Journal of Pharmacokinetics and Pharmacodynamics (2018) 45:693–705
https://doi.org/10.1007/s10928-018-9599-4

ORIGINAL PAPER

Mathematical analysis and drug exposure evaluation of pharmacokinetic models with endogenous production and simultaneous first-order and Michaelis–Menten elimination: the case of single dose

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Received: 8 February 2018 / Accepted: 30 June 2018 / Published online: 9 July 2018

Abstract
Drugs with an additional endogenous source often exhibit simultaneous first-order and Michaelis–Menten elimination and are becoming quite common in pharmacokinetic modeling. In this paper, we investigate the case of single dose intravenous bolus administration for the one-compartment model. Relying on a formerly introduced transcendent function, we were able to analytically express the concentration time course of this model and provide the pharmacokinetic interpretation of its components. Using the concept of the corrected concentration, the mathematical expressions for the partial and total areas under the concentration time curve (AUC) were also given. The impact on the corrected concentration and AUC is discussed as well as the relative contribution of the exogenous part in presence of endogenous production. The present findings theoretically elucidate several pharmacokinetic issues for the considered drug compounds and provide guidance for the rational estimation of their pharmacokinetic parameters.

Keywords Pharmacokinetic model · *X* function · Endogenous production · Simultaneous first-order and Michaelis–Menten elimination · Area under the concentration time curve (AUC)

Introduction

In clinical pharmacology, quantitative pharmacokinetic modeling has been proved to effectively link the administered drug amount and the induced therapeutic outcome by describing the complete concentration time course for the desired and/or undesired effect [1, 2]. With the increasing complexity involved in these models, their quantitative analysis and interpretation become determinant for the prediction quality of direct observations and other pharmacological properties. Historically, linear pharmacokinetic compartment models have greatly contributed to the explanation and prediction of many pharmacological phenomena. However, many of new drug compounds, such as hormones or monoclonal antibodies, can have more complex kinetics [3–6]. A typical example is the recombinant human granulocyte colony-stimulating factor (rhG-CSF), which is molecularly similar to endogenous produced granulocyte colony-stimulating factor (G-CSF) and generally used as a stimulant agent to mitigate the toxic effect of chemical drugs on white blood cells during chemotherapy. G-CSF functions by promoting the generation, differentiation and maturation of neutrophils, a major part of white blood cells that play a crucial role in the immune system [3, 4, 6]. The elimination of G-CSF not only undergoes the traditional renal pathway, generally of linear type, but also combines a saturate internalization process, in which the G-CSF molecules bind to neutrophil receptors and are transformed into substances readily to be eliminated. Other

Electronic supplementary material The online version of this article (doi:https://doi.org/10.1007/s10928-018-9599-4) contains supplementary material, which is available to authorized users.

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blood stimulants, such as erythropoietin (EPO) and thrombopoietin (TPO) show similar PK properties [7–9].

In order to predict plasma concentration time courses of these drugs, compartment models with nonlinear elimination is a reasonable choice. The general approach is to model the saturate drug elimination with Michaelis–Menten kinetics [10–12]. However, refined models using parallel elimination mechanisms, with a first-order kinetics characterizing the renal elimination pathway and a Michaelis–Menten kinetics for the saturate metabolism pathway, were proposed as well [6, 9, 13]. Many efforts are solely based on numerical solutions, and are limited to pointing out the existence of an implicit function for the solution [14, 15]. However, it would be helpful to concretely find a closed form solution, which allows to explore the underlying mechanisms and easily extract various relevant pharmacological properties. It has become a challenge to search for analytical solutions of these complex models. For instance, in the case of compartment models with Michaelis–Menten elimination alone, *Lambert W* function proved to be the sought-for element able to express their solutions under a closed form [16, 17]. Specifically, the time course of drug plasma concentration $C_m(t)$ after a single intravenous (IV) bolus dose administration D can be expressed as

$$C_m(t) = K_m \cdot W\left(\frac{D}{K_m V_d}\exp\left(\frac{D - V_{max}t}{V_d K_m}\right)\right), \tag{1}$$

where "W" represents *Lambert W* function [18]; V_{max} is the maximum velocity of Michaelis–Menten kinetics in unit of amount/time, and K_m, known as the Michaelis–Menten constant, is the concentration value at which the rate of change of Michaelis–Menten kinetics reaches half of V_{max}; V_d is the body's apparent volume of distribution. Recently, motivated by *Lambert W* function, we introduced the X function and obtained the corresponding closed form solution of $C(t)$ for drugs modeled with a one-compartment structure and having simultaneous first-order (k_{el}) and Michaelis–Menten elimination (K_m and V_{max}) [19]. For the case of a single dose D, $C(t)$ is therefore expressed as

$$C(t) = C_\beta \cdot X\left(\left(\frac{D}{C_\beta V_d}\right)^{p_1}\left(\frac{D}{C_\beta V_d}+1\right)^{p_2}\exp(-t), p_1, p_2\right), \tag{2}$$

where

$$p_1 = \frac{K_m V_d}{k_{el} V_d K_m + V_{max}}, \quad p_2 = \frac{V_{max}}{k_{el}(k_{el} V_d K_m + V_{max})}, \quad C_\beta = K_m + \frac{V_{max}}{k_{el} V_d}. \tag{3}$$

Note that the symbol C_β used here replaces β that was formally used in [19] to make the content easier to understand.

Apart from their simultaneous linear and saturate elimination properties, compounds such as hormones or monoclonal antibodies can have more complex properties due to their endogenous production. While endogenous production has been accounted for in compartment PK models, it only remained at the level of parameters fitting of plasma concentration data [3, 20]. The systematic analysis of these models is still absent, either for closed form solutions, or for model-based estimation of PK parameters, particularly for the area under concentration time curve (AUC). Even though in the linear case, where several algebraic formulas have been established and used to estimate such parameters in practice, the rationale behind these estimations is still lacking when endogenous production is present. It is therefore important to understand how the endogenous production can impact the disposition of these molecules. Consequently, the mathematical validity of current AUC estimation should be revisited. This will be the focus of the present work.

The paper is organized as follows: the relationship between *Lambert W* and X functions is clarified in the next section, followed by the closed form solution for the model of single IV bolus administration and the PK interpretation of newly introduced entities. The analytical formulas for the estimation of AUC in the case of constant endogenous production using the corrected concentration and the impact of endogenous production on the corrected concentration and AUC are then studied. Finally, the limits and perspectives of the current PK models, either from a pharmacological or a bio-mathematical standpoint are discussed in the last section.

Lambert W and *X* functions

Lambert W function is a transcendental function widely used for the closed form solutions of various differential equations describing exponential phenomena, particularly for delay differential equations [21, 22]. In pharmacokinetics, it has been used to express the closed form solutions of drug plasma concentration time courses when only Michaelis–Menten elimination is involved [16, 17]. In order to analytically express solutions of one-compartment PK models of simultaneous first-order and Michaelis–Menten elimination with intravenous bolus administration, we have introduced the X function as a natural extension of *Lambert W* function [19]. As shown below, we can see how these two functions are related.

Definition 1 [18] The *Lambert W* function is the multi-valued inverse of the function $f(z) = z\exp(z)$, i.e.,

$$W(z)\exp(W(z)) = z \tag{4}$$

where z is a complex number.

Definition 2 [19] The X function is the multivalued inverse of the function $f(z) = z^p(z+1)^q$, $p, q \in \mathbb{R}^+$, i.e.,

$$(X(z,p,q))^p (X(z,p,q)+1)^q = z \tag{5}$$

where z is a complex number.

The PK model having simultaneous first-order and Michaelis–Menten elimination is an extension of the model involving only a Michaelis–Menten elimination. Hence the X function can be considered an extension to the *Lambert W* function. However, this extension is neither simple nor direct. In fact, instead of being a particular case of the X function, the *Lambert W* function can only be obtained through a limit process of the former.

