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ARTICLE

Predicting the Onset of Nonlinear Pharmacokinetics

Andrew M. Stein¹ and Lambertus A. Peletier²

When analyzing the pharmacokinetics (PK) of drugs, one is often faced with concentration C vs. time curves, which display a sharp transition at a critical concentration C_{crit} . For $C > C_{\text{crit}}$, the curve displays linear clearance and for $C < C_{\text{crit}}$ clearance increases in a nonlinear manner as C decreases. Often, it is important to choose a high enough dose such that PK remains linear in order to help ensure that continuous target engagement is achieved throughout the duration of therapy. In this article, we derive a simple expression for C_{crit} for models involving linear and nonlinear (saturable) clearance, such as Michaelis-Menten and target-mediated drug disposition (TMDD) models.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Mathematical models of nonlinear PK and TMDD of mAbs are widely used to guide drug development. Often, it is important to choose a high enough dose such that PK remains linear to help ensure that continual target engagement is achieved throughout the duration of therapy. There has not yet been a demonstration for how the PK/pharmacodynamic parameters impact the onset concentration at which the nonlinearity is observed.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ How the PK and binding properties of the drug impact the onset of nonlinear PK.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ C_{crit} was derived and was found to be equal to V_{max}/CI for the Michaelis-Menten model or $k_{\text{syn}}/(CI/V_c)$ for the TMDD model.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

✓ The C_{crit} parameter can be used to provide better intuition for how the PK parameters impact drug concentration profiles and, in particular, guide the modeler in understanding where the random effects may need to be added and what parameters of the model are identifiable.

When analyzing the pharmacokinetics (PK) of drugs, one is often faced with concentration vs. time curves which display a sudden increase in the elimination rate below a certain critical concentration (C_{crit}). Examples of this phenomenon, in which the PK exhibit this nonlinear behavior, are shown in **Figure 1** for efalizumab (anti-CD11a),¹ mavrilimumab (antigranulocyte-macrophage colony-stimulating factor receptor),² and romosozumab (antisclerostin).³

This nonlinearity shown in **Figure 1** results from a combination of two pathways of drug clearance: (i) a linear, nonspecific clearance due to endocytosis; and (ii) a nonlinear, saturable clearance due to internalization of the target receptor:

- At high drug concentrations, the target receptor is saturated and the rate of elimination is governed by the nonspecific clearance.
- At lower drug concentrations, when the target receptor is no longer saturated, both the nonspecific route and the

saturable route contribute to drug clearance and, hence, the rate of elimination increases as the concentration decreases.

A common goal when selecting the dose and regimen of a drug is to maintain a drug concentration that stays above the C_{crit} . There are two reasons for this goal.

1. Ensure lower PK variability in the population, because C_{crit} may vary between subjects.
2. Ensure that target occupancy remains high, as maintaining drug concentrations above C_{crit} is thought to be a necessary (although not sufficient) condition to maintain target saturation.⁴

In this article, we show examples of systems that have a simple critical value for the drug concentration C_{crit} such that as long as the drug concentration remains above this value, target mediated elimination is saturated and the PK is linear. In **Figure 1**, C_{crit} is illustrated; when the concentration falls below C_{crit} , the elimination rate suddenly increases.

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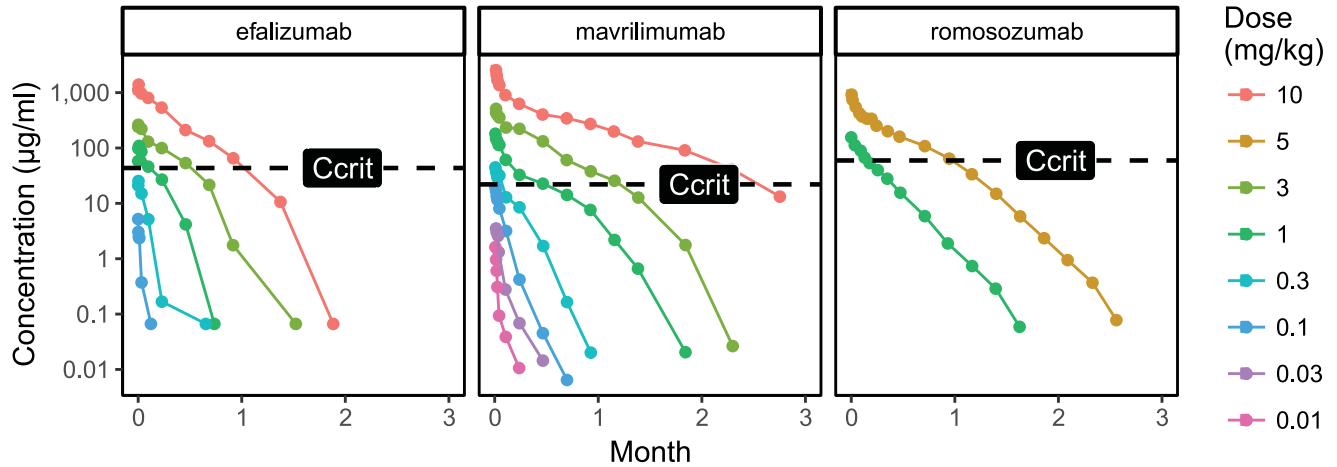


