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# A Dynamical Systems Analysis of the Indirect Response Model with Special Emphasis on Time to Peak Response[1]

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*In this paper we present a mathematical analysis of the four classical indirect response models. We focus on characteristics such as the evolution of the response $R(t)$ with time $t$, the time of maximal/minimal response $T_{\max}$ and the area between the response and the baseline $AUC_R$, and the way these quantities depend on the drug dose, the dynamic parameters such as $E_{\max}$ and $EC_{50}$ and the ratio of the fractional turnover rate $k_{\text{out}}$ to the elimination rate constant $k$ of drug in plasma. We find that depending on the model and on the drug mechanism function, $T_{\max}$ may increase, decrease, decrease and then increase, or stay the same, as the drug dose is increased. This has important implications for using the shift in $T_{\max}$ as a diagnostic tool in the selection of an appropriate model.*

**KEY WORDS:** Indirect Response models, Turnover models, Time of maximal response, Peak shift, Differential equations, Pharmacodynamics.

## INTRODUCTION

The re-introduction of the turnover models (Ackerman *et. al.* (1), Nagashima and Levy (2), Ekblad and Licko (3)) by Jusko and colleagues in the early 90s (Dayneka *et. al.* (4)), the extension of those to the feedback situation (Holford *et. al.* (5), and Wakelkamp *et. al.* (6)), and integrating receptor-interaction models with feed-back governed turnover models (Sun *et. al.* (7), Zuideveld *et. al.* (8)) have rejuvenated the field of mechanism-based pharmacodynamic modeling.

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The turnover model, more recently also called the indirect response model, provides a unique tool for the pharmacokineticists, in that it logically combines features of pharmacokinetics with pharmacodynamics. It clearly distinguishes drug properties (such as $EC_{50}$) from system properties ($k_{\text{out}}$ and $k_{\text{in}}$). The turnover model is applicable to a wide range of modeling situations, ranging from modeling homeostatic features of the water balance to induction of metabolic enzymes, and pharmacological responses (see Gabrielsson and Wiener (9), and Mager *et. al.* (10) for a mini review). Few researchers have during recent years so elegantly laid out the mathematical properties of this class of models and exemplified their use as Jusko and co-workers have done in a series of papers (cf. (11-15)).

When the pharmacological response takes time to develop, and the observed response is not instantaneously related to plasma concentration of the drug, a model for this time-delay has to be incorporated. Currently, there are at least three conceptually different approaches to capture this time-delay, namely biological/mechanistic, empirical/ distributional, and receptor on/off rate models. When the time delay then has been assumed to be of distributional origin, a first-order effect-compartment (or link) model has been applied. Provided first-order plasma kinetics, a prerequisite has been a dose independent $T_{\max}$ value for experimental response data. If this is not the case a turnover (or indirect response) model has often been shown to be the solution. In other words, peak-shift or no peak-shift has become a discriminative tool for selection of the class of model. Unfortunately, lack of peak-shift with increasing doses has implied an effect-compartment model and a peak-shift has implied a turnover model by some investigators (16).

The indirect response models are constructed from a function describing the plasma kinetics, a drug mechanism function relating plasma kinetics to the type of mechanistic action (inhibition $I_{\max}/IC_{50}$ or stimulation $E_{\max}/EC_{50}$), and the turnover rates $k_{\text{in}}$ and $k_{\text{out}}$). Provided linear kinetics, the pharmacokinetic function *per se* will not contribute to a peak-shift in the pharmacological response. Also, the turnover function behaves linearly with proportional changes of the turnover rate. What is left, as a potential source of this peak-shift, is then the drug mechanism function. Simulations have shown that a peak shift may or may not occur with increasing doses, and that they can be toward earlier as well as later times (Gabrielsson and Wiener (9)). The aim of this paper is to cast light on this phenomenon from a mathematical analytical point of view and to make general statements about the dynamics that may be useful for model discrimination and experimental design purposes.