From Eq. (2), we have

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

which can be further rearranged into

$$(C(t))^{p_1}\left(\frac{C(t)}{C_\beta}+1\right)^{p_2} = \left(\frac{D}{V_d}\right)^{p_1}\left(\frac{D}{C_\beta V_d}+1\right)^{p_2}\exp(-t), \tag{6}$$

where p_1, p_2 and C_β are given in Eq. (3). Using the dependence of the models on these parameters, we have

$$\lim_{k_{el}\to 0} C(t) = C_m(t).$$

When taking $k_{el} \to 0$, it can be proved that

$$\lim_{k_{el}\to 0} p_1 = \frac{K_m V_d}{V_{max}}, \quad \lim_{k_{el}\to 0} \frac{p_2 C(t)}{C_\beta} = \frac{V_d C_m(t)}{V_{max}}$$

$$\text{and} \quad \lim_{k_{el}\to 0}\left(\frac{C(t)}{C_\beta}+1\right)^{\frac{C_\beta}{C(t)}} = e$$

where e is the Euler's number.

Using the above relationships, we have

$$\begin{aligned}\lim_{k_{el}\to 0}\left(\frac{C(t)}{C_\beta}+1\right)^{p_2} &= \lim_{k_{el}\to 0}\left[\left(\frac{C(t)}{C_\beta}+1\right)^{\frac{C_\beta}{C(t)}}\right]^{\frac{p_2 C(t)}{C_\beta}} \\ &= \lim_{k_{el}\to 0}\left[\left(\frac{C(t)}{C_\beta}+1\right)^{\frac{C_\beta}{C(t)}}\right]^{\lim_{k_{el}\to 0}\frac{p_2 C(t)}{C_\beta}} \\ &= \exp\left(\frac{V_d C_m(t)}{V_{max}}\right).\end{aligned}$$

Moreover, we have

$$\lim_{k_{el}\to 0}\left(\frac{D}{C_\beta V_d}+1\right)^{p_2} = \exp\left(\frac{D}{V_{max}}\right).$$

For both sides of Eq. (6), we take the limit as $k_{el} \to 0$, then

$$(C_m(t))^{\frac{V_d K_m}{V_{max}}}\exp\left(\frac{V_d C_m(t)}{V_{max}}\right) = \left(\frac{D}{V_d}\right)^{\frac{V_d K_m}{V_{max}}}\exp\left(\frac{D}{V_{max}}\right)\exp(-t).$$

Simplifying the above equation, we have

$$\frac{C_m(t)}{K_m}\exp\left(\frac{C_m(t)}{K_m}\right) = \frac{D}{V_d K_m}\exp\left(\frac{D - V_{max}t}{V_d K_m}\right). \tag{7}$$

If we use *Lambert W* function to express the solution of Eq. (7), it will correspond to the one given by Eq. (1).

Following the definitions of *Lambert W* and X functions, the relation between these two functions can be summarized as:

Theorem 1 *Write* $z = \frac{D}{V_d K_m}\exp\left(\frac{D - V_{max}t}{V_d K_m}\right)$, *then Lambert W function is a limit of X functions as* $k_{el} \to 0$, *which can be expressed in the following limit form*:

$$\lim_{k_{el}\to 0}\frac{C_\beta}{K_m}\cdot X\left(\left(\frac{D}{C_\beta V_d}\right)^{p_1}\left(\frac{D}{C_\beta V_d}+1\right)^{p_2}\exp\left(-\frac{D}{V_{max}}\right)\left(\frac{K_m V_d}{D}z\right)^{\frac{V_d K_m}{V_{max}}}, p_1, p_2\right) = W(z).$$

Remark 1 $K_m W\left(\frac{D}{K_m V_d}\exp\left(\frac{D - V_{max}t}{V_d K_m}\right)\right)$ is the solution of the PK model with the Michaelis–Menten elimination alone (Eq. 1), and $C_\beta X\left(\left(\frac{D}{C_\beta V_d}\right)^{p_1}\left(\frac{D}{C_\beta V_d}+1\right)^{p_2}\exp(-t), p_1, p_2\right)$ is the solution of the model with simultaneous first-order and Michaelis–Menten elimination (Eq. 2). The former is the limit of the latter when the linear elimination tends to fade.

As for the case of *Lambert W* function, the X function has multiple real branches. However there is only one real branch in the first quadrant, which we need to express the analytical solutions of PK models. In the rest of the paper, we will use the symbol X to denote this unique real branch. A brief discussion of this topic is given in the Appendix 4.

It is practical to have the X function implemented into mathematical software such as *Matlab*, which is what we have done here to compute the drug plasma concentration of the discussed PK model.

Pharmacokinetic model of endogenous production and simultaneous first-order and Michaelis–Menten elimination

The X function was introduced to express the closed form solution of a PK model with simultaneous first-order and Michaelis–Menten elimination in a previous work [19]. For the more general PK model considered in the current paper, we will show how the X function can serve its closed form solution.

The description of the PK model

As mentioned in the introduction, it is not rare that drug substances (given exogenously) are also endogenously produced, and eliminated through parallel pathways [3, 23, 24]. Indeed, their elimination can involve a first-order process generally through kidneys, in a proportional way to the drug plasma concentration, accompanied by a non-linear elimination of Michaelis–Menten kinetics, likely attributed to drug-mediated metabolism or internalization. It is usually assumed that endogenous production occurs at a constant rate, denoted by r_{prod}, if circadian effect can be ignored [3]. The following differential equation is used to describe the PK model considered here:

$$\frac{d}{dt}C(t) = r_{prod} - k_{el}\,C(t) - \frac{1}{V_d}\frac{V_{max}C(t)}{K_m + C(t)}, \quad t > 0, \tag{8}$$

with initial conditions

$$C(0^+) = C_{hs} + D/V_d \overset{def}{=} C_0, \ at\ t = 0^+, \tag{9}$$

where k_{el}, V_{max}, K_m, V_d, D are as previously defined, and C_{hs} having the form

$$C_{hs} = \frac{1}{2}\left(\frac{r_{prod}}{k_{el}} - C_\beta + \sqrt{\left(\frac{r_{prod}}{k_{el}} - C_\beta\right)^2 + 4\frac{r_{prod}}{k_{el}}K_m}\right) \tag{10}$$

is the baseline concentration calculated from the system at homeostasis. The well-posedness of the model (8) is provided in Appendix 1.

It is worth noting that the baseline concentration can be estimated prior to drug administration [25–27]. We also have to mention that if $r_{prod} = 0$, the current model goes back to the model with simultaneous first-order and Michaelis–Menten elimination studied in [19]. Moreover, without loss of generality and for the rest of the paper, the concentration value immediately after dose administration is referred to as the concentration at time zero (Eq. 9).

Closed form solution of $C(t)$

The closed form solution of the concentration time course of the considered model (Eqs. 8–9) can be expressed as follows.

Theorem 2 *For an intravenous bolus dose D, the closed form solution of Eqs. (8)–(9) is*

$$C(t) = C_{hs} + \left(C_{hs} + C_\beta^{en}\right)\cdot X\left(\left(\frac{D/V_d}{C_{hs} + C_\beta^{en}}\right)^p\left(\frac{D/V_d}{C_{hs} + C_\beta^{en}} + 1\right)^q e^{-t}, p, q\right), \ t > 0 \tag{11}$$

where

$$p = \frac{1}{k_{el}}\frac{C_{hs} + K_m}{C_{hs} + C_\beta^{en}}, \quad q = \frac{1}{k_{el}}\frac{C_\beta^{en} - K_m}{C_{hs} + C_\beta^{en}}, \quad C_\beta^{en} = C_{hs} - \frac{r_{prod}}{k_{el}} + C_\beta. \tag{12}$$

Proof Since a single dose is added to the system, we have $C(t) > C_{hs}$, thus Eq. (8) can be transformed into

$$\left(\frac{p}{C(t) - C_{hs}} + \frac{q}{C(t) + C_\beta^{en}}\right)dC(t) = -\,dt, \tag{13}$$

with the notations p, q and C_β^{en} as defined in Eq. (12). It can be proved that p, q and C_β^{en} are positive, and $C_\beta^{en} > K_m$ (see Appendix 2). Moreover, $p + q = 1/k_{el}$ is the average time during which all drug compounds are assumed to be eliminated through the linear elimination pathway alone; p and q represent the partition of the time $1/k_{el}$ modulated by $\frac{C_{hs}+K_m}{C_{hs}+C_\beta^{en}}$ and $\frac{C_\beta^{en}-K_m}{C_{hs}+C_\beta^{en}}$, respectively.

