K_{ren}+K_{int})$, $p_2 = K_{int}/(K_{ren}(K_{ren}+K_{int}))$, and $K_{int} = V_m/K_m$ represents the intrinsic clearance constant of Michaelis-Menten kinetics. Based on the closed-form solution, some important pharmacokinetic surrogates, such as elimination half-life and AUC were analytically derived.

Though nonlinear saturate Michaelis-Menten kinetics is extensively used in the literature, it does not always indicate elimination mode for all biologic drugs. A new nonlinear elimination of Hill equation has been introduced for some drugs. For example, recombinant human granulocyte colony-stimulating factor (G-CSF) is a hematopoietic growth factor that acts on granulocyte progenitor cells and allows neutrophils to proliferate and differentiate into mature neutrophils [15]. It exhibits linear elimination through the kidneys and the internalization process of neutrophils, where drug molecules bind to receptors, internalize into the inside of cells, and then disappear inside the cells. Moreover, Wiczling et al. [22] have studied a population pharmacokinetic model of filgrastim in healthy adults for the cases of intravenous and subcutaneous drug administrations, and they have concluded that the clearance of the drug is mainly related to the binding of drug molecules to their corresponding receptors, exhibiting the 1:2 binding relationship between receptors and ligands in the process of biochemical reactions or internalization.

The famous Hill equation [11] is

$$v = \frac{V_m C^n(t)}{K_D^n + C^n(t)}, \tag{1.3}$$

which was originally used to describe the equilibrium relationship between the saturation of hemoglobin and oxygen tension [12], and widely used in mathematics, probability, and pharmacokinetics later [11]. It indicates that the interaction relationship between the drug molecule and its receptor is nonlinear and saturable [20]. n is called the Hill coefficient. When $n < 1$, it explores a negative synergistic effect, that is, when a part of the receptor binds to the ligand, the affinity of the adjacent receptor decreases; When $n = 1$, it is expressed as a non-synergistic effect, which is commonly modeled by Michaelis-Menten equation, implying that the interaction between the receptor and the ligand takes place only at one site of the receptor, and each point proceeds independently. Simply, the receptor binds the ligand on 1:1. When $n > 1$, it exhibits a positive synergy. Namely, when a part of the receptor binds to the ligand, the affinity of the adjacent receptor increases [1, 3].

In this paper, we consider the special case of Hill-type elimination, and study a one-compartment pharmacokinetic model with simultaneous first-order and nonlinear Hill elimination with Hill coefficient $n = 2$. The main objective of our work

is to develop the closed-form solution of drug concentration over time of such a model for the case of intravenous bolus administration, derive important pharmacokinetic parameters as elimination half-life ($t_{1/2}$) and total drug exposure (AUC), and conduct some qualitative analysis. The results will have an important effect on the drug development and rational clinical design of related drugs. The structure of this article is organized as follows. In the next section, we introduce the pharmacokinetic model of Hill elimination with $n = 2$ and derive the closed-form solution of the plasma concentration with time. In Section 3, the pharmacokinetic of elimination half-life, drug exposure AUC and the dominant role of two parallel elimination pathways under bolus administration are derived theoretically well, which will guide pharmacologists to estimate and fit data. In Section 4, a case of G-CSF is analyzed to illustrate our theoretical results. Finally, the paper ends with a conclusion.

2. Nonlinear pharmacokinetic model

The one-compartment pharmacokinetic model with simultaneous first-order and nonlinear Hill-type elimination ($n = 2$) for the case of intravenous bolus administration can be described by the following differential equation:

$$\begin{cases} \dfrac{dC(t)}{dt} = -K_{ren}C(t) - \dfrac{V_m C^2(t)}{K_D^2 + C^2(t)}, \quad t > 0, \\ C(0^+) = \frac{D}{V_d} \triangleq C_0, \quad t = 0, \end{cases} \tag{2.1}$$

where $C(t)$ is the drug concentration (unit: mass/volume) in the central compartment at time t; K_{ren} is the linear elimination rate constant (unit: 1/time); V_m is the maximum elimination rate of Hill kinetics (unit: concentration/time); K_D is the usual dissociation constant (unit: mass/volume), and its value corresponds to the change of the drug concentration when the rate reaches half of the maximum rate; D is the administered dose amount (unit: mass); V_d is the apparent volume of distribution of the compartment (unit: volume). Here, all parameters are positive in terms of the actual meaning of pharmacology.

To better present our results, let us define $K_{H,max} = \frac{V_m}{2K_D}$, which is the maximum elimination rate of the Hill-type elimination at case of $n = 2$ [13]. In fact, the clearance rate constant (K) corresponding to the Hill equation is defined as:

$$K = \frac{v}{C(t)} = \frac{V_m C^{n-1}(t)}{K_D^n + C^n(t)}. \tag{2.2}$$

Taking the derivative of $C(t)$ on both sides of Eq.(2.2), we have:

$$\frac{d(v/C(t))}{dC(t)} = \frac{(n-1)K_D^n V_m C^{n-2}(t) - V_m C^{2(n-1)}(t)}{(K_D^n + C^n(t))^2}.$$

Let the above formula be equal to 0. We can get $C(t) = K_D \sqrt[n]{n-1}$. Substituting it into Eq.(2.2), we have the maximum elimination rate of Hill-type kinetics as

$$K_{max} = \frac{(n-1)V_m}{n(n-1)^{1/n}K_D}. \tag{2.3}$$

Put $n = 2$ into Eq.(2.3), and we can obtain $K_{H,max}$.

2.1. Closed-form solutions of model (2.1)

In this subsection, we focus on the closed-form precise solutions of time course of drug concentration. The first equation in model (2.1) can be transformed into:

$$\frac{C^2(t)+K_D^2}{K_{ren}C^3(t)+V_mC^2(t)+K_{ren}K_D^2C(t)}dC(t)=-dt. \tag{2.4}$$

To find the closed-form solution of $C(t)$ of the above equation, we will divide it into three cases for the classified discussion because its denominator is a cubic polynomial in one variable.

Due to two parallel elimination pathways involved, we will discuss the closed-form solution of $C(t)$ according to the different relationship between the elimination rate constant from the linear pathway and saturated nonlinear pathway. For convenience, let us denote $r=\frac{K_{ren}}{K_{H,max}}=\frac{2K_DK_{ren}}{V_m}$, which is the ratio of the first-order elimination rate constant compared to the maximum elimination rate constant of Hill kinetics.

2.1.1. Case 1: $0<r<1$

When the linear elimination rate constant is less than the maximum Hill elimination rate constant of Hill kinetics, Eq.(2.4) can be simply transformed into:

$$\left(\frac{\sqrt{1-r^2}}{C(t)}-\frac{1}{C(t)+C_{\alpha^-}}+\frac{1}{C(t)+C_{\alpha^+}}\right)dC(t)=-K_{ren}\sqrt{1-r^2}dt, \tag{2.5}$$

where $C_{\alpha^+}=\frac{K_D}{r}(1+\sqrt{1-r^2})$, $C_{\alpha^-}=\frac{K_D}{r}(1-\sqrt{1-r^2})$. Obviously, as $0<r<1$, $C_{\alpha^+}>0$, $C_{\alpha^-}>0$.