Specifically, we have two objectives:

I. Establish qualitative properties of the response curves of turnover models. Specifically, we derive upper and lower bounds for the size of the response, for the time of maximal response, or *Peak Time*, $T_{\max}$ and we obtain estimates for the behavior of these quantities as the drug dose becomes large. Many of these properties have been established before. The novelty will be, however, that here these properties will be derived by qualitative methods which involve a geometric analysis of the turnover

equation based on the theory of dynamical systems (17). An important feature of this approach is that it can also be used for the analysis of nonlinear generalizations of the basic linear turnover models and for more complex pharmacodynamic systems.

II. Study the dependence of $T_{\max}$ on the drug dose, and determine the influence of the parameters and the drug mechanism functions involved. To that end we present an asymptotic analysis for small and large drug doses, and a numerical study to cover the range of intermediate values of the drug dose.

The outline of this paper is the following. After an introduction of the different types of *turnover models*, we first present the main analytical results about the response curves and the *Peak Time* $T_{\max}$. To complete the picture, we present the outcome of a series *numerical simulations*. We then turn to a detailed *qualitative analysis* of the turnover equations and an *asymptotic analysis* of the peak time $T_{\max}(D)$ for small and large values of the drug dose. Some indications are then given of *generalizations* of these results to more general drug functions and to nonlinear versions of the turnover equation. Finally, we present a discussion and offer some conclusions of the methods we used and the results we established in this paper. We end this paper with a series of appendices in which the more delicate mathematical arguments, needed to prove our results, are presented.

For the numerical rendering of solution graphs we have used the ODE solver XPPAUT (18) and for the graphs of the Peak Time versus the drug dose we used the package Maple 9 (19).

## TURNOVER MODELS

In the basic linear turnover model the pharmacological response $R(t)$ is governed by the equation

$$\frac{dR}{dt} = k_{\text{in}} - k_{\text{out}} R \tag{1}$$

in which the turnover rate $k_{\text{in}}$ and the fractional turnover rate $k_{\text{out}}$ are the rate constants involved in the zeroth order gain term and the first order loss term, respectively (20). The action of the drug takes place through the *drug mechanism function* $H(C)$, where $C = C(t)$ is the plasma concentration of the drug as a function of time (the *drug function*) (3,4). This action may take place either via the gain term $k_{\text{in}}$, in which case Eq. (1) becomes

$$\frac{dR}{dt} = k_{\text{in}} H(C) - k_{\text{out}} R \tag{2a}$$

or via the loss term $k_{\text{out}}$, when

$$\frac{dR}{dt} = k_{\text{in}} - k_{\text{out}} H(C) R \tag{2b}$$

We consider two types of drug mechanism functions: those which *inhibit* and so reduce the effect of either the gain or the loss term:

$$H(C) = I(C) \stackrel{\text{def}}{=} 1 - I_{\max}\frac{C}{IC_{50} + C} \tag{3}$$

and those which *stimulate* and increase the effect of the gain or the loss term:

$$H(C) = S(C) \stackrel{\text{def}}{=} 1 + E_{\max}\frac{C}{EC_{50} + C} \tag{4}$$

Here the symbol $\stackrel{\text{def}}{=}$ means that the quantity on the left is *defined* to be the quantity on the right. Since the drug mechanism function needs to be positive, we will require that $0 < I_{\max} \leq 1$. An important feature of these drug mechanism functions is their boundedness:

$$1 - I_{\max} < I(C) < 1 \qquad \text{and} \qquad 1 < S(C) < 1 + E_{\max} \qquad \text{for all} \qquad C > 0.$$

In addition to these *nonlinear*, *saturating* drug mechanism functions we will discuss results for the *linear* functions

$$I(C) = 1 - \alpha C \qquad \text{and} \qquad S(C) = 1 + \alpha C \tag{5}$$

in which $\alpha$ is a positive constant. They can be viewed as approximations of the nonlinear functions when $C \ll IC_{50}$ or $C \ll EC_{50}$. In the case of inhibition we must require that $\alpha$ and $C$ are so small that $I(C)$ remains positive.