Integrating Eq. (13) from 0^+ to t leads to

$$p\ln(C(t) - C_{hs}) + q\ln\left(C(t) + C_\beta^{en}\right) = p\ln(C_0 - C_{hs}) + q\ln\left(C_0 + C_\beta^{en}\right) - t \tag{14}$$

since $C(t) > C_{hs}$.

Equation (14) can be rearranged as

$$(C(t) - C_{hs})^p\left(C(t) + C_\beta^{en}\right)^q = (C_0 - C_{hs})^p\left(C_0 + C_\beta^{en}\right)^q e^{-t}. \tag{15}$$

Dividing both sides of Eq. (15) by $(C_{hs} + C_\beta^{en})^{p+q}$ gives rise to

$$\left(\frac{C(t)-C_{hs}}{C_{hs}+C_\beta^{en}}\right)^p\left(\frac{C(t)-C_{hs}}{C_{hs}+C_\beta^{en}}+1\right)^q = \left(\frac{C_0-C_{hs}}{C_{hs}+C_\beta^{en}}\right)^p\left(\frac{C_0+C_\beta^{en}}{C_{hs}+C_\beta^{en}}\right)^q e^{-t}.$$

In terms of X function, we have

$$\frac{C(t)-C_{hs}}{C_{hs}+C_\beta^{en}} = X\left(\left(\frac{C_0-C_{hs}}{C_{hs}+C_\beta^{en}}\right)^p\left(\frac{C_0+C_\beta^{en}}{C_{hs}+C_\beta^{en}}\right)^q e^{-t}, p, q\right), \quad t>0. \tag{16}$$

Substituting C_0 with $C_{hs}+D/V_d$ in Eq. (16), the closed form solution of $C(t)$ shown in Eq. (11) is obtained. □

Pharmacokinetic interpretation of C_β^{en}

C_β^{en} can be rewritten as

$$C_\beta^{en} = C_{hs} - C_{L,hs} + C_\beta \tag{17}$$

where C_{hs} is the baseline concentration given in Eq. (10); $C_{L,hs} = r_{prod}/k_{el}$ is the baseline concentration of Eq. (8) if Michaelis–Menten kinetics is absent; and $C_\beta = \frac{V_{max}}{k_{el}V_d} + K_m$ is a parameter defined for the model with no endogenous production in our previous study [19]. Specifically, C_β is the concentration at which a linear PK model with an elimination coefficient k_{el} can have the same rate of change as produced in another linear model at concentration K_m, which has an elimination rate constant $k_{el} + \frac{V_{max}}{K_m V_d}$.

In fact, C_β^{en} is the extension of C_β for the PK model that takes into account the endogenous production. Indeed, let us consider two linear models:

$$\frac{dC_1(t)}{dt} = k_{el}C_{hs} - k_{el}C_1(t) \tag{18}$$

and

$$\frac{dC_2(t)}{dt} = k_{el}C_{L,hs} - \left(k_{el}+\frac{V_{max}}{K_m V_d}\right)C_2(t). \tag{19}$$

Then, C_β^{en} is the concentration value of $C_1(t)$ in Eq. (18) that gives the same change rate of concentration for $C_2(t) = K_m$ in Eq. (19), i.e.,

$$\left.\frac{dC_1(t)}{dt}\right|_{C_1(t)=C_\beta^{en}} = \left.\frac{dC_2(t)}{dt}\right|_{C_2(t)=K_m}. \tag{20}$$

In short, C_β^{en} is the concentration of a linear model having endogenous production rate $k_{el}C_{hs}$ and elimination coefficient k_{el}, that gives the same change rate of concentration for another linear model having endogenous production rate $k_{el}C_{L,hs}$ and elimination coefficient $k_{el} + \frac{V_{max}}{K_m V_d}$ at concentration K_m. If the drug has no endogenous production, we then have $C_{hs} = C_{L,hs} = 0$. In this case, $C_\beta^{en} = C_\beta$.

We can also show that p and q generalize p_1 and p_2 given in [19], respectively.

Area under the curve (AUC)

As there is a baseline concentration, the validity of a direct calculation of AUC from the observed concentrations using the trapezoidal rule has to be justified and adapted to this context. For drug compounds that are also endogenously produced, the use of the corrected concentrations has been recommended for the calculation of PK parameters. This corrected concentration, $C(t) - C_{hs}$, which is obtained by subtracting the baseline concentration from the observed concentration, is actually used to recover the exogenous drug contribution [25–27].

Partial area under the curve ($\mathbf{AUC_{0-t}}$)

We will first investigate the partial area under the curve from drug administration time zero until a certain time t, noted AUC_{0-t}. Considering the current PK model where there is a baseline concentration, we can define AUC_{0-t} as

$$\mathrm{AUC}_{0-t} = \int_0^t (C(t) - C_{hs})\,dt, \tag{21}$$

where $C(t)$ is the observed concentration, and C_{hs} is the baseline concentration.

Theorem 3 *Given the PK model described by the Eqs. (8)–(9), the partial drug exposure AUC* $_{0-t}$ is

$$\mathrm{AUC}_{0-t} = \frac{1}{k_{el}}\left(\frac{D}{V_d} + C_{hs} - C(t)\right) + \frac{C_\beta^{en} - K_m}{k_{el}}\ln\frac{C(t)+C_\beta^{en}}{D/V_d + C_{hs} + C_\beta^{en}}, \tag{22}$$

where all parameters are as previously defined. Moreover, if Michaelis–Menten elimination pathway is absent, the corresponding partial area under the curve, $\mathrm{AUC}_{L,0-t}$, *becomes*

$$\mathrm{AUC}_{L,0-t} = \frac{D}{k_{el}V_d}\left(1 - e^{-k_{el}t}\right), \tag{23}$$

and we have

$$\mathrm{AUC}_{0-t} < \mathrm{AUC}_{L,0-t} \text{ if } V_{max} > 0, \text{ and } \lim_{V_{max}\to 0}\mathrm{AUC}_{0-t} = \mathrm{AUC}_{L,0-t}. \tag{24}$$

Proof The obtention of Eq. (22) is straightforward. We can multiply both sides of Eq. (13) by $C(t) - C_{hs}$ and then make a simple rearrangement, which gives

$$(C(t)-C_{hs})\,dt=-\left\{p+q-q\frac{C_{hs}+C_{\beta}^{en}}{C(t)+C_{\beta}^{en}}\right\}dC(t). \tag{25}$$

Integration of Eq. (25) yields

$$\begin{aligned}\mathrm{AUC}_{0-t}&=\int_0^t (C(t)-C_{hs})\,dt\\&=(p+q)\left(\frac{D}{V_d}+C_{hs}-C(t)\right)\\&\quad+q(C_{hs}+C_{\beta}^{en})\ln\frac{C(t)+C_{\beta}^{en}}{D/V_d+C_{hs}+C_{\beta}^{en}}\\&=\frac{1}{k_{el}}\left(\frac{D}{V_d}+C_{hs}-C(t)\right)\\&\quad+\frac{C_{\beta}^{en}-K_m}{k_{el}}\ln\frac{C(t)+C_{\beta}^{en}}{D/V_d+C_{hs}+C_{\beta}^{en}}.\end{aligned}$$

Furthermore, the model (Eqs. 8–9) satisfies

$$\frac{dC(t)}{dt}=r_{prod}-k_{el}C(t)-\frac{V_{max}C(t)}{V_d(K_m+C(t))}\le r_{prod}-k_{el}C(t), \tag{26}$$

with the same initial condition D/V_d+C_{hs}. This leads to the partial area under the curve of the linear model (Michaelis–Menten elimination is absent in Eq. (8)) as

$$\mathrm{AUC}_{L,0-t}=\int_0^t\frac{D}{V_d}e^{-k_{el}t}\,dt=\frac{D}{k_{el}V_d}\left(1-e^{-k_{el}t}\right).$$

By the Comparison Theorem [28], the solution of the current model (i.e. the concentration time curve) is upper bounded by that of the linear model, which gives rise to Eq. (24). □

Remark 2 AUC_{0-t} given by Eq. (22) can be directly calculated using the X function, by applying the expression of $C(t)$ given in Theorem 2.