Let $p_1=\sqrt{1-r^2}$. Integrating Eq.(2.5) from 0^+ to t, then dividing both sides by p_1, we can get

$$\ln C(t)+\ln\left(\frac{C(t)+C_{\alpha^+}}{C(t)+C_{\alpha^-}}\right)^{1/p_1}=\ln C_0+\ln\left(\frac{C_0+C_{\alpha^+}}{C_0+C_{\alpha^-}}\right)^{1/p_1}-K_{ren}t. \tag{2.6}$$

In order to obtain the analytic expression for the explicit solution of the drug concentration, we further transform Eq.(2.6) into

$$C(t)\left(1+\frac{1}{\frac{C(t)+C_{\alpha^-}}{C_{\alpha^+}-C_{\alpha^-}}}\right)^{1/p_1}=C_0\left(1+\frac{1}{\frac{C_0+C_{\alpha^-}}{C_{\alpha^+}-C_{\alpha^-}}}\right)^{1/p_1}e^{-K_{ren}t}. \tag{2.7}$$

To find the connection with $r=1$, we take

$$X(t)=\frac{C(t)+C_{\alpha^-}}{C_{\alpha^+}+C_{\alpha^-}}. \tag{2.8}$$

At this point, Eq.(2.7) can be rewritten as

$$C(t)\left(1+\frac{1}{\frac{C(t)+C_{\alpha^-}}{C_{\alpha^+}+C_{\alpha^-}}\cdot\frac{C_{\alpha^+}+C_{\alpha^-}}{C_{\alpha^+}-C_{\alpha^-}}}\right)^{1/p_1}=C_0\left(1+\frac{1}{\frac{C_0+C_{\alpha^-}}{C_{\alpha^+}-C_{\alpha^-}}}\right)^{1/p_1}e^{-K_{ren}t}\triangleq g(t).$$

From (2.8), we have $C(t) = (C_{\alpha^+} + C_{\alpha^-})X(t) - C_{\alpha^-}$. Substituting it into the above formula yields

$$[(C_{\alpha^+} + C_{\alpha^-})X(t) - C_{\alpha^-}] \left(1 + \frac{1}{\frac{C_{\alpha^+}+C_{\alpha^-}}{C_{\alpha^+}-C_{\alpha^-}} X(t)}\right)^{1/p_1} = g(t),$$

which is equivalent to

$$\left[X(t) - \frac{C_{\alpha^-}}{C_{\alpha^+} + C_{\alpha^-}}\right] \left(1 + \frac{1}{\frac{C_{\alpha^+}+C_{\alpha^-}}{C_{\alpha^+}-C_{\alpha^-}} X(t)}\right)^{1/p_1} = \frac{g(t)}{C_{\alpha^+} + C_{\alpha^-}} \triangleq g_1(t). \quad (2.9)$$

Noticing that $\frac{C_{\alpha^-}}{C_{\alpha^+}+C_{\alpha^-}} = \frac{1-p_1}{2}$, $\frac{C_{\alpha^+}+C_{\alpha^-}}{C_{\alpha^+}-C_{\alpha^-}} = \frac{1}{p_1}$, we have from (2.9)

$$\left(X(t) - \frac{1/p_1 - 1}{2/p_1}\right) \left(1 + \frac{1}{X(t)/p_1}\right)^{1/p_1} = g_1(t). \quad (2.10)$$

It is easy to see that the right side of the Eq.(2.10) is nothing to do with the variable $X(t)$, and the left side is an expression related to the variable $X(t)$. Inspired by the Lambert W transcendental function [5], we can introduce a new transcendental function to represent the closed-form expression $C(t)$ of model (2.1), where we maintain the number of parameter as less as possible.

Definition 2.1. $F(t, q)$ is defined to be the solution of the following equation

$$\left(F(t,q) - \frac{q-1}{2q}\right) \left(1 + \frac{1}{qF(t,q)}\right)^q = t, \quad (2.11)$$

where $q > 1$ is a constant, and t is a variable.

It can be proved that for any given $t > 0$, there is a unique principle branch $F_0(t, q)$ satisfying Eq.(2.11). In fact, taking the derivative of $F_0(t, q)$, we have

$$\frac{dF_0(t,q)}{dt} = \frac{1}{t}\left[\frac{1}{F_0(t,q) - \frac{q-1}{2q}} - \frac{1}{F_0^2(t,q) + \frac{1}{q}F_0(t,q)}\right]^{-1} > 0, \ t > 0,$$

which indicates that $F_0(t, q) > \frac{q-1}{2q}$ is smooth and strictly increasing for $t > 0$. Therefore, the closed-form solution of Eq.(2.10) is $X(t) = F_0(g_1(t), 1/p_1)$, that is, the solution of model (2.1) can be expressed by

$$C(t) = (C_{\alpha^+} + C_{\alpha^-})F_0(g_1(t), 1/p_1) - C_{\alpha^-}, \ t \geq 0. \quad (2.12)$$

Replacing D/V_d by C_0 , we obtain the closed-form solution of model (2.1) in terms of the model parameters as follows

$$\begin{aligned} C(t) =& (C_{\alpha^+} + C_{\alpha^-}) \\ & \times F_0\left(\frac{D/V_d}{C_{\alpha^+} + C_{\alpha^-}} \left(1 + \frac{C_{\alpha^+} - C_{\alpha^-}}{D/V_d + C_{\alpha^-}}\right)^{1/p_1} e^{-K_{rent}}, \frac{1}{p_1}\right) - C_{\alpha^-}, \ t \geq 0. \end{aligned} \quad (2.13)$$

2.1.2. Case 2: $r = 1$

When the linear elimination rate constant is equal to the maximum elimination rate constant of Hill kinetics, Eq.(2.4) can be rewritten as:

$$\left(\frac{1}{C(t)} + \frac{-2K_D}{(C(t)+K_D)^2}\right) dC(t) = -K_{ren}dt. \tag{2.14}$$

Integrating on both sides of Eq.(2.14) form 0^+ to t leads to

$$\ln C(t) + \frac{2K_D}{C(t)+K_D} = \ln C_0 + \frac{2K_D}{C_0+K_D} - K_{ren}t. \tag{2.15}$$

We change Eq.(2.15) into the following form for having the closed-form solution of the blood drug concentration:

$$C(t)\exp\frac{2K_D}{C(t)+K_D} = C_0\exp\left(\frac{2K_D}{C_0+K_D} - K_{ren}t\right), \tag{2.16}$$

which is corresponding to Eq.(2.7) in Case 1. In fact,

$$\lim_{r\to 1^-}\left(\frac{C(t)+C_{\alpha^+}}{C(t)+C_{\alpha^-}}\right)^{1/p_1} = \exp\left(\frac{2K_D}{C(t)+K_D}\right).$$