Figure 1 Nonlinear pharmacokinetics for efilizumab, mavrilumab, and romosozumab. Note that for all three drugs, as the concentration drops below the critical concentration (C_{crit}), the elimination rate suddenly increases.

We derive an analytical expression for C_{crit} for both the Michaelis-Menten model^{1,5} and the target-mediated drug disposition model (TMDD).^{6–8} Both models have two routes of clearance: nonspecific-linear elimination and saturable-nonlinear elimination. Both analyses will be discussed in the absence and in the presence of a peripheral compartment. In the presence of a peripheral compartment, the analysis becomes more complex, but it is still transparent in common cases, such as rapid exchange between the two compartments. In all cases, C_{crit} is independent of drug dose and volume of distribution.

METHODS

For modeling the onset of the PK nonlinearity, we focus on the two models that are frequently used by the pharmacometrics community: Michaelis-Menten and TMDD. A more general theoretical derivation of C_{crit} for any PK model is beyond the scope of this article. We start by focusing on the simpler case of the one-compartment model and then extend this analysis to the two-compartment scenario. The two-compartment models are shown schematically in **Figure 2** below. The corresponding one-compartment models are identical with the models shown in **Figure 2**, except that the peripheral compartments (C_p) are removed.

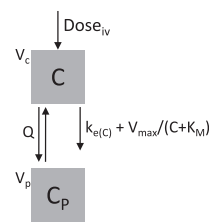
Michaelis-Menten elimination

One-compartment model. The basic model for linear and nonlinear drug elimination involves a single (central) compartment and a single differential equation for the concentration C of the drug involving linear and saturable elimination side by side:

$$V_c \frac{dC}{dt} = -Cl \cdot C - V_{max} \frac{C}{C + K_M}. \quad (1)$$

Here, V_c is the volume of the central compartment, Cl a first order clearance rate, V_{max} is the maximum rate of

(a) Michaelis-Menten



(b) Full TMDD Model

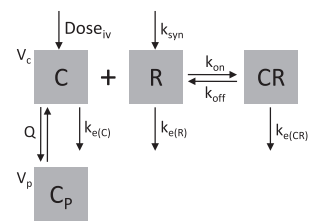


Figure 2 Structural scheme of the basic model describing **(a)** Michaelis-Menten kinetics and **(b)** target-mediated drug disposition (TMDD) where a drug C binds a target receptor R which is synthesized by a zero order reaction and degenerates according to a first order reaction. Drug and target form a complex CR , which internalizes through a first-order reaction.

saturable elimination and K_M is the Michaelis-Menten constant. For an initial i.v. bolus dose D , the initial concentration is given by $C(0) = D/V_c$.

Two-compartment model. When the drug is distributed over a central compartment with concentration C_c and a peripheral compartment C_p , with linear and nonlinear elimination occurring only from the central compartment, the PK are described by the system of equations:

$$\begin{cases} V_c \frac{dC_c}{dt} = -Cl \cdot C_c - V_{max} \frac{C_c}{C_c + K_M} - Q(C_c - C_p) \\ V_p \frac{dC_p}{dt} = +Q(C_c - C_p) \end{cases} \quad (2)$$

in which exchange between the compartments is driven by the difference in drug concentration in the two compartments (i.e., by the term $Q(C_c - C_p)$ where Q denotes a non-specific clearance rate).