In this paper we focus on four different linear turnover models: two models in which the turnover rates $k_{\text{in}}$ and $k_{\text{out}}$ are inhibited; we denote these models by Model I and Model II. In the other two models these turnover rates are stimulated. They will be called, respectively, Model III and Model IV (4). We do this for the nonlinear, as well as for the linear drug mechanism functions given in Equations (3)-(5). The four models are shown schematically in Figure 1.

Since the emphasis in this paper is on the dynamics of the four turnover models, we will often assume a very simple drug function:

$$C(t) = De^{-kt}, \qquad k > 0 \tag{6}$$

where $k$ is the elimination rate and $D$ a positive constant which is a measure for the amount of drug that has been administered. We shall call it the *Drug Dose*. The volume of distribution is set equal to unity. Many of the methods used in this paper can also be applied when the drug function is more complex. As an example we shall discuss the dynamics of the turnover models when the drug function is the *Bateman function*, which mimics a first order input ($k_a$) – output ($k$) process:

$$C(t) = D(e^{-kt} - e^{-k_a t}), \qquad k_a > k \tag{7}$$

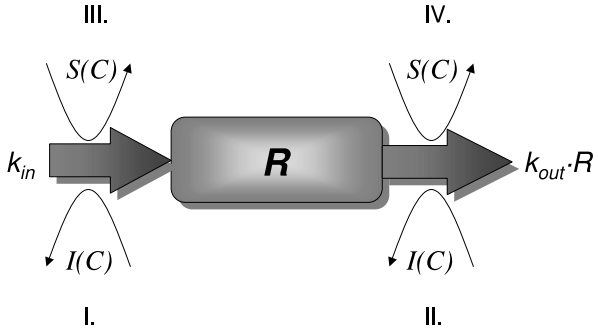



Figure 1: Schematic illustration of the four turnover models. The models I and II represent inhibition $I(C)$ of, respectively, the turnover rates $k_{\text{in}}$ and $k_{\text{out}}$, and the models III and IV represent stimulation $S(C)$ of these turnover rates(4)

When no drug is present, i.e. when $D = 0$ and hence $H = 1$, the Equations (2a) and (2b) reduce to Eq. (1). This equation has a unique equilibrium state, often referred to as the *Baseline*:

$$R = R_0 \stackrel{\text{def}}{=} \frac{k_{\text{in}}}{k_{\text{out}}} \tag{8}$$

and any solution $R(t)$ converges to $R_0$ as $t \to \infty$. Henceforth we assume that the system is in this state when, at $t = 0$, the drug is administered, i.e.

$$R(0) = R_0 \tag{9}$$

When a drug has been given, and the plasma concentration is given by Eq. (6) or Eq. (7), the response $R(t)$ is determined by the differential equation (2a) or (2b) together with the initial value given by Eq. (9). We shall show that in the models I and IV, the response decreases monotonically after administration, reaches a minimum, and then increases monotonically to the initial state $R_0$. In the models II and III the order is reversed: the response first rises to a maximum and then drops monotonically back to the initial state. In Figure 2 we show four typical sets of graphs of $R(t)$.

The time at which the response $R(t)$ reaches its extreme value, either a minimum or a maximum, will be called $T_{\max}$. We shall often refer to it as the *Peak Time*. We shall be interested to learn how $T_{\max}$ depends on the drug dose $D$, and derive qualitative properties of the response curves in the four models, both for nonlinear and for linear drug mechanism functions.