Therefore, we also take

$$X(t) = \lim_{r\to 1^-}\frac{C(t)+C_{\alpha^-}}{C_{\alpha^+}+C_{\alpha^-}} = \frac{C(t)+K_D}{2K_D},$$

which yields $C(t) = 2K_DX(t) - K_D$. Put it into Eq.(2.16), and then we have

$$(2K_DX(t) - K_D)\exp\left(\frac{1}{X(t)}\right) = C_0\exp\left(\frac{2K_D}{C_0+K_D} - K_{ren}t\right). \tag{2.17}$$

To derive the accordantly transcendental function as $F(t,q)$, we divide both sides of (2.17) by $2K_D$ and obtain

$$\left(X(t) - \frac{1}{2}\right)\exp\left(\frac{1}{X(t)}\right) = \frac{C_0}{2K_D}\exp\left(\frac{2K_D}{C_0+K_D} - K_{ren}t\right) \triangleq g_2(t). \tag{2.18}$$

In the same way, we can make the following definition.

Definition 2.2. We define $G(t)$ as the solution of the following equation

$$\left(G(t) - \frac{1}{2}\right)e^{\frac{1}{G(t)}} = t. \tag{2.19}$$

It can be proved that, for any $t > 0$, there admits a unique principle real branch $G_0(t)$ satisfying the above equation (2.19). Using the definition of $G(t)$, we obtain the closed-form solution of model (2.1) from Eq.(2.18) given by

$$C(t) = 2K_D \times G_0(g_2(t)) - K_D,\ t \geq 0.$$

Replace C_0 with D/V_d, we can get

$$C(t) = 2K_D \times G_0\left(\frac{D}{2V_dK_D}\exp\left(\frac{2K_D}{D/V_d+K_D} - K_{ren}t\right)\right) - K_D,\ t \geq 0.$$

2.1.3. Case 3: $r > 1$

When the linear elimination rate is greater than the maximum elimination rate constant of Hill kinetics. Then Eq.(2.4) can be reduced to

$$\left(\frac{1}{C(t)} - \frac{\frac{2K_D}{r}}{C^2(t) + \frac{2K_D}{r}C(t) + K_D^2}\right) dC(t) = -K_{ren}dt. \tag{2.20}$$

The integration of Eq.(2.20) leads to

$$\ln C(t) - \frac{2}{p_2}\arctan\frac{C(t)+\frac{K_D}{r}}{\frac{K_D}{r}p_2} = \ln C_0 - \frac{2}{p_2}\arctan\frac{C_0+\frac{K_D}{r}}{\frac{K_D}{r}p_2} - K_{ren}t, \tag{2.21}$$

where $p_2 = \sqrt{r^2-1}$. Similarly, we need to further perform an equivalent transformation on (2.21) for expressing closed-form solution. By the property of arc-tangent function, (2.21) becomes

$$\ln C(t) - \frac{2}{p_2}\left(\frac{\pi}{2} - \arctan\frac{\frac{K_D}{r}p_2}{C(t)+\frac{K_D}{r}}\right) = \ln C_0 - \frac{2}{p_2}\left(\frac{\pi}{2} - \arctan\frac{\frac{K_D}{r}p_2}{C_0+\frac{K_D}{r}}\right) - K_{ren}t,$$

which is equivalent to

$$\ln C(t) + \frac{2}{p_2}\arctan\frac{\frac{K_D}{r}p_2}{C(t)+\frac{K_D}{r}} = \ln C_0 + \frac{2}{p_2}\arctan\frac{\frac{K_D}{r}p_2}{C_0+\frac{K_D}{r}} - K_{ren}t,$$

then we have

$$C(t)\exp\left(\frac{2}{p_2}\arctan\frac{\frac{K_D}{r}p_2}{C(t)+\frac{K_D}{r}}\right) = C_0\exp\left(\frac{2}{p_2}\arctan\frac{\frac{K_D}{r}p_2}{C_0+\frac{K_D}{r}} - K_{ren}t\right). \tag{2.22}$$

Note that

$$\lim_{r\to 1^+}\frac{2}{p_2}\arctan\frac{\frac{K_D}{r}p_2}{C(t)+\frac{K_D}{r}} = \frac{2K_D}{C(t)+K_D},$$

which is consistent to the reciprocal of variable substitution of Case 2 as $r \to 1^+$. We thus take

$$\frac{1}{X(t)} = \frac{2}{p_2}\arctan\frac{\frac{K_D}{r}p_2}{C(t)+\frac{K_D}{r}}.$$

Then we obtain

$$C(t) = \frac{2K_D}{r}\left(\frac{p_2}{2}\cot\frac{p_2}{2X(t)} - \frac{1}{2}\right). \tag{2.23}$$

Substituting (2.23) into (2.22) and then dividing both sides by $\frac{2K_D}{r}$, we get

$$\left(\frac{p_2}{2}\cot\frac{p_2}{2X(t)} - \frac{1}{2}\right)\exp\left(\frac{1}{X(t)}\right) = \frac{rC_0}{2K_D}\exp\left(\frac{2}{p_2}\arctan\frac{\frac{K_D}{r}p_2}{C_0+\frac{K_D}{r}} - K_{ren}t\right) \triangleq g_3(t). \tag{2.24}$$

We make the following definition.

Definition 2.3. Given a positive parameter p and the variable t, $H(t,p)$ is defined as the multi-valued solution satisfying the following equation

$$\left(\frac{p}{2}\cot\frac{p}{2H(t,p)}-\frac{1}{2}\right)e^{\frac{1}{H(t,p)}}=t. \tag{2.25}$$

It also can be proved that, for any positive t, there admits a unique principal real branch $H_0(t,p)$ satisfying the above equation (2.25). Using the definition of $H_0(t,p)$, we obtain the solution of model (2.1) from (2.24) :

$$C(t)=\frac{2K_D}{r}\left(\frac{p_2}{2}\cot\frac{p_2}{2H_0(g_3(t),p_2)}-\frac{1}{2}\right),\ t\geq 0.$$

Replace C_0 with D/V_d, we have

$$C(t)=\frac{2K_D}{r}\left(\frac{p_2}{2}\cot\frac{p_2}{2H_0\left(\frac{rD}{2K_DV_d}\exp\left(\frac{2}{p_2}\arctan\frac{K_Dp_2}{rD/V_d+K_D}-K_{ren}t\right),p_2\right)}-\frac{1}{2}\right),t\geq 0.$$

Remark 2.1. It follows from (2.11) that

$$\lim_{q\to+\infty}\left(F_0(t,q)-\frac{q-1}{2q}\right)\left(1+\frac{1}{qF_0(t,q)}\right)^q=\left(F_0(t)-\frac{1}{2}\right)e^{\frac{1}{F_0(t)}},$$

that is, as r tends to 1^- (p_1 tends to 0^+), the transcendental function $F_0(t,1/p_1)$ tends to $G_0(t)$ in Case 2. And from (2.25), we get

$$\lim_{p\to 0}\left(\frac{p}{2}\cot\frac{p}{2H_0(t,p)}-\frac{1}{2}\right)e^{\frac{1}{H_0(t,p)}}=\left(H_0(t)-\frac{1}{2}\right)e^{\frac{1}{H_0(t)}},$$

that is, as r tends to 1^+ (p_2 tends to 0^+), the transcendental function $H_0(t,p_2)$ also tends to $G_0(t)$ in Case 2. Therefore, it is interesting and significant that we find a centralized variable substitution to obtain these three transcendent functions, and establish the connection among them.