Table 1 Parameters for mavrilimumab, efalizumab, and romosozumab, based on fits to data

	Mavrilimumab	Efalizumab	Romosozumab	Units
Weight-based dose	10	10	10	mg/kg
Equivalent molar dose	4667	4667	4667	nmol
V_c	2.8	2.4	2.4	L
V_p	5.6	3.6	2.6	L
Cl	0.3	0.46	0.25	L/d
Q	1.7	9.7	0.54	L/d
$k_{\text{syn}} = V_{\text{max}}/V_c$	2.4	8.5	6.1	nM/d
$K_{\text{ss}} = K_M$	1.1	1.2	12	nM
$k_{e(R)}$	2.2	4400	860	1/d
$k_{e(CR)}$	2.2	4400	860	1/d
k_{off}	10	–	–	1/d
$k_{\text{on}} = (k_{\text{off}} + k_{e(CR)})/K_{\text{ss}}$	11	–	–	1/(nM · d)

Cl, clearance; $k_{e(C)}$, drug elimination rate; $k_{e(R)}$, receptor elimination rate; K_M , Michaelis-Menten constant; k_{off} , dissociation rate; k_{on} , association rate; K_{ss} , quasi-steady-state constant; k_{syn} , receptor synthesis rate; Q , intercompartmental clearance; V_c , central volume; V_{max} , maximal rate of saturable (nonlinear) elimination; V_p , peripheral volume.

If initially, an i.v. bolus dose D is supplied to the central compartment while the peripheral compartment is empty, the initial conditions are here $C_c(0) = D/V_c$ and $C_p(0) = 0$.

Target-mediated drug disposition

In its most elementary form, TMDD target kinetics is assumed to follow a zero-order production rate k_{syn} and a first-order elimination rate $k_{e(R)}R$. The formation of drug-target complex CR takes place via a second-order process $k_{\text{on}}C \cdot R$, a first-order loss of the drug-receptor complex via $k_{\text{off}}CR$, and an irreversible first-order elimination process $k_{e(CR)}CR$. In **Figure 2** this system of reactions is shown schematically.

One-compartment model. Mathematically, the one-compartment TMDD model is described by the system of differential equations below:

$$\begin{cases} \frac{dC}{dt} = -k_{\text{on}}C \cdot R + k_{\text{off}}CR - k_{e(C)}C; & k_{e(C)} = \frac{Cl}{V_c} \\ \frac{dR}{dt} = k_{\text{syn}} - k_{\text{on}}C \cdot R + k_{\text{off}}CR - k_{e(R)}R \\ \frac{dCR}{dt} = k_{\text{on}}C \cdot R - k_{\text{off}}CR - k_{e(CR)}CR \end{cases} \quad (3)$$

Note that in the absence of drug, the steady-state target concentration is given by $R_0 = k_{\text{syn}}/k_{e(R)}$. Here, we assume that the drug is supplied through an i.v. bolus dose D to the system when it is free from drug and the target is at steady state (i.e., $C(0) = D/V_c$, $R(0) = R_0$ and $CR(0) = 0$).

By adding the first and the third equations, we obtain an equation for the total amount of drug $C_{\text{tot}} = C + CR$ and, similarly, by adding the second and the third equations we obtain an equation for the total amount of the target, $R_{\text{tot}} = R + CR$:

$$\begin{cases} \frac{dC_{\text{tot}}}{dt} = -k_{e(C)}C - k_{e(CR)}CR \\ \frac{dR_{\text{tot}}}{dt} = k_{\text{syn}} - k_{e(R)}R - k_{e(CR)}CR \end{cases} \quad (4)$$

Note that the on-rate and the off-rate constants k_{on} and k_{off} no longer appear in these equations.

In practice, drug binding and complex internalization is fast, so that after a short time drug, target, and drug-target complex are in quasi-steady-state (QSS)⁹ (i.e., C , R , and CR) are approximately related through the expressions:

$$CR = R_{\text{tot}} \frac{C}{C + K_{\text{ss}}} \quad \text{and} \quad R = R_{\text{tot}} \frac{K_{\text{ss}}}{C + K_{\text{ss}}} \quad (5)$$

where

$$K_{\text{ss}} = \frac{k_{\text{off}} + k_{e(CR)}}{k_{\text{on}}} \quad (6)$$

Two-compartment model. The two-compartment model is similar to the one-compartment model with the addition of a peripheral compartment with the initial condition $C_p(0) = 0$.

$$\begin{cases} \frac{dC_{\text{tot}}}{dt} = -k_{e(C)}C - k_{e(CR)}CR - Q(C - C_p) \\ \frac{dC_{\text{ptot}}}{dt} = +Q(C - C_p) \\ \frac{dR_{\text{tot}}}{dt} = k_{\text{syn}} - k_{e(R)}R - k_{e(CR)}CR \end{cases} \quad (7)$$

Model analysis, fitting, and simulation

A mathematical analysis of the above equations was performed to derive C_{crit} for each model above. To test the theory, the data from **Figure 1** was fit to the two-compartment TMDD model from **Eq. 7** where it was assumed that $k_{e(R)} = k_{e(CR)}$. This assumption is typically made when fitting the PK for membrane-bound targets where it can be especially difficult to estimate $k_{e(R)}$.¹⁰ Good fits can still be achieved even when implementing this constraint.