Total drug exposure ($\mathbf{AUC_{0-\infty}}$)

The total drug exposure, as represented by $\mathrm{AUC}_{0-\infty}$ can be defined as

$$\mathrm{AUC}_{0-\infty}=\int_0^{\infty}(C(t)-C_{hs})\,dt, \tag{27}$$

where $C(t)$ and C_{hs} are the observed and baseline concentrations, respectively.

If Michaelis–Menten elimination pathway is absent in Eqs. (8)–(9), the following result is known for linear kinetics.

Lemma 1 *For the one-compartment PK model with linear elimination and constant endogenous production, the total drug exposure,* $\mathrm{AUC}_{L,0-\infty}$*, after a single IV bolus dose D, is*

$$\mathrm{AUC}_{L,0-\infty}=\frac{D}{k_{el}V_d}. \tag{28}$$

Proof Solving the linear PK model of

$$\frac{dC(t)}{dt}=r_{prod}-k_{el}C(t),\quad C(0^+)=D/V_d+C_{L,hs} \tag{29}$$

yields the corrected concentration as

$$C(t)-C_{L,hs}=\frac{D}{V_d}e^{-k_{el}t},\quad t>0. \tag{30}$$

Accordingly, this total drug exposure is

$$\begin{aligned}\mathrm{AUC}_{L,0-\infty}&=\int_0^{\infty}(C(t)-C_{L,hs})\,dt\\&=\int_0^{\infty}\frac{D}{V_d}e^{-k_{el}t}\,dt=\frac{D}{k_{el}V_d}.\end{aligned} \tag{31}$$

□

However, we have

Theorem 4 *For the considered PK model described by Eqs. (8)–(9), the total drug exposure over time defined by Eq. (27),* $AUC_{0-\infty}$*, is*

$$\mathrm{AUC}_{0-\infty}=\frac{D}{k_{el}V_d}-\frac{C_{\beta}^{en}-K_m}{k_{el}}\ln\left(1+\frac{D/V_d}{C_{hs}+C_{\beta}^{en}}\right). \tag{32}$$

Moreover, we have

$$\begin{aligned}&\mathrm{AUC}_{0-\infty}<\mathrm{AUC}_{L,0-\infty}\ \text{if}\ V_{max}>0,\\&\text{and}\ \lim_{V_{max}\to 0}\mathrm{AUC}_{0-\infty}=\frac{D}{k_{el}V_d}=\mathrm{AUC}_{L,0-\infty}.\end{aligned} \tag{33}$$

Proof Integration of Eq. (25) from 0 to ∞ yields

$$\begin{aligned}\mathrm{AUC}_{0-\infty}&=\int_0^{\infty}(C(t)-C_{hs})\,dt\\&=\int_0^{\infty}-\left\{p+q-q\frac{C_{hs}+C_{\beta}^{en}}{C(t)+C_{\beta}^{en}}\right\}dC(t)\\&=-(p+q)(C(\infty)-C_0)+q(C_{hs}\\&\quad+C_{\beta}^{en})\ln\left(\frac{C(\infty)+C_{\beta}^{en}}{C_0+C_{\beta}^{en}}\right)\\&=\frac{D}{k_{el}V_d}-\frac{C_{\beta}^{en}-K_m}{k_{el}}\ln\left(1+\frac{D/V_d}{C_{hs}+C_{\beta}^{en}}\right),\end{aligned}$$

where $C(\infty)=C_{hs}$ and $C_0=C_{hs}+D/V_d$.

Since $C_{\beta}^{en}>K_m$, the second term in the expression of $\mathrm{AUC}_{0-\infty}$ is positive when $V_{max}>0$. Then we have

$$\mathrm{AUC}_{0-\infty} < \frac{D}{k_{el}V_d} = \mathrm{AUC}_{L,0-\infty}.$$

Moreover, when the maximum velocity of Michaelis–Menten kinetics tends to zero, we have

$$C_{hs} \to \frac{r_{prod}}{k_{el}} \quad \text{and} \quad C_{\beta}^{en} \to K_m,$$

which leads to

$$\lim_{V_{max}\to 0} \mathrm{AUC}_{0-\infty} = \frac{D}{k_{el}V_d} = \mathrm{AUC}_{L,0-\infty}.$$

□

Remark 3 If the endogenous production rate $r_{prod} = 0$, then total drug exposure over time turns to

$$\mathrm{AUC}_{0-\infty} = \frac{D}{k_{el}V_d} - \frac{C_{\beta} - K_m}{k_{el}} \ln\left(1 + \frac{D/V_d}{C_{\beta}}\right). \tag{34}$$

Moreover, if the endogenous production rate r_{prod} tends to infinity, we have

$$\lim_{r_{prod}\to\infty} \mathrm{AUC}_{0-\infty} = \frac{D}{k_{el}V_d}. \tag{35}$$

Remark 4 In fact, AUC_{0-t} can be rewritten as

$$\mathrm{AUC}_{0-t} = \frac{D}{k_{el}V_d} - \frac{C_{\beta}^{en} - K_m}{k_{el}} \ln\left(1 + \frac{D/V_d}{C_{hs} + C_{\beta}^{en}}\right) - \frac{1}{k_{el}}(C(t) - C_{hs}), \tag{36}$$

which coincides with $\mathrm{AUC}_{0-\infty}$ in Eq. (32) when time tends to infinity.

Impact of endogenous production on the corrected concentration and AUC

Endogenous production and the corrected concentration

Though the use of the corrected concentration $C(t) - C_{hs}$ seems a logic way for a fair estimation of exogenous compound's pharmacokinetics, its suitability and validation should be further investigated. The question would be to know if the corrected concentration is the same as the concentration generated by the system where no endogenous production is involved.

For this, two PK models are considered here: (1) the current PK model described by Eqs. (8)–(9); and (2) the linear model obtained by dropping the Michaelis–Menten elimination pathway from the former PK model. The following results are obtained.

- *Linear pharmacokinetic model* The corrected concentration is identical to the concentration generated by the system not involving endogenous production. It is understandable that for linear PK, endogenous production and exogenous administration contribute in parallel to the resulting drug concentration time course, a property known as the superposition principle for the linear time invariant system. Hence, the corrected concentration is a rational and fair choice for linear kinetics.
- *Nonlinear pharmacokinetic model* As observed in Fig. 1, the corrected concentration curves are different from the concentration curves generated by the systems with no endogenous production. Generally, these concentrations are even higher when r_{prod} increases (Fig. 1b). The ratio of the corrected concentration to that of the system with no endogenous production (Fig. 1d) grows exponentially with time for the system with endogenous production. As the superposition principle is no more valid for nonlinear PK, we can explain that a larger r_{prod} will make the accumulation of the resulting concentration even higher, and with exogenously administered drug fading over time, this becomes more imposing as reflected in the ratios. Therefore the corrected concentration is nonlinearly dependent on the endogenous production, even with a constant rate of endogenous production.