Up to now, through defining three transcendental functions $F(t,q), G(t), H(t,p)$, we have obtained the closed-form solutions of the drug concentration at time t of model (2.1) which are delineated three situations, respectively. By implementing these three new-developed transcendent functions F, G, H into mathematical software such as Matlab, we can generate the time-course of drug concentration with time t as shown in Figure 1, which allows pharmacist to easily calculate the drug concentration at any time.

2.2. Pharmacokinetic interpretations of C_{α^+} and C_{α^-}

For the new-developed parameters C_{α^+} and C_{α^-}, it is necessary to provide the pharmacokinetic meanings to better understand the closed-form solutions of drug concentration of model (2.1). In fact, let us consider two linear one-compartment models with different elimination rate constants as:

$$\frac{dC_1(t)}{dt}=-K_{ren}C_1(t), \tag{2.26}$$

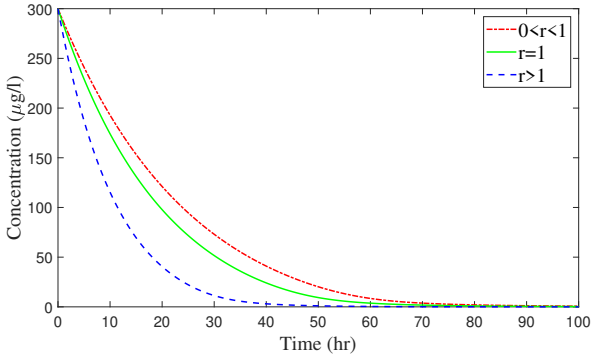

Figure 1. Time courses of drug concentration of model (2.1) for different three cases, where $V_m = 1\,\mu g/(L\cdot h)$; $K_D = 10\,\mu g/L$; $V_d = 1\,L$; $D = 300\,\mu g/L$ and $K_{ren} = 0.04\,h^{-1}$, $0.05\,h^{-1}$, $0.09\,h^{-1}$, respectively for $0 < r < 1$, $r = 1$, $r > 1$.

and

$$\frac{dC_2(t)}{dt} = -K_{H,max}(1 \pm \sqrt{1-r^2})C_2(t). \tag{2.27}$$

Then we have

$$\left.\frac{dC_1(t)}{dt}\right|_{C_1=C_{\alpha^\pm}} = \left.\frac{dC_2(t)}{dt}\right|_{C_2=K_D},$$

indicating that $C_{\alpha^\pm}$ is the concentration of model (2.26) that gives the same change rate of model (2.27) at concentration K_D. Here, $C_{\alpha^\pm}$ represents C_{α^+} or C_{α^-}, and corresponds to taking the positive or negative sign of the right side of Eq.(2.27), respectively.

3. Pharmacokinetic characterization

3.1. Elimination half-life $t_{1/2}$

The elimination half-life of a drug is one of the important indicators of pharmacokinetics, which is commonly used to decide the time that the next dose should be injected. It refers to the time required from the current drug concentration in plasma to half. As we all know, when the pharmacokinetic model only involves linear elimination, the elimination half-life is a constant [24]. In this subsection, we study the elimination half-life of model (2.1), where both first-order linear elimination pathway and nonlinear saturate Hill-type elimination ($n = 2$) pathway are involved.

Replacing C_0 by $C(t)$ and $C(t)$ by $C(t)/2$ in Eq.(2.6), Eq.(2.15) and Eq.(2.21), we obtain

$$t_{1/2} = \begin{cases} \dfrac{\ln 2}{K_{ren}} - \dfrac{1}{p_1 K_{ren}} \ln \dfrac{(C(t)+C_{\alpha^-})(C(t)+2C_{\alpha^+})}{(C(t)+2C_{\alpha^-})(C(t)+C_{\alpha^+})}, & 0 < r < 1, \\ \dfrac{\ln 2}{K_{ren}} - \dfrac{2K_D}{K_{ren}}\left[\dfrac{2}{C(t)+2K_D} - \dfrac{1}{C(t)+K_D}\right], & r = 1, \\ \dfrac{\ln 2}{K_{ren}} - \dfrac{2}{p_2 K_{ren}}\left(\arctan\dfrac{rC(t)+K_D}{p_2 K_D} - \arctan\dfrac{rC(t)+2K_D}{2p_2 K_D}\right), & r > 1. \end{cases}$$

It is obvious that elimination half-life of model (2.1) is concentration-dependent. Moreover, from the explicit formulaes, we can see that $t_{1/2}$ is the difference between two parts, and the first part is just elimination half-life of model (2.1) when the Hill elimination is absent, and the second part, which is concentration dependent, is largely influenced by the nonlinear elimination.

We concern how time-course concentration changes the elimination half-life, and which plays an important role for dosage design during clinical pharmacology. Let us consider the case of $0 < r < 1$. Taking derivative of $t_{1/2}$ with regard to $C(t)$, we have

$$t_{1/2}^{'}(C(t)) = \frac{(C_{\alpha^+} - C_{\alpha^-})(C^2(t) - 2C_{\alpha^+}C_{\alpha^-})}{p_1 K_{ren}(C(t) + 2C_{\alpha^+})(C(t) + C_{\alpha^-})(C(t) + C_{\alpha^+})(C(t) + 2C_{\alpha^-})}.$$

Setting $t_{1/2}^{'}(C(t)) = 0$, we find a unique stationary point

$$C^* = \sqrt{2C_{\alpha^+}C_{\alpha^-}} = \sqrt{2}K_D,$$

such that $t_{1/2}^{'}(C^*) = 0$. Moreover, we further find $t_{1/2}^{'}(C(t)) > 0$ if $C(t) > C^*$, and $t_{1/2}^{'}(C(t)) < 0$ if $C(t) < C^*$. Pharmacokinetically, when a dose D is intravenously injected, the drug concentration of model (2.1) will consistently decrease as time elapses. When time-course concentration $C(t)$ is higher than the critical concentration $C^* = \sqrt{2}K_D$, $t_{1/2}$ appears the decreasing trend as time elapses since concentration is decreasing, that is, less time is required from the current concentration to be reduced to a half. On the contrary, when concentration $C(t)$ is lower than the critical concentration $C^* = \sqrt{2}K_D$, $t_{1/2}$ conversely appears the increasing trend as time elapses. That is, more time is required for the drug concentration to be reduced to a half. As a result, $C^* = \sqrt{2}K_D$ is a critical value such that $t_{1/2}$ reaches the minimum value of model (2.1), which is an unexpected phenomena we observed. It is worthwhile to note that the actual trend of $t_{1/2}$ with time should depend on the value of initial drug concentration.