Sensitivity analyses were performed for the one-compartment Michaelis-Menten and TMDD models and the

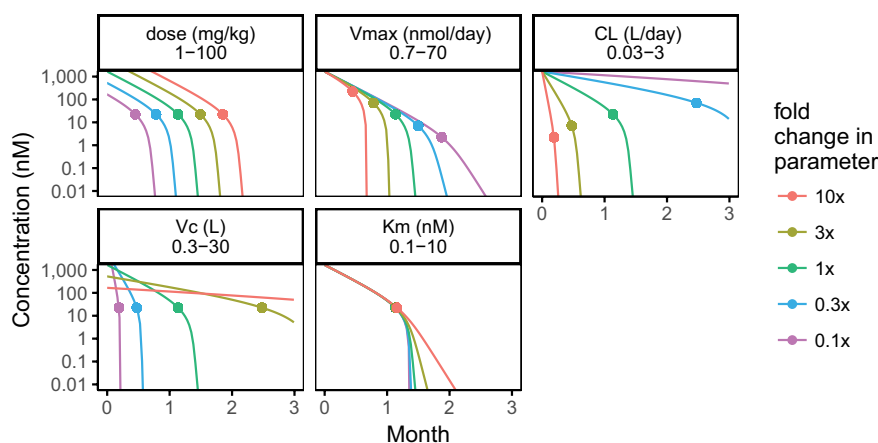


Figure 3 Mavrilimumab: one-compartment model in **Eq. 1** in which the base parameter values are in **Table 1**. Each plot shows a sensitivity analysis where the parameter in the title is changed from 0.1-fold to 10-fold. The dot shows critical concentration. CL, clearance; $V_{\max}$, maximal rate of saturable elimination.

two-compartment Michaelis-Menten model. In the sensitivity analysis, one parameter at a time was changed while all other parameters were held fixed, and the calculated C_{crit} was plotted together with the simulated PK data.

Because dosing of monoclonal antibodies (mAbs) is usually reported in mg/kg, but the binding model requires doses of nmol and concentrations of nM, a dose of 10 mg/kg is converted to nanomoles for the model simulations using the formula below, which assumes a 70 kg patient and a 150 kDa drug (typical antibody).

$$\frac{10 \text{ mg}}{\text{kg}} \cdot \frac{70 \text{ kg}}{\text{patient}} \cdot \frac{1 \text{ g}}{1000 \text{ mg}} \cdot \frac{1 \text{ mol}}{150 \cdot 10^3 \text{ g}} \cdot \frac{10^9 \text{ nmol}}{\text{mol}} = 467 \text{ nmol}$$

RESULTS

Model fit

The model fits to the data are shown in the **Supplementary Material** and the parameters from the fits that are subsequently used for simulations are listed in **Table 1**. These parameters were also used to compute the C_{crit} lines, as described below. Note that the large values for $k_{e(R)}$ and $k_{e(CR)}$ for romosozumab and efalizumab are due to the practical unidentifiability of these parameters.¹¹

Michaelis-Menten elimination

One-compartment model. For drug concentrations, which are either large or small with respect to K_M , **Eq. 1** can be approximated by the following simpler equations:

$$\begin{cases} V_c \frac{dC}{dt} = -Cl \cdot C - V_{\max} \approx -Cl \cdot C \text{ for } C \gg K_M, \\ V_c \frac{dC}{dt} = -\left(Cl + \frac{V_{\max}}{K_M}\right) C \text{ for } C \ll K_M. \end{cases} \quad (8)$$

Thus, on a logarithmic scale, the graph of $C(t)$ will be approximately linear for both large and small values of C ; for

the range of concentrations in between, the graph curves down connecting the upper linear segment with the lower linear segment (see **Figure 3**).

Of particular interest is the situation when the rate of elimination increases substantially at low concentrations. According to **Eq. 8**, this is the case when:

$$\frac{V_{\max}}{K_M} \gg Cl \implies K_M \ll \frac{V_{\max}}{Cl}. \quad (9)$$

Throughout this article, it will be assumed that **Eq. 9** holds. The sensitivity analysis for romosozumab in the **Supplementary Material** demonstrates that for small values of $V_{\max}$ or large values of K_M , the shoulder (where the onset of the PK nonlinearity is observed) disappears entirely and the PK appears linear.