Endogenous production and AUC

For the PK model (Eqs. 8–9), we have found the explicit expressions of AUC_{0-t} and $\mathrm{AUC}_{0-\infty}$ based on the corrected concentrations and established their relationships (Eqs. 24 and 32) with the corresponding linear PK model obtained by dropping the Michaelis–Menten elimination pathway. This relationship can be better perceived graphically. Indeed, $\mathrm{AUC}_{0-\infty}$ of the model (Eqs. 8–9) increases with r_{prod} in a sigmoid fashion but is always bounded above by $\mathrm{AUC}_{L,0-\infty}$, which is the total drug exposure of the linear model (Fig. 2a). Moreover, the shapes of these $\mathrm{AUC}_{0-\infty}$ are controlled by V_{max} values. For a high V_{max}, $\mathrm{AUC}_{0-\infty}$is lower and needs a relatively high endogenous production r_{prod} to reach the saturate level given by $\mathrm{AUC}_{L,0-\infty}$. Moreover it is obvious to see that $\mathrm{AUC}_{0-\infty}$ curve converges to the constant $\mathrm{AUC}_{L,0-\infty}$ when V_{max} tends to zero, i.e., when the model tends to be linear as shown in Theorem 4.

It is interesting to explore how $\mathrm{AUC}_{0-\infty}$ responds to both endogenous production rate r_{prod} and exogenous dose D. For this, we calculated and displayed the contour plots of $\mathrm{AUC}_{0-\infty}$ vs. r_{prod} and D (Fig. 2b). For a large r_{prod}, the increase in $\mathrm{AUC}_{0-\infty}$ is almost equidistant for each increase

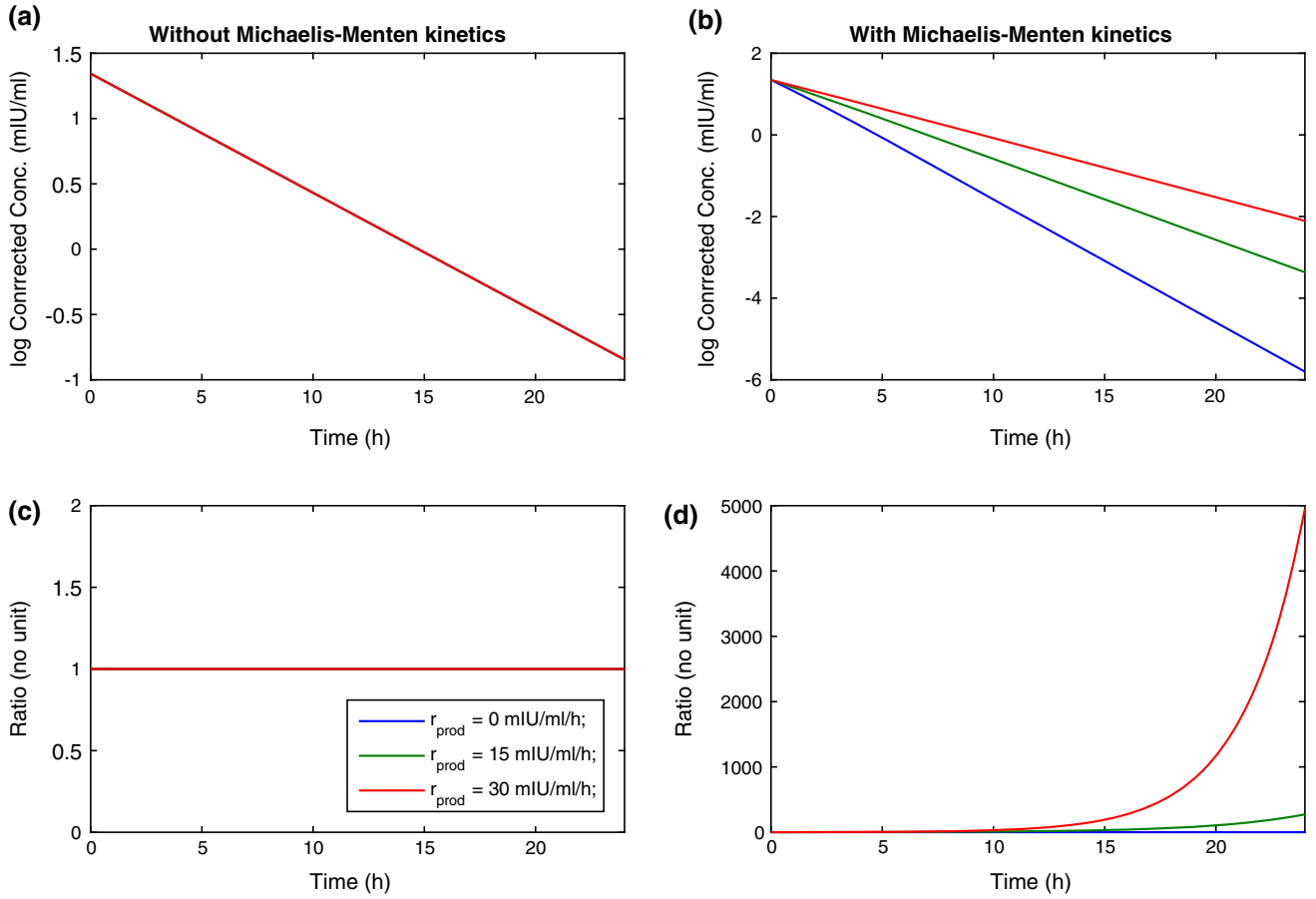


Fig. 1 (Online color) The impact of r_{prod} on the corrected concentration for linear and nonlinear PK models for $r_{prod} = 0$, 15, 30 mIU/ml/h. $D = 1350$ mIU/kg, $V_d = 61.18$ ml/kg; $k_{el} = 0.21$/h, $V_{max} = 1993$ mIU/h/kg and $K_m = 67.23$ mIU/ml. **a** Time courses of log corrected concentration for the linear models; **b** time courses of log corrected concentration for the nonlinear models; **c** ratios for the linear models; **d** ratios for the nonlinear models

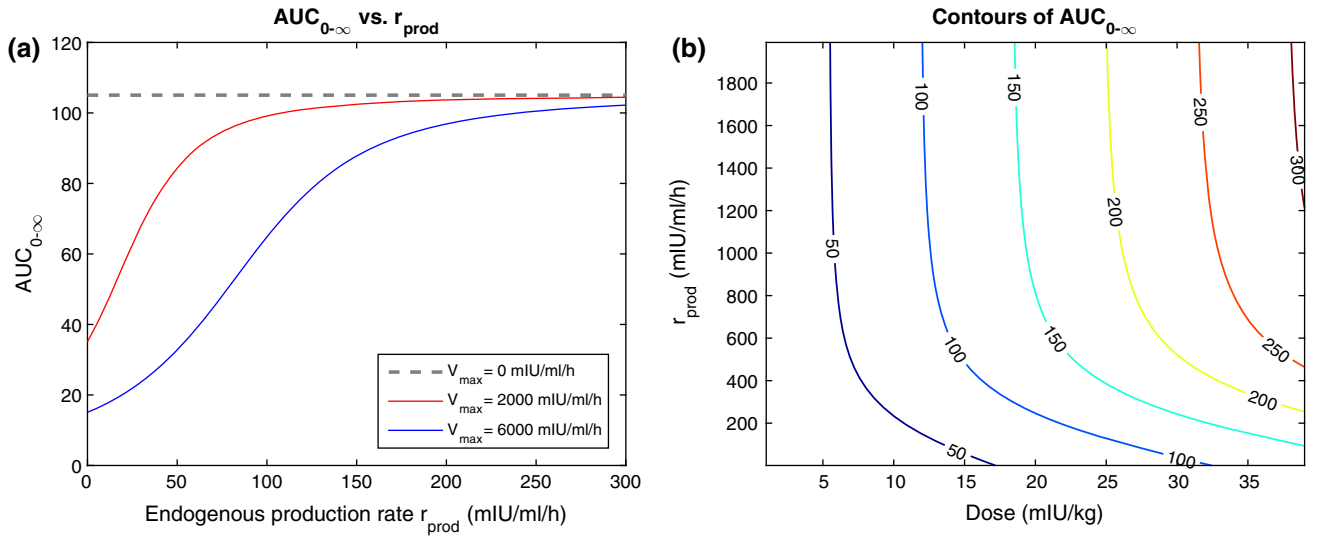


Fig. 2 (Online color) Drug exposure versus endogenous production rate r_{prod} and administered dose D. **a** $AUC_{0-\infty}$ versus r_{prod} for $V_{max} = 0, 2000, 6000$ mIU/h/kg, $D = 1375$ mIU/kg; **b** contour plot of $AUC_{0-\infty}$ in function of r_{prod} and D, where $V_{max} = 2000$ mIU/h/kg. The other parameters are the same as those in Fig. 1