Moreover, if we consider the limit of $t_{1/2}$ as concentration goes to infinity or zero, we find

$$\lim_{C(t)\to+\infty} t_{1/2}(C(t)) = \lim_{C(t)\to 0^+} t_{1/2}(C(t)) = \frac{\ln 2}{K_{ren}},$$

which indicate the elimination half-life of model (2.1) is upper bounded by the one of the same model (2.1) if the nonlinear elimination is absent.

Note that the changes of $t_{1/2}(C(t))$ for the other two cases are the same to the case of $0 < r < 1$. Figure 2 shows the relationships among $t_{1/2}$, drug concentration and time. As shown in Figure 2(a), the drug concentration always decreases until to zero as time elapses, if the initial concentration is large enough (i.e., $C(0) = 11.1857 > C^* = 2.0365$), while $t_{1/2}$ decreases first, reaches to local minima, then increases again, and eventually tends to a limit fixed value which is the one of model (2.1) when the nonlinear Hill elimination is gotten rid of. If the initial concentration is less than C^*, and close to C^* (i.e., $C(0) = 1.9575 < C^*$), we find the elimination half-life increases from concave downward to concave upward as the concentration persistently decreases, showing a trend of first slow, then fast and then slow, and an inflection point of $t_{1/2}$ is existent (Figure 2(b)). If the initial concentration is small enough as shown in Figure 2(c) (i.e., $C(0) = 0.2237 \ll C^*$), the elimination half-life increases slowly as the concentration continuously decreases, and eventually tends

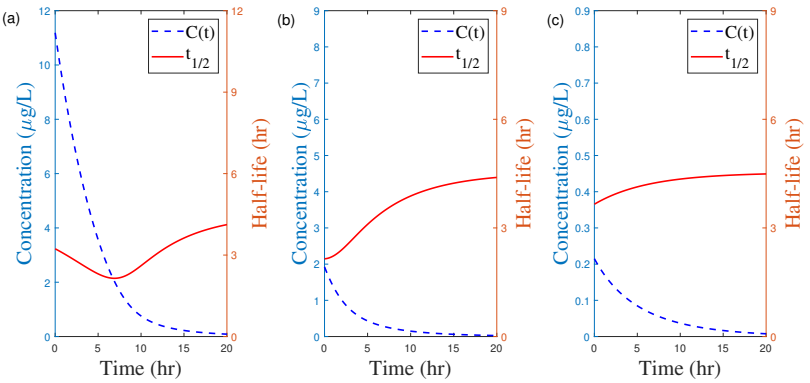

Figure 2. The relationship between elimination half-life ($t_{1/2}$) and concentration on the case of $0 < r < 1$. The parameter values are: $K_{ren} = 0.153/h, V_m = 0.5\mu g/(L \cdot h), K_D = 1.44\mu g/L, V_d = 1.788L$, (a)$D = 20\mu g$; (b)$D = 3.5\mu g$; (c)$D = 0.4\mu g$.

to a constant value which is the $t_{1/2}$ of the linear model by getting rid of the Hill elimination in model (2.1).

This phenomenon tells us that the change of elimination half-life is complex if a drug involves a simultaneous first-order and nonlinear Hill ($n = 2$) elimination. To maintain an effective therapeutic window, the used dosage has to be taken with cautions, and the precise measurement of concentration frequently is necessary.

3.2. Drug exposure AUC

The area under the drug concentration-time curve is another important surrogates that allows us to deserve investigation. In pharmacokinetics, it represents the total drug amount absorption into the system after a single dose administration and reflects the degree of absorption of the drug, and many pharmacokinetic indicators can be derived and estimated from AUC. For example, the clearance for the linear pharmacokinetic model is estimated as $CL = D/\text{AUC}$. In practice, estimate of AUC is based on drug concentration samplings which definitely exists certain deviation. From the compartment pharmacokinetic models, the explicit formula form the mathematical derivation is desirable, and our estimation method is more effective [16].

In order to obtain the drug exposure of the model (2.1), we deform the model (2.1) to

$$C(t)dt = -\frac{K_D^2 + C^2(t)}{K_{ren}C^2(t) + V_mC(t) + K_{ren}K_D^2}dC(t).$$

By the definition of AUC, we have

$$\begin{aligned}\text{AUC} = \int_0^\infty C(t)dt &= \int_0^\infty -\frac{K_D^2 + C^2(t)}{K_{ren}C^2(t) + V_mC(t) + K_{ren}K_D^2}dC(t) \\ &= -\frac{1}{K_{ren}}\int_0^\infty \left(1 - \frac{\frac{2K_D}{r}C(t)}{C^2(t) + \frac{2K_D}{r}C(t) + K_D^2}\right)dC(t).\end{aligned} \tag{3.1}$$

Since the term of $C^2(t)+\frac{2K_D}{r}C(t)+K_D^2$ is involved in denominator, we need consider three cases to obtain AUC.

(i) $0 < r < 1$
Using the same notation in Section 2, Eq.(3.1) can be written as

$$\mathrm{AUC} = -\frac{1}{K_{ren}} \int_0^\infty \left(1 - \frac{(C_{\alpha^+} + C_{\alpha^-})C(t)}{(C(t) + C_{\alpha^+})(C(t) + C_{\alpha^-})}\right) dC(t).$$

Through rigorous mathematical derivation and calculation, we obtain the explicit expression of total drug exposure as

$$\mathrm{AUC} = \frac{1}{K_{ren}} \left(\frac{D}{V_d} - \frac{C_{\alpha^+}}{\sqrt{1-r^2}} \ln\left(1 + \frac{D}{V_d C_{\alpha^+}}\right) + \frac{C_{\alpha^-}}{\sqrt{1-r^2}} \ln\left(1 + \frac{D}{V_d C_{\alpha^-}}\right)\right), \tag{3.2}$$

which is obviously nonlinearly dose dependent.
(ii) $r = 1$
In this case, we can get from Eq.(3.1)

$$\begin{aligned} \mathrm{AUC} &= -\frac{1}{K_{ren}} \int_0^\infty \left(1 - \frac{2K_D C(t)}{(C(t) + K_D)^2}\right) dC(t) \\ &= \frac{1}{K_{ren}} \left(\frac{D}{V_d} - 2K_D \ln\left(1 + \frac{D}{V_d K_D}\right) + \frac{2DK_D}{D + V_d K_D}\right), \end{aligned} \tag{3.3}$$