As the concentration drops, the elimination rate increases, and it is important to know at which concentration this transition takes place. We define this critical concentration, C_{crit} , as the value of C where the rate of elimination doubles from its value at large drug concentrations. This definition was chosen because when the rate of elimination doubles, that means the linear and nonlinear components of elimination contribute equally. C_{crit} is derived by dividing **Eq. 1** by C , which gives:

$$V_c \frac{d}{dt} \log(C) = -\left(Cl + \frac{V_{\max}}{C + K_M}\right) \quad (10)$$

It can readily be seen that for large concentrations, the slope is Cl and, thus, the rate of elimination doubles when:

$$\frac{V_{\max}}{C + K_M} = Cl \quad \text{or} \quad C = \frac{V_{\max}}{Cl} - K_M \quad (11)$$

By assumption of **Eq. 9**, we may neglect K_M in the right expression in **Eq. 11** and, thus, define the critical concentration to be:

$$C_{\text{crit}} \stackrel{\text{def}}{=} \frac{V_{\text{max}}}{Cl}. \quad (12)$$

Note that neither the drug dose nor the volume V_c of the central compartment enters the definition of C_{crit} .

In **Figure 3**, we show simulations of concentration graphs based on **Eq. 1** for data from mavrilimumab in which $Cl = 0.3 \text{ L/d}$, $V_{\text{max}} = 6.7 \text{ nmol/d}$, and $K_M = 1.1 \text{ nM}$ (**Table 1**). Then, according to **Eq. 12**, $C_{\text{crit}} = 22 \text{ nM}$. Note that here C_{crit} is large compared to K_M so that for the base values condition **Eq. 9** is satisfied.

Figure 3 shows how C_{crit} , computed from **Eq. 12** and indicated by a dot, changes when one of the parameters involved in the model is varied. In addition, it shows where C_{crit} fits in the concentration-time curve of the drug. The graph for the largest parameter value is drawn in red and the graph for the smallest is drawn in magenta.

In the first panel in **Figure 3**, in which the dose is varied while keeping $C(0) > C_{\text{crit}}$, it is shown how both numerically and geometrically C_{crit} corresponds to the kink in the graph, irrespective of the dose value. According to **Eq. 12**, as V_{max} increases, C_{crit} moves up, while as Cl increases C_{crit} moves down, and this is observed in the second and third panels. Because C_{crit} does not depend on either V_c or K_M , it does not move in the fourth and the fifth panels.

Two-compartment model. As we shall see, for initial drug concentrations that are large enough, the switch from linear to nonlinear drug elimination is apparent in this situation as well, and it is possible to identify a critical drug concentration C_{crit} . Here, we only derive the formula for C_{crit} for the special case when drug exchange between the two compartments is fast relative to the nonspecific

clearance (Cl) and the saturable clearance (V_{max}), such as when:

$$Q \gg Cl \quad \text{and} \quad Q \gg V_{\text{max}}. \quad (13)$$

Under these conditions, it is found that the two concentrations, C_c and C_p , rapidly coalesce (i.e., $C_c(t) - C_p(t) \rightarrow 0$), and C_{crit} in both the central and peripheral compartments is given by the same formula as for the one-compartment model (i.e., by **Eq. 12**):

$$C_{\text{crit}} = \frac{V_{\text{max}}}{Cl}. \quad (14)$$

The details of the derivation of **Eq. 14** are provided further below.

In **Figure 4**, we show simulations for the two-compartment Michaelis-Menten model for parameter values, which are varied around the base parameters listed in **Table 1**, as indicated in the headings of the different panels. The graphs in the different panels are comparable to those shown in **Figure 3** for the one-compartment model, except that many show a weak point of inflection below the C_{crit} .

Evidently, the location of C_{crit} on the graphs, as defined by **Eq. 14**, has not changed much from what was seen in **Figure 3**. This is remarkable because the condition in **Eq. 13** is not satisfied by the base values of the parameters. Specifically, the value of the intercompartmental clearance Q is not large compared to V_{max} . On the other hand, Q is indeed large compared to the nonspecific clearance Cl , as is also borne out by the different graphs shown in **Figure 4**, which exhibit a clear two-phase structure during the initial development.