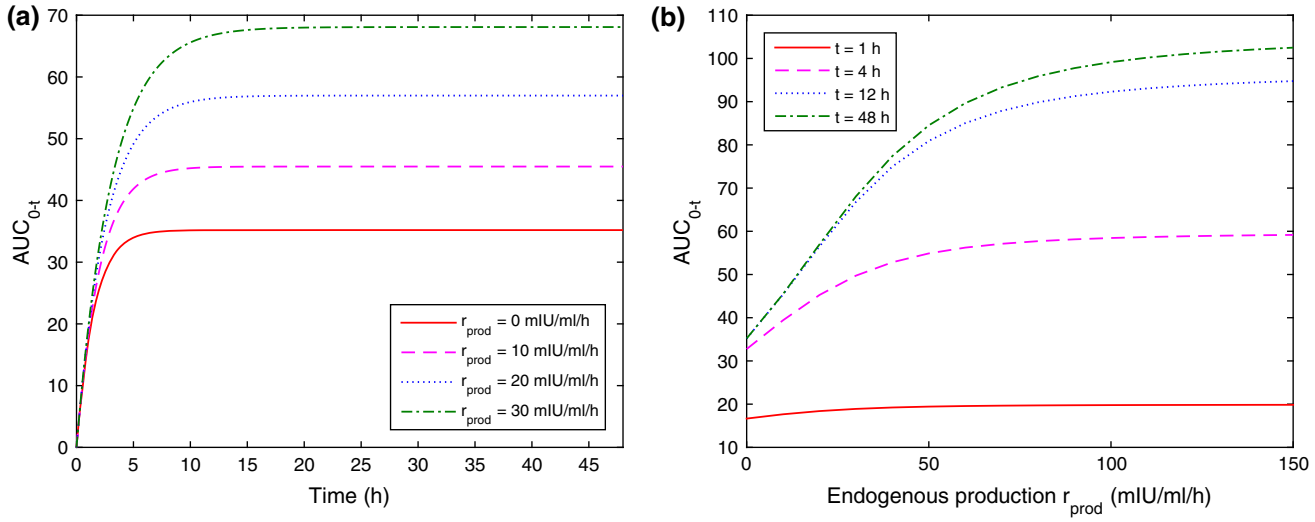


Fig. 3 (Online color) Partial area under the curve AUC_{0-t} versus time t or endogenous production rate r_{prod}. **a** AUC_{0-t} versus time t for different r_{prod} as 0, 10, 20, 30 mIU/ml/h; **b** AUC_{0-t} versus endogenous production rate r_{prod} for time $t = 1, 4, 12, 48$ h. Except time t and endogenous production rate r_{prod}, other parameters are fixed as $D = 1375$ mIU/kg, $k_{el} = 0.21$ /h, $V_{max} = 1993$ mIU/h/kg, $K_m = 67.23$ mIU/ml, $V_d = 61.18$ ml/kg [9]

in D, hence proportional to the dose. However, this linear increase is not maintained for low levels of r_{prod}. This phenomenon can be explained with the concept of dominant elimination pathway that we found in [19], where the linear and nonlinear elimination pathways can have their dominant role altered depending on drug concentration levels. A large value of r_{prod} leads to a high level of plasma concentration, making thus the first-order elimination dominant. However, when the clearance from the linear elimination pathway ($k_{el}V_d$) is less than the intrinsic clearance following Michaelis–Menten kinetics (V_{max}/K_m), a small r_{prod} leads to a low baseline concentration, thus giving rise to a low level of drug plasma concentration where Michaelis–Menten elimination pathway dominates, and this is particularly true for a small dose D. Moreover, for a given $AUC_{0-\infty}$, dose can be estimated as $D = k_{el}V_d \cdot AUC_{0-\infty}$ when $r_{prod} \to \infty$, while dose D can only be numerically estimated from Eq. (34) when $r_{prod} = 0$.

Similar observations can be found and explained for the partial AUC_{0-t} (Fig. 3).

The net total drug exposure (AUC_{net})

We have calculated the baseline concentration C_{hs} for the steady state of Eq. (8). At this state, the system elimination is balanced with the endogenous input rate r_{prod}. Thus the validity of using C_{hs} as a proxy of the contribution of endogenous input can only be established when the system is not altered by any exogenous drug input. For a constant r_{prod}, C_{hs} stays constant. However, in the presence of exogenous drug administration, the fair share of endogenous input in the whole drug exposure can not be constant. Instead, the transient endogenous contribution should be a function of time that varies with the PK of the exogenous drug input. It is hence important to differentiate the fair contributions of endogenous and exogenous inputs to the total drug exposure.

Estimation of the contribution of endogenous production to the total drug exposure cannot be directly obtained as the case for the determination of the baseline concentration, where only several blood samples collected prior to drug administration are needed. However, in the actual modeling framework, we can separately model the contribution of endogenous and exogenous inputs, and numerically calculate the net drug exposure from exogenous contribution by removing the endogenous part.

In fact, the current model (Eqs. 8–9) can be further separated into the following submodel

$$\frac{d}{dt}C_{en}(t) = r_{prod} - k_{el}C_{en}(t) - \frac{V_{max}C_{en}(t)}{V_d(K_m + C_{en}(t) + C_{ex}(t))}, \quad C_{en}(0) = C_{hs}, \tag{37}$$

$$\frac{d}{dt}C_{ex}(t) = -k_{el}C_{ex}(t) - \frac{V_{max}C_{ex}(t)}{V_d(K_m + C_{en}(t) + C_{ex}(t))}, \quad C_{ex}(0^+) = D/V_d, \tag{38}$$

which describe the concentrations $C_{en}(t)$ and $C_{ex}(t)$, generated by endogenous and exogenous inputs, respectively. Note that adding Eqs. (37) and (38) gives the original model, where $C = C_{en} + C_{ex}$. Moreover, the non-