which is also nonlinearly dose dependent.
(iii) $r > 1$
Similar to above procedure, we directly have

$$\begin{aligned} \mathrm{AUC} =& -\frac{1}{K_{ren}} C(t)|_0^\infty \\ &+ \frac{K_D}{rK_{ren}} \int_0^\infty \frac{d(C^2(t) + \frac{2K_D}{r}C(t) + K_D^2)}{C^2(t) + \frac{2K_D}{r}C(t) + K_D^2} - \frac{2K_D^2}{r^2 K_{ren}} \int_0^\infty \frac{dC(t)}{C^2(t) + \frac{2K_D}{r}C(t) + K_D^2}, \\ =& \frac{D}{K_{ren}V_d} - \frac{K_D}{rK_{ren}} \ln\left(1 + \frac{D^2}{K_D^2 V_d^2} + \frac{2D}{rK_D V_d}\right) \\ &- \frac{2K_D}{rK_{ren}\sqrt{r^2-1}} \left(\arctan\frac{1}{\sqrt{r^2-1}} - \arctan\frac{rD + V_d K_D}{V_d K_D \sqrt{r^2-1}}\right), \end{aligned} \tag{3.4}$$

which is nonlinearly dose dependent as well.

Remark 3.1. In many nonlinear models, it is hard to find the explicit formula of AUC. We are fortunate to obtain AUC of this one-compartment model with simultaneous first-order and Hill-type elimination ($n = 2$). With these explicit formulas (Eqs.$(3.2 - 3.4)$), we are able to study the effect of dosage on the change of AUC.

Though the formulae of AUC are complicated, we find AUC is a monotonic increasing function with the dosage D as shown in Figure 3. That is, the drug exposure of model (2.1) monotonically increases with the increase of the single administrated dose D. Moreover, we find that there admits an inflection point $D^* = K_D V_d$, such that $\frac{d^2\mathrm{AUC}}{dD^2}|_{D=D^*} = 0$. Pharmacokinetically, AUC increases slowly with the dosage if $D < D^*$, and increases fast if the dose D is larger than the threshold D^*.

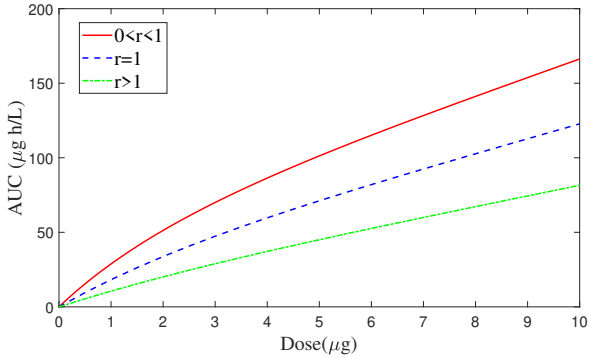

Figure 3. The relationship between AUC and dose D. The parameter values are: $V_m = 1\mu g/(L \cdot h)$, $K_D = 10\mu g/L$, $V_d = 1L$ and $K_{ren} = 0.04/h,\ 0.05/h,\ 0.09/h$ respectively for $0 < r < 1$, $r = 1$, $r > 1$.

Figure 4 shows the relationship among AUC, dissociation constant and the maximum change rate of Hill kinetics which helps us to better understand the influence of those non-linear parameters on change of AUC [14]. We can see that AUC increases as K_D increases, showing a positive correlation, while decreases as V_m increases, showing a negative correlation.

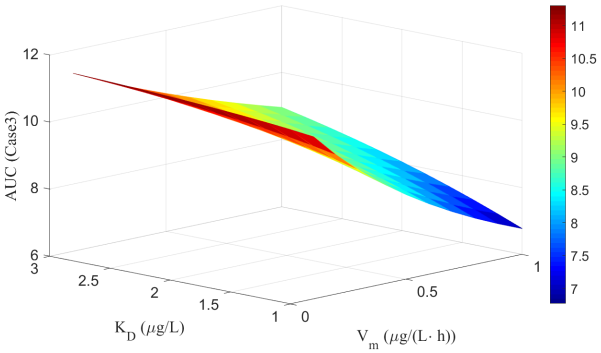

Figure 4. The relationship between AUC and nonlinear parameters K_D and V_m for $r > 1$. The parameter values are: $K_{ren} = 0.429/h, V_d = 1L, D = 20\mu g$.

3.3. Dominant role of elimination pathways

Because two elimination pathways are involved in model (2.1), it does not necessarily mean that their effects on drugs are equal or unchanged throughout the PK process. It is better to understand the dominant role of the two parallel elimination pathways behind the kinetic mechanism of the model. From model (2.1), it is clear that drug concentration eliminated from the compartment at time t are $K_{ren}C(t)$ and $\frac{V_m C^2(t)}{K_D^2+C^2(t)}$ through linear and Hill ($n = 2$) pathways respectively. Considering their difference, we have

$$K_{ren}C(t) - \frac{V_m C^2(t)}{K_D^2 + C^2(t)} = \frac{K_{ren}C(t)}{K_D^2 + C^2(t)} \left(C^2(t) - \frac{2K_D}{r} C(t) + K_D^2 \right). \tag{3.5}$$

Because of $\frac{K_{ren}C(t)}{K_D^2+C^2(t)} > 0$, the analysis of dominant role reduces to the sign of a quadratic function $f(C(t)) = C^2(t) - \frac{2K_D}{r}C(t) + K_D^2$.

If $0 < r < 1$, the function $f(C(t))$ can be decomposed into

$$C^2(t) - \frac{2K_D}{r}C(t) + K_D^2 = (C(t) - C_{\alpha^+})(C(t) - C_{\alpha^-}).$$

Therefore, the linear elimination will dominate for $0 < C(t) < C_{\alpha^-}$ or $C(t) > C_{\alpha^+}$ since $f(C(t)) > 0$, and the Hill elimination will dominate for $C_{\alpha^-} < C(t) < C_{\alpha^+}$ since $f(C(t)) < 0$. When $r \geq 1$, Eq.(3.5) must be non-negative, so the linear elimination is always dominant. The dominance of two different elimination pathways is plotted in Figure 5, which jointly depends on the level of drug concentration C_{α^+} and C_{α^-} as r is different.

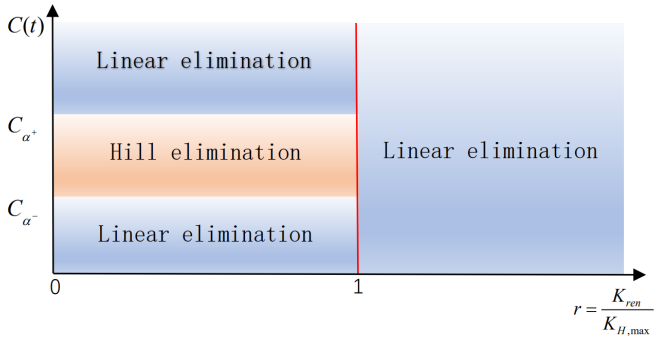

Figure 5. The dominant role of two parallel, linear elimination and Hill-type elimination ($n = 2$) of model (2.1).