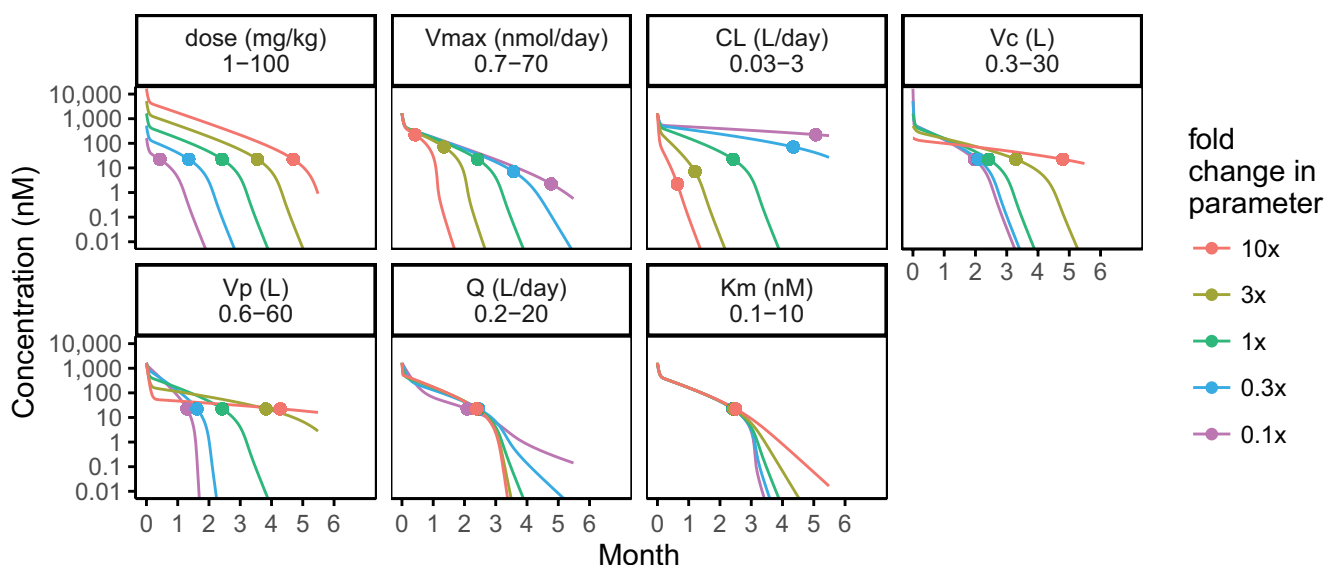


Figure 4 Mavrilimumab two-compartment Michaelis-Menten model, in which the base parameter values are listed in **Table 1**, and each plot shows a sensitivity analysis in which the parameter in the title is changed from 0.1-fold to 10-fold. The dot shows critical concentration. Cl , clearance; V_{max} , maximal rate of metabolism.

Rapid exchange between central and peripheral compartments

Suppose that $Q \gg Cl$ and $Q \gg V_{\max}$. Then, when we divide the system of **Eq. 2** by Q , and scale the time variable according to $\tau = Qt$, we obtain, with $x(\tau) = C_c(\tau/Q)$ and $y(\tau) = C_p(\tau/Q)$,

$$\begin{cases} V_c \frac{dx}{d\tau} = -\epsilon \cdot x - (x - y) - v(\tau), \\ V_p \frac{dy}{d\tau} = x - y \end{cases} \quad (15)$$

where

$$\epsilon = \frac{Cl}{Q} \ll 1 \quad \text{and} \quad v(\tau) = \frac{V_{\max}}{Q} \frac{C_c}{C_c + K_M} \ll 1 \quad (16)$$

Adding the two equations we find for the total amount of drug:

$$A(\tau) \stackrel{\text{def}}{=} V_c x(\tau) + V_p y(\tau), \quad (17)$$

the conservation law:

$$\frac{d}{d\tau}(V_c x + V_p y) = -\epsilon \cdot x - v \approx 0 \quad (18)$$

Thus, there is very little loss of drug: on the fast time scale $\tau = O(1)$ (i.e., $t = O(1/Q)$). Similarly, by dividing the equations by their respective volumes and then subtracting the two equations we obtain:

$$\frac{d}{d\tau}(x - y) \approx -\left(\frac{1}{V_c} + \frac{1}{V_p}\right)(x - y) \quad (19)$$

so that $C_c(t) - C_p(t) \rightarrow 0$ on the fast timescale as well. Therefore, within a very short time, we may write $A(t) = (V_c + V_p)C_c(t)$.

We now go back to **Eq. 18** and multiply it by Q so that the original time variable t is returned. In light of **Eq. 19**, this yields the following equation:

$$V_{ss} \frac{dC_c}{dt} = -Cl \cdot C_c - V_{\max} \frac{C_c}{C_c + K_M} \quad (20)$$

$$V_{ss} = V_c + V_p \quad (21)$$

where V_{ss} is the volume of distribution at steady state.