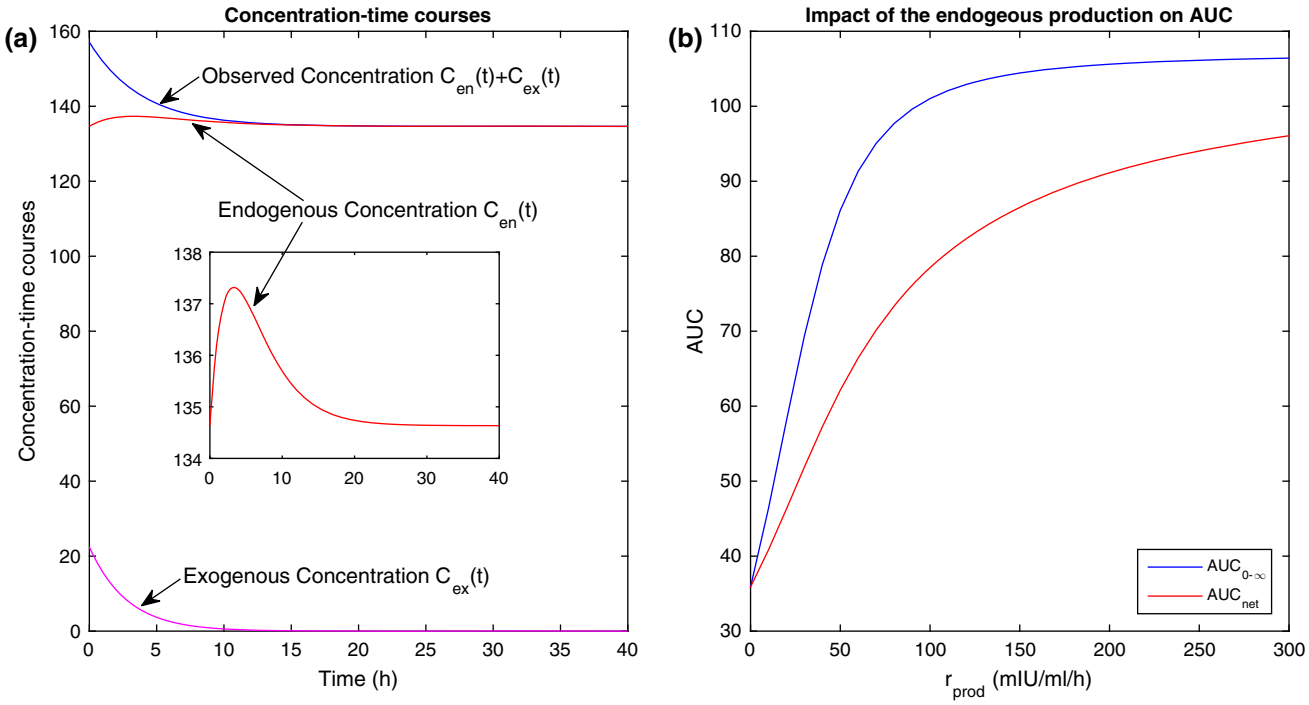


Fig. 4 (Online color) Profiles of time course of observed, endogenous and exogenous concentrations and impact of endogenous production on AUC. **a** Time course of observed, endogenous and exogenous concentrations in the case of $r_{prod} = 50$ mIU/ml/h simulated from the model (Eqs. 37–38). **b** Impact of endogenous production ($r_{prod} \in [0,300$ mIU/ml/h]) on $AUC_{0-\infty}$ and AUC_{net}. In all simulations, other parameters are fixed as $D = 1375$ mIU/ml, $k_{el} = 0.21$/h, $V_{max} = 2000$ mIU/h/kg, $K_m = 67.23$ mIU/ml, $V_d = 61.18$ ml/kg

negativity of the submodel and local stability of the unique steady state $E^* = (C^*_{en}, C^*_{ex}) = (C_{hs}, 0)$ are given in Appendix 3.

Then the net total drug exposure should be

$$\mathrm{AUC}_{net} = \int_0^\infty (C(t) - C_{en}(t))\, dt = \int_0^\infty C_{ex}(t)\, dt. \qquad (39)$$

Based on Eqs. (37)–(38), $C_{en}(t)$ and $C_{ex}(t)$ are simulated numerically to estimate the net drug exposure, and the results are displayed in Fig. 4.

In Fig. 4a, we can observe the influence of exogenous drug input on the PK of endogenous production. Instead of being an independent concentration curve of constant value C_{hs}, $C_{en}(t)$ is driven by the PK of exogenous drug administration. In fact, initially at the value of C_{hs}, $C_{en}(t)$ increases after the dose administration and follows a bell curve then decreases towards C_{hs}. This justifies our argument on the improper use of C_{hs} in the estimation of drug exposure under the conditions of the current model. In Fig. 4b, $\mathrm{AUC}_{0-\infty}$ estimated using the baseline concentration C_{hs} and AUC_{net} are reported versus r_{prod}. It clearly shows that $\mathrm{AUC}_{0-\infty}$ overestimates the drug exposure of the exogenous administration. However, it is still interesting to see that, even when the endogenous contribution is more properly dropped, AUC_{net} remains dependent on r_{prod}, which is in fact increasing to finally saturate with r_{prod}. The nonlinear Michaelis–Menten elimination pathway, which saturates at high concentration values, is responsible for this unusual phenomenon. With a large r_{prod}, drug concentration is inclined to accumulate to reach a high level such that the drug is less easily eliminated, leading to a higher AUC_{net}. Moreover, for a very large r_{prod}, linear pathway dominates the whole drug elimination. In this case, the system is likely to manifest a linear PK and reaches a plateau of AUC_{net}.

Discussion and conclusions

In the current paper, we have formulated the closed form solution for the one-compartment PK model involving simultaneous first-order and Michaelis–Menten elimination with endogenous production in the case of a single IV dose. This model extends the one that we have previously studied with the additional consideration here of the endogenous production [19]. The extension is physiologically natural since it allows to mathematically outreach to those substances that are also endogenously produced. While our progress in this direction is a significant step forward, this is not the end of the story since more refined drug models and modeling approaches are being proposed and for which a rigorous mathematical analysis is still lacking [3, 29–32]. Such models could include multiple compartments [32],

involving feedback mechanisms regulating endogenous production [3, 33–35], or target-mediated drug disposition (TMDD) [29–31]. Though endogenous production is considered constant here, this work definitely provides a foundation for the understanding of the influence of endogenous production on PK and sheds light on the inner structure of PK components and their intertwined relationships.

Our work indicates the need to revisit and update the estimation of relevant PK parameters, especially for the case of more complex drugs exhibiting non-linear kinetics. In the presence of endogenous production, the current study shows that it can have a great impact on the estimation of drug exposure, whether using the corrected concentration or net exogenous concentration curve. A further practical strategy to rationally estimate drug exposure needs to be developed.

As previously mentioned, the introduction of the X function was motivated by the usefulness of the *Lambert W* function to express the closed form solution of one-compartment PK models involving the Michaelis–Menten elimination alone [17]. In fact, through a limiting process, we were able to show that the X function can be linked to the *Lambert W* function. We proved that this newly introduced X function was also suitable for the expression of the closed form solution of one-compartment PK models with simultaneous first-order and Michaelis–Menten elimination [19]. In the current paper, we have shown that the use of X function can be further extended to the case of endogenous production. Indeed, the X function has its own specific mathematical properties such as the real branches as illustrated in the Appendix 4 using typical parameter values. More complex branches can be explored as what is known for the case of the *Lambert W* function [18]. For numerical purposes, we have implemented the X function into *Matlab*, with the aim to make it accessible to the users.

Acknowledgements This work is supported by FRQNT Fellowship (X. Wu) and the NSERC-Industrial Chair in Pharmacometrics (co-funded by InVentiv Health and Pfizer) and FRQNT Projet d'équipe led by F. Nekka. X. Wu and J. Li also thank the support from NSFC (No.11501358). We thank the referees for their careful reading and valuable comments which helped improving the quality of the paper.

Appendix 1: Well-posedness of the model (Eq. 8)

Lemma 2 *For the model (Eq. 8), we have the following results*:

(i) *There is a unique positive solution C_{hs} as shown in Eq. (10).*

(ii) *$C(t) > 0$ for all $t > 0$ provided that $C(0) > 0$ and $\lim_{t\to\infty} C(t) = C_{hs}$.*

Proof (i) In order to find the positive solution of Eq. (8), letting the right hand be zero yields

$$r_{prod} - k_{el}C(t) - \frac{1}{V_d}\frac{V_{max}C(t)}{K_m + C(t)} = 0.$$

This can be further transformed into the following quadratic equation

$$C^2(t) + \left(\frac{V_{max}}{k_{el}V_d} + K_m - \frac{r_{prod}}{k_{el}}\right)C(t) - \frac{r_{prodK_m}}{k_{el}} = 0.$$

Since the product of the roots of the above quadratic equation is $-\frac{r_{prodK_m}}{k_{el}} < 0$, hence the roots must be real with one negative and one positive C_{hs} as shown in Eq. (10).