In the model (2.1), both renal elimination and internalization are included. The clinical understanding believes that the elimination of G-CSF through internalization is the main elimination mechanism of homeostasis [6]. While, from the mathematical study, we find the nonlinear internalization dominates only for the conditions that the concentration level is between C_{α^+} and C_{α^-} when the maximum elimination rate of Hill-type kinetic is larger than the linear elimination rate constant.

4. Case study

G-CSF drugs are mainly used to prevent and treat the symptoms of neutropenia after chemotherapy, which are important adjuvant therapy drugs for cancer patients [7]. The filgrastim, a commercially available form of G-CSF on the market, is widely applicable in the treatment of various diseases, which is used as an auxiliary agent to promote the production of neutrophils in treatment [17], during the process of internalization proposed as 2:1 [15]. The binding ratio between G-CSF molecules to receptors in the human body is 2:1. Accordingly, model (2.1) is applicable to G-CSF drugs, and the corresponding model parameters are found as [7]: $K_{ren} = 0.429/h, V_d = 1.788L, V_m = 0.5593\,\mu g/(L \cdot h), K_D = 1.44\mu g/L$. Within these paraments, we calculate $r = 2.2091 > 1$. Based on our previous derivation, we can directly write down explicit expression of drug concentration over time

through the defined transcendental function as:

$$C(t) = 1.3037 \times \left(0.9849 \cot \frac{0.9849}{H_0\left(0.429D \exp\left(1.0153 \arctan \frac{2.8365}{1.2355D+1.44} - 0.429t\right), 1.9698\right)} - \frac{1}{2} \right).$$

The corresponding pharmacokinetic surrogates of elimination of half-life and total drug exposure have also their explicit expressions as:

$$t_{1/2} = 1.6157 - 2.3667 \times \left(\arctan \frac{2.2091C(t)+1.44}{2.8365} - \arctan \frac{2.2091C(t)+2.88}{5.673} \right),$$

$$\begin{aligned} \mathrm{AUC} =& \frac{D}{0.7671} - 1.5195 \times \ln\left(1 + \frac{D^2}{6.6292} + \frac{D}{0.3516}\right) \\ & - 1.5428 \times \left(\arctan 0.5077 - \arctan \frac{2.2091D + 2.5747}{5.6878} \right). \end{aligned}$$

We can see that $t_{1/2}$ is concentration-dependent, and the concentration can be calculated the well-defined mathematical function H_0, which can be similarly implemented into mathematical software as Lambert W function.

Given the initial dose D, we can also quantitatively calculate the values of the elimination half-life and AUC which are shown in Table 1.

Table 1. The value of biomarkers given dose D as $r > 1$. The parameter values are: $K_{ren} = 0.429/h, V_d = 1.788L, V_m = 0.5593\,\mu g/(L \cdot h), K_D = 1.44\mu g/L$ [7].

Dose (μg)	0	10	20	50	100	200	300
$C(t)$ ($\mu g/L$)	0	5.5928	11.1857	27.9642	55.9284	111.8568	167.7852
$t_{1/2}$ ($/h$)	1.6157	1.2520	1.3915	1.5147	1.5633	1.5890	1.5978
AUC ($\mu g \cdot h/L$)	0	9.9014	21.1860	57.7265	120.8760	249.1743	378.3232

It is showed that when the dosage of G-CSF increases, the elimination half-life decreases first, then increases, and eventually tends to a constant value as $D \to \infty$:

$$\lim_{C(t)\to\infty} t_{1/2} = \lim_{C(t)\to 0} t_{1/2} = \frac{\ln 2}{K_{ren}} = 1.6157(h).$$

While AUC monotonically increases with the increased dosages.

5. Discussion and conclusion

In this paper, we have studied the closed-form solutions, including time-course of drug concentration, elimination half-life, total drug exposure and dominate elimination pathways of a one-compartment pharmacokinetic model with simultaneous first-order and Hill-type elimination ($n = 2$) for the case of intravenous bolus administration. This work is motivated by Lambert W function [5, 21] and recent well-defined transcedent X function [23, 24].

By defining three transcendental functions F, G, H, we are able to accurately express the closed-form solution of time-course of the drug concentration $C(t)$ of the model. We have to mention that the three function F, G, H are not arbitrarily defined, a consistent substitution is found to connect the relationship for three different cases. Moreover, not all closed-form solutions of differential equations can be solved by the method of self-defined functions. We are lucky here to acquire

the closed-form solution of such a nonlinear differential equation. In the future, we can further investigate mathematical properties of these three functions and implement into pharmacological professional software (e.g. NONMEN) or mathematical software (e.g., Matlab), similar to Lambert W function, which allows pharmacist to easily calculate the drug concentration for such kinds of drugs. We think the closed-form solutions are applied more widely and conveniently than the numerical solutions derived from pharmacokinetic models, and the calculation precision is much high as well.

In addition, according to the specific closed-form solution expression, it is possible to quantitatively analyze the change of the model parameters on the trend of blood drug concentration with time. It is impossible to do numerical simulation alone, because the numerical solution is a series of discrete values. The solution obtained from the algebraic equation is superior to the result obtained from the differential equation. And small changes in drug concentration have important effects on pharmacokinetics: too low drug concentration will cause ineffectiveness, and too high drug concentration will cause toxicity. Besides, drug modelers can use closed-form solutions to fit drug data and obtain pharmacokinetic parameters to understand the process of drug absorption, distribution, metabolism, and excretion in the body. In pharmacokinetics, closed-form solutions are easily amenable to further mathematical operations, and through the closed-form solution, the properties of the solution, or the performance of the physical phenomenon can be more qualitatively analyzed.

We also have obtained the analytical expression of elimination half-life ($t_{1/2}$) of this model, which is concentration dependent. Moreover, we can intuitively observe that as the time elapses, concentration decreases, while the elimination half-life curve first decreases, then increases, and finally reaches a stable trend. The result shows the unexpected trend comparing those existing the elimination half-life in the literature. Our finding in this study precisely delineates the behavior of $t_{1/2}$, and provides guiding suggestions for practical applications. By developing the explicit expressions of pharmacokinetic surrogates, such as elimination half-life and AUC parameters, it is beneficial to improve the optimal design of drug regimens and reduce the risk of side effects.