Following the arguments given for the one-compartment model, we find that the formula for C_{crit} , as given by **Eq. 12**, has not changed.

Target-mediated drug disposition

One-compartment model. Suppose that the drug concentration is large compared to the dissociation constant (i.e., $C(t) \gg K_{SS}$ over a period $0 < t < t_0$). Then **Eq. 5** implies that during this interval we have:

$$CR \approx R_{\text{tot}} \text{ and } R \approx 0 \quad (22)$$

With these equalities, the system in **Eq. 4** can be approximated by the following pair of equations:

$$\begin{cases} \frac{d}{dt}(C + R_{\text{tot}}) = -k_{e(C)}C - k_{e(CR)}R_{\text{tot}} \\ \frac{dR_{\text{tot}}}{dt} = k_{\text{syn}} - k_{e(CR)}R_{\text{tot}} \end{cases} \quad (23)$$

Thus, when we subtract the second equation in **Eq. 23** from the first we obtain for $0 < t < t_0$

$$\frac{dC}{dt} = -k_{e(C)}C - k_{\text{syn}} \quad (24)$$

or, when we multiply by V_c ,

$$V_c \frac{dC}{dt} = -Cl \cdot C - V_{\max} \quad \text{where} \quad V_{\max} = V_c k_{\text{syn}} \quad (25)$$

This equation is formally the same as the first equation in the system of **Eq. 8**. Following the reasoning used in the Michaelis-Menten elimination Subsection to derive C_{crit} , we assume, as in **Eq. 9**, that:

$$\frac{V_{\max}}{Cl} \gg K_{ss} \quad \text{or} \quad \frac{k_{\text{syn}}}{k_{e(C)}} \gg K_{ss} \quad (26)$$

and show that

$$C_{\text{crit}} = \frac{V_{\max}}{Cl} = \frac{k_{\text{syn}}}{k_{e(C)}} \quad (27)$$

Thus, by assuming rapid drug binding and complex internalization, drug clearance can be seen as the sum of linear and Michaelis-Menten type elimination resulting in the same expression for the C_{crit} .

In **Figure 5**, we show simulations for the one-compartment Michaelis-Menten and TMDD models and we see that for mavrimumab, a typical antibody for which **Eq. 26** is satisfied, simulations give corresponding results and, as we have seen in **Figures 3 and 4** for the Michaelis-Menten model, C_{crit} fits snugly in the arm of the concentration curves.

In the first five graphs, in which simulations for the Michaelis-Menten model and the TMDD model are shown together (the Michaelis-Menten model is dashed and the TMDD is solid), the Michaelis-Menten model curves lie below the TMDD curves. This can be understood by comparing the equations for C_{tot} and R_{tot} in **Eqs. 4 and 23** and remembering that $CR < R_{\text{tot}}$.

The similarity between the Michaelis-Menten and TMDD models has been reported elsewhere.^{10,11} Comparable findings were observed for the two-compartment model as well. Note that the similarity of the Michaelis-Menten and TMDD models may not apply for other biologics, such as bispecific