(ii) If $C(0) = C_{hs} > 0$, then $\frac{dC(t)}{dt}|_{t=0} = 0$ implying $C(t) = C_{hs} > 0$ for all $t > 0$. If $C(0) > C_{hs} > 0$, we have $\frac{dC(t)}{dt}|_{t=0} < 0$ implying a decrease of $C(t)$ at $t = 0$. By the continuity of solution, $C(t)$ will continue to decrease as long as $C(t) > C_{hs}$ for $t > 0$, and will eventually converge to C_{hs} since $\frac{dC(t)}{dt}|_{C(t)=C_{hs}} = 0$. Therefore, in this case $C(t)$ is a strictly decreasing sequence and has C_{hs} as a lower bound. By the monotone convergence theorem, we have $\lim_{t\to\infty} C(t) = C_{hs}$. Similarly, if $0 < C(0) < C_{hs}$, $C(t)$ increases and eventually converges to C_{hs}. □

Appendix 2: Claim "p, q and C_β^{en} are positive and $C_\beta^{en} > K_m$"

Proof $C_{L,hs}$ satisfies $r_{prod} = k_{el}C_{L,hs}$, and C_{hs} satisfies $r_{prod} = k_{el}C_{hs} + \frac{V_{max}}{V_d}\frac{C_{hs}}{K_m + C_{hs}}$, thus we have

$$k_{el}(C_{hs} - C_{L,hs}) = -\frac{V_{max}}{V_d}\frac{C_{hs}}{K_m + C_{hs}}.$$

This yields

$$C_{hs} - C_{L,hs} = -\frac{V_{max}}{k_{el}V_d}\frac{C_{hs}}{K_m + C_{hs}}.$$

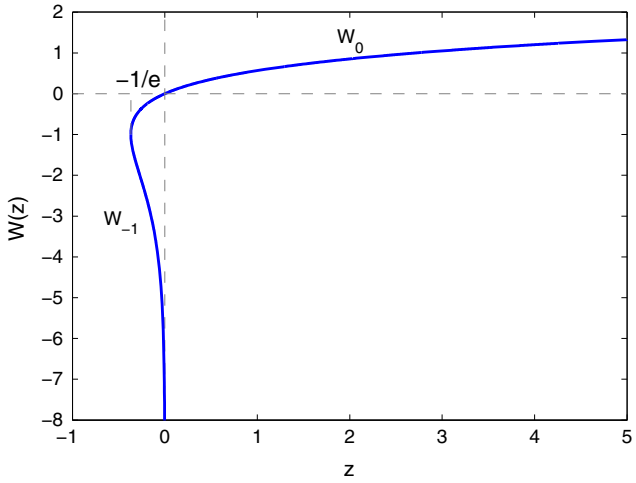
Accordingly, we have

$$C_\beta^{en} - K_m = C_{hs} - C_{L,hs} + C_\beta - K_m$$
$$= -\frac{V_{max}}{k_{el}V_d}\frac{C_{hs}}{K_m + C_{hs}} + \frac{V_{max}}{k_{el}V_d} = \frac{V_{max}}{k_{el}V_d}\frac{K_m}{K_m + C_{hs}} > 0.$$

It is thus obvious that p and q are positive. □

Appendix 3: Stability of the steady state solution of the model (Eqs. 37–38)

Lemma 3 *For the model (Eqs. 37–38), the solution is non-negative for any initial conditions $C_{en}(0) = C_{hs} > 0$ and*



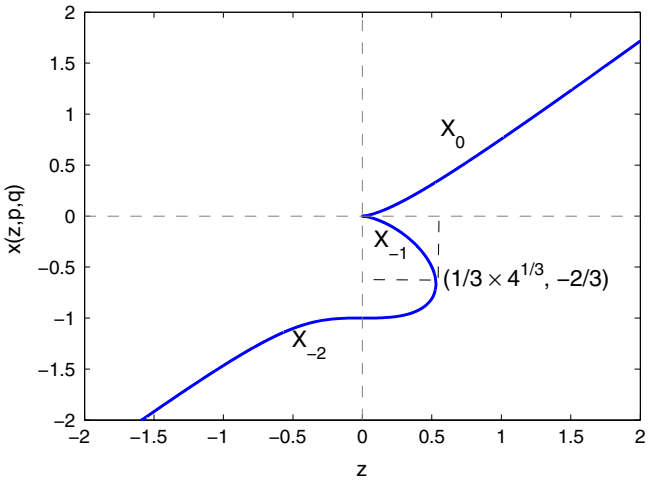


Fig. 5 Real branches of *Lambert W* and *X* functions. Left panel: *Lambert W* function has two real branches, $W_0 \in (-1,\infty)$ for $z \in (-1/e,\infty)$ and $W_{-1} \in (-\infty,-1)$ for $z \in (-1/e,0)$. Right panel: *X* function ($p = 2/3$, $q = 1/3$) has three real branches, $X_0 \in (0,\infty)$ for $z \in (0,\infty)$, $X_{-1} \in (-2/3,0)$ for $z \in (0, 1/3 \times 4^{1/3})$ and $X_{-2} \in (-\infty,-2/3)$ for $z \in (-\infty, 1/3 \times 4^{1/3})$

$C_{ex}(0) > 0$, *and there is a unique equilibrium* $E^* = (C^*_{en}, C^*_{ex}) = (C_{hs}, 0)$ *which is locally asymptotically stable.*

Proof The nonnegativity of $C_{en}(t)$ and $C_{ex}(t)$ follows immediately from Theorem 5.2.1 on page 81 in [28]. Letting the right hands of Eqs. (37)–(38) be zeroes, we can simply have $C^*_{en} = C_{hs}$ and $C^*_{ex} = 0$.

The linearized the system at the equilibrium E^* is

$$\begin{cases} C'_{en}(t) &= -\left(k_{el} + \dfrac{V_{max}}{V_d}\dfrac{K_m}{(K_m + C_{hs})^2}\right) C_{en}(t) + \dfrac{V_{max}}{V_d}\dfrac{C_{hs}}{(K_m + C_{hs})^2} C_{ex}(t), \\ C'_{ex}(t) &= -\left(k_{el} + \dfrac{V_{max}}{V_d}\dfrac{1}{K_m + C_{hs}}\right) C_{ex}(t). \end{cases}$$

Thus, the Jacobian matrix is

$$J(E^*) = \begin{pmatrix} -(k_{el} + \dfrac{V_{max}}{V_d}\dfrac{K_m}{(K_m + C_{hs})^2}) & \dfrac{V_{max}}{V_d}\dfrac{C_{hs}}{(K_m + C_{hs})^2} \\ 0 & -(k_{el} + \dfrac{V_{max}}{V_d}\dfrac{1}{K_m + C_{hs}}) \end{pmatrix},$$

and the two eigenvalues λ_1 and λ_2 satisfy

$$\lambda_1 + \lambda_2 = tr(J(E^*)) < 0 \quad \text{and} \quad \lambda_1\lambda_2 = \det(J(E^*)) > 0.$$

These imply λ_1 and λ_2 are negative, which ensures the local asymptotic stability of E^*. □

Appendix 4: Real branches of *Lambert W* and *X* functions

Lambert W function is known to have two real branches, with one branch $W_0 \in (-1,\infty)$ for z defined in $(-1/e,\infty)$, and the other $W_{-1} \in (-\infty,-1)$ for z defined in $(-1/e,0)$ (left panel, Fig. 5) [17, 18]. However, the case of *X* function is more complex. Without going into details, we simply illustrate here a case of real branches of an *X* function, with the aim to show its particularity compared to *Lambert W* function (right panel, Fig. 5).

As observed in the right panel of Fig. 5, there is only one real branch in the first quadrant. In fact, this is true for all *X* functions. Taking the derivative of *X* function, we have

$$\frac{d}{dz}X(z,p,q) = \frac{1}{z}\cdot\left(\frac{p}{X(z,p,q)} + \frac{q}{1+X(z,p,q)}\right)^{-1} > 0, \tag{40}$$

which guarantees there is only one real branch in the first quadrant. In the current study, we are interested only in this real branch $X(z,p,q) \in (0,\infty)$ and use it to express the analytical solutions of PK models. Thus we use the letter *X* to denote this unique real branch in the current paper.

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