For drugs exhibiting simultaneous first-order and Michaes-Menten elimination, Wu et al. have developed the closed-form solution of drug concentration through introducing a transcendent X function [24]. We are here to extend the nonlinear Michaes-Menten elimination to Hill-type elimination with $n = 2$, which increases the difficulty of the problem solving, where three transcendent functions are needed to fully characterize the mathematical solutions. Though Hill coefficient ($n = 2$) is studied here since stoichiometric ratio of G-CSF drug molecules binding to the receptor of neutrophils is 1:2 [7], for most of actual drugs, it is unlikely that the receptor and the drug molecule will be combined in exact form of 1:2. Therefore, Hill coefficient n should between 1 and 2, which leads to the drug concentration between the resulting concentrations induced by $n = 1$ and $n = 2$. For instance, regarding the data fitting between butyl-FLIP and Bacillus cereus phosphatidylinositol-specific phospholipase C (enzyme), it is found that the Hill coefficient is 1.2-1.5 [4]. With the established result if $n = 1$ [24], this allows us to compare and estimate the time course of drug concentration if Hill coefficient $1 < n < 2$. Figure 6 shows the concentrations when $n = 1$ and $n = 2$, where the shade range of drug concentration represents the concentration when n is between 1 and 2. It is interesting to find

that, there is a critical concentration C^{**}. When drug concentration is larger than the critical value C^{**}, the upper bound of actual drug concentration is controlled by model (2.1) with $n = 2$, and lower bounded by (1.2) with $n = 1$. As time elapses, when drug concentration is lower than the critical value C^{**}, the boundedness is turned to be contrary to the former case. Moreover, as the concentration continuously decreases, the discrepancy becomes larger and larger.

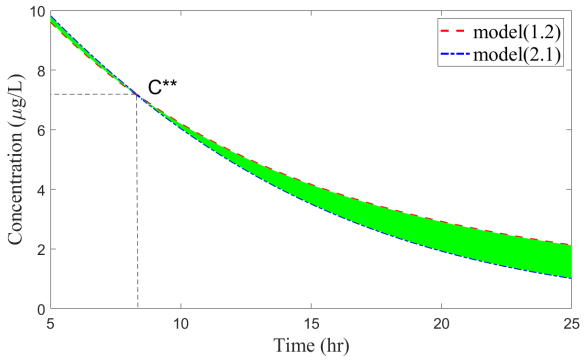

Figure 6. The range of drug concentration induced by model (1.2) and model (2.1)$(0 < r < 1)$ with $K_{ren} = 0.04/h, V_m = 1\mu g/(L \cdot h), K_D = 10\mu g/L, V_d = 1L, D = 20\mu g$.

Another important finding in this study is the elimination half-life ($t_{1/2}$) which is a key pharmacokinetic surrogate during clinical pharmacology. If we consider the relationship between $t_{1/2}$ and dose amount (D) for the studied model, it is found that $t_{1/2}$ of model (2.1) first decreases, then increases, and finally tends to a limit value as dose increases. This tendency of $t_{1/2}$ significantly differs from the drugs exhibiting simultaneous first-order and Michaelis-Menten elimination, as shown in Figure 7, where the latter continuously increases with dose amount D and then tends a limit.

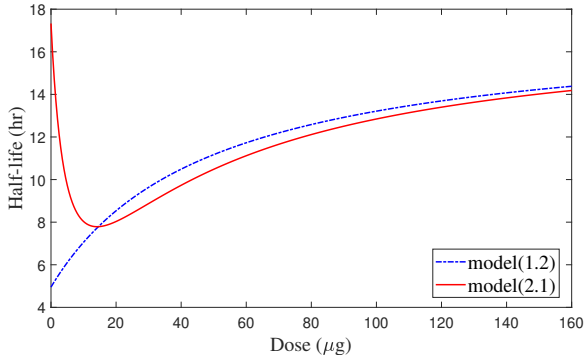

Figure 7. The relationship between $t_{1/2}$ and dose amount D of model (1.2) and model (2.1)$(0 < r < 1)$ with $K_{ren} = 0.04/h, V_m = 1\mu g/(L \cdot h), K_D = 10\mu g/L, V_d = 1L,\ D = 20\mu g$.

Since two elimination pathways are involved in model (2.1), it is always a good value to determine which elimination pathway dominates the other. The resultant conclusions are beneficial for precisely performing data fitting, simplifying the model structure and so on. For model (2.1), it is found that there exist three critical values

$(r, C_{\alpha+}$ and $C_{\alpha-})$ to jointly determine the dominance of elimination pathways. It is worthwhile to note that the nonlinear Hill-type elimination $(n = 2)$ pathway dominates only for the conditions: $0 < r < 1$ and $C_{\alpha-} < C(t) < C_{\alpha+}$. In order to better illustrate our theoretical results, we have used G-CSF drugs for case study.

The mathematical solutions of this work are definitely helpful in clinical trial, which can be used to improve the rational use of drugs, and eventually enhance the drug efficacy of disease treatment. However, the drugs suitable for the model are limited, more drugs should be found to enhance the credit of the work. Moreover, this work only limits to the case of intraveneous bolus administration, and how this approach is applicable to the case of multiple-dose administrations is not studied yet, leaving it for our future investigation.

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Appendix: Principal real branch of transcendental functions

Definition 2.1 can be written as the following equation:

$$x = \left(f(x) - \frac{q-1}{2q}\right)\left(1 + \frac{1}{qf(x)}\right)^q.$$

Then considering the derivative of $f(x)$ with respect to x, when $f(x) > \frac{q-1}{2q}$, $f(x)$ increases monotonically with respect to x. Therefore, there is a unique solution corresponding to any given equation whose left side is positive.

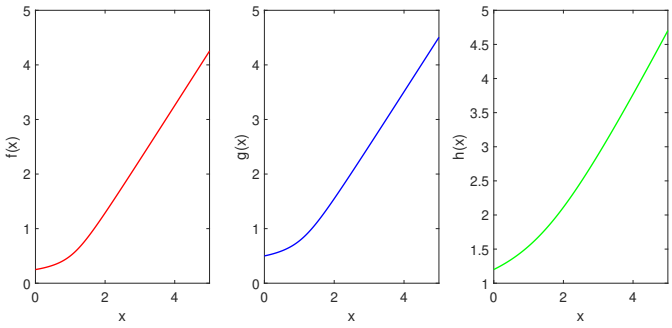

Figure 8. Three real branch images corresponding to defined functions. The abscissa is the independent variable x, and the ordinate is the definition function. It can be observed that in the first quadrant, $f(x), g(x), h(x)$ are all monotonically increasing functions, with good properties in the first quadrant. The parameter values are the same as those in Figure 1.

For G function in Definition 2.2, we can similarly define the function about $g(x)$: $x = (g(x) - \frac{1}{2})\exp(\frac{1}{g(x)})$. When $g(x) > \frac{1}{2}$, x is positive. And it can be proved that when $x > 0$, $g'(x) > 0$, that is, $g(x)$ increases monotonically.

In the same way, as $h(x) > \frac{p}{2\arctan p}$, $x > 0$. When $x > 0$, $h'(x) > 0$, that is, $h(x)$ increases monotonically.

Therefore, the three transcendental functions defined in this paper are well defined in the first quadrant. At the same time, we also draw three real branch images of transcendental functions in Figure 8.

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