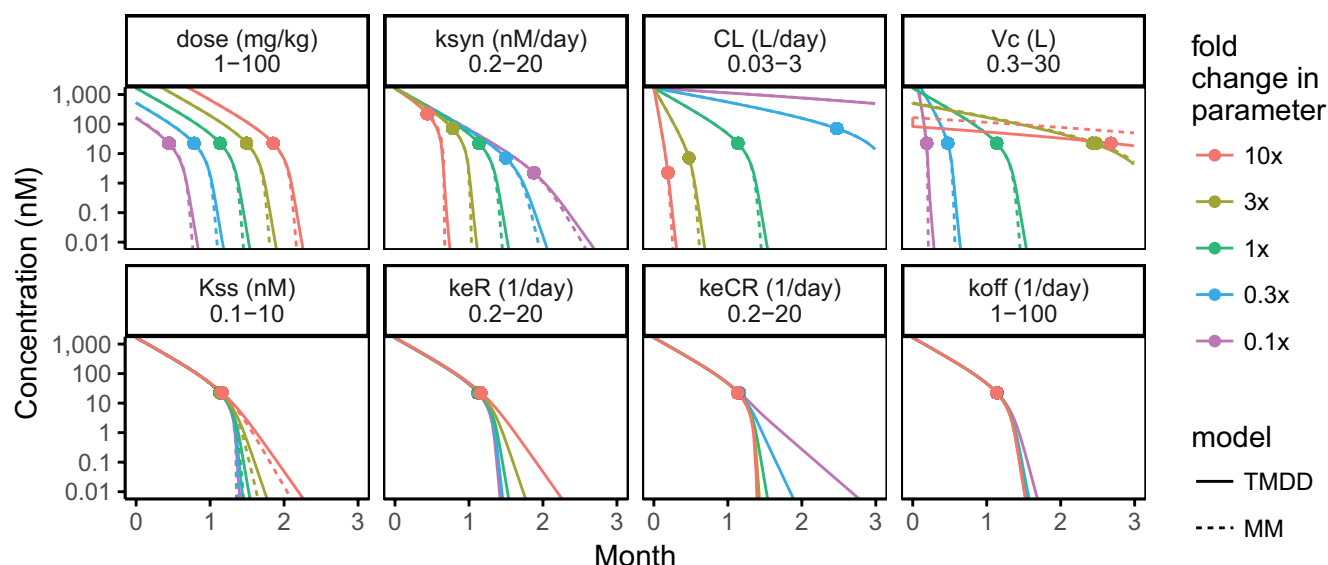


Figure 5 Mavrilimumab one-compartment Michaelis-Menten model (MM; solid line) and target-mediated drug disposition (TMDD; dashed line) model, in which the base parameter values are in **Table 1** and each plot shows a sensitivity analysis where the parameters in the title is changed from 0.1-fold to 10-fold. The dot shows critical concentration. For the TMDD model, $k_{\text{syn}} = V_{\text{max}}/V_c$, $K_{\text{ss}} = K_M$

target engagers or cytokines where the doses are much lower.^{7,12}

DISCUSSION

In practice, C_{crit} is a useful quantity. We list a few applications below.

One application of C_{crit} is in providing an initial estimate for V_{max} or k_{syn} from a graphical inspection of the data. For large, i.v. doses, CI can be estimated by non-compartmental analysis by computing the area under the curve (AUC)_{0-∞} for a single dose and then computing $\text{CI} = \text{Dose}/\text{AUC}_{0-\infty}$. Then, C_{crit} can be estimated from a graph of the PK and **Eq. 14** is then applied to get $V_{\text{max}} = C_{\text{crit}} \cdot \text{CI}$ or $k_{\text{syn}} = C_{\text{crit}} \cdot \text{CI}/V_c$.

Another application is that when fitting a population PK model, there may be patients who have similar PK above C_{crit} (and, thus, similar CI) but different C_{crit} levels. When this is observed, we have found that a random effect on V_{max} was needed to capture the intersubject variability in the low concentration data.

Finally, C_{crit} is also useful in understanding the identifiability of TMDD models when fit to data of the type shown in **Figure 1**. Here, it has been shown that once the linear PK parameters have been identified (say from high-dose data) k_{syn} is the only remaining parameter needed to determine C_{crit} . Then, given k_{syn} , K_{ss} is the only remaining parameter needed to determine the slope of the nonlinearity. Thus, these two parameters are often estimable from the nonlinear PK alone. However, other

parameters of the TMDD model, such as the receptor density $R_0 = k_{\text{syn}}/k_{\text{e(R)}}$ (often assumed to be constant with $k_{\text{e(R)}} = k_{\text{e(CR)}}$) is often not identifiable with PK data alone, as previously reported.^{10,11}

One key assumption for the C_{crit} estimate to apply is that initially, the drug concentration is large so that the nonlinear elimination term initially has a negligible contribution to the PK curve. If this assumption does not hold, there may be no kink and hence no C_{crit} . In addition, there may be a kink, but if the dose is low enough such that the nonlinear component already contributes significantly to the elimination, C_{crit} as calculated here will not describe the kink. In the extreme case that $\text{CI} \rightarrow 0$ for a drug with only saturable elimination, $C_{\text{crit}} \rightarrow \infty$ and is essentially unobservable. Thus C_{crit} as defined here is no longer of practical value in scenarios where the saturable route of elimination dominates for all observable drug concentrations, as is the case for drugs that are given at low doses, such as bispecific target engagers and cytokines. To describe the kink in the PK curve in these scenarios (shown in more detail in the **Supplementary Material**) an alternative definition of C_{crit} would be needed. C_{crit} is of its greatest utility for mAbs (or other drugs) given at sufficiently high doses, such that both linear and nonlinear elimination phases are observable.

In summary, when developing antagonists, it is often the goal to pick a dosing regimen where the drug concentration stays above C_{crit} . In this article, we have developed a simple formula for this critical concentration: $C_{\text{crit}} = V_{\text{max}}/\text{CI} = k_{\text{syn}}/k_{\text{e(C)}}$.

Supplementary Information

Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website.(www.psp-journal.com)

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