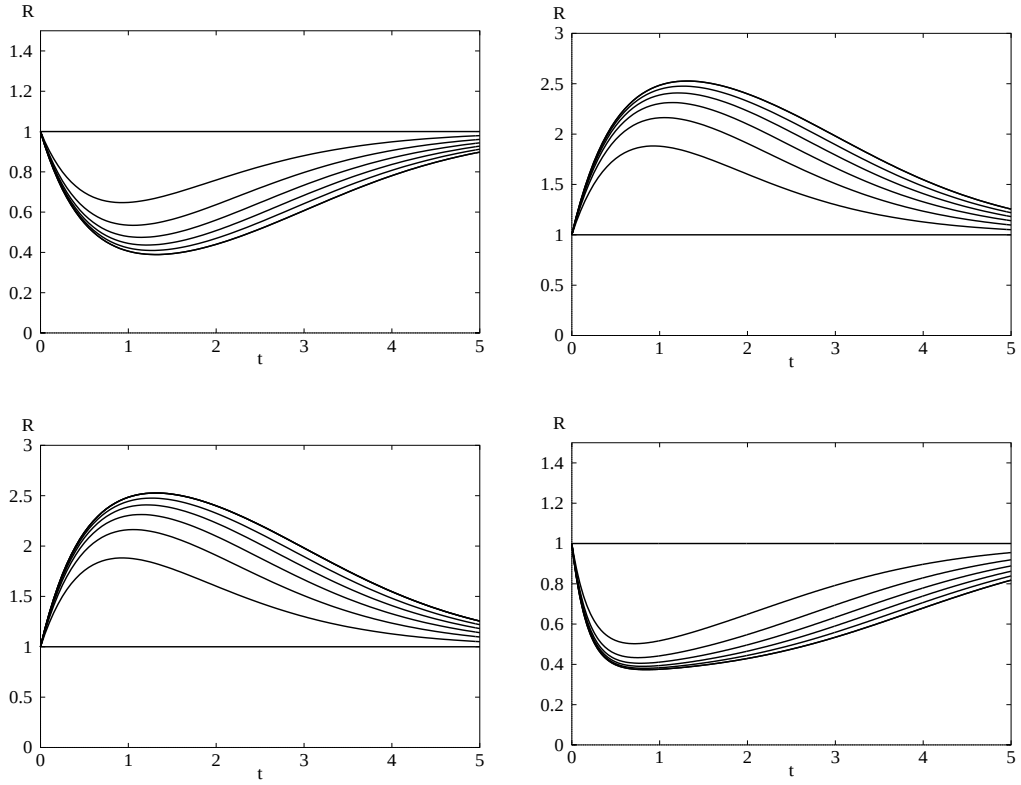



Figure 2: Response curves $R(t)$ versus time $t$ for the models I (top left), II (top right), III (bottom left) and IV (bottom right) when $k_{\text{in}} = 2$, $k_{\text{out}} = 2$, $k = 1$, $I_{\max} = 0.8$, $E_{\max} = 2$, $IC_{50} = 1$, $EC_{50} = 1$, and $D = 2$, 4, 6, 8, 10, 12

Many of the methods used in this paper are qualitative, and can also be applied to nonlinear turnover models, such as described by the equation

$$\frac{dR}{dt} = k_{\text{in}} - k_{\text{out}} \frac{R}{R_{50} + R} \tag{10}$$

in which the loss term saturates and $k_{\text{in}}$, $k_{\text{out}}$ and $R_{50}$ are positive constants (cf. (21,22)). At the end of this paper we shall obtain some qualitative results for this nonlinear model.

## THE PEAK TIME $T_{\max}$

In this section we first present a series of analytical results about the way the response $R(t)$ and the peak time $T_{\max}$ depend on the drug dose $D$. We begin with a few qualitative observations and then present the behavior of $T_{\max}$ for small and large doses. To complete the picture, we give in the next section numerically computed graphs of the function $T_{\max}(D)$ for the four different models I-IV, both when $H$ is nonlinear, and when it is linear.

**Dimensionless variables**

The basic equations (2a) and (2b) feature a range of constants: the turnover-related rates $k_{\text{in}}$ and $k_{\text{out}}$, the kinetic constants $I_{\max}$, $IC_{50}$ and $E_{\max}$, $EC_{50}$, and finally the constants in the drug function: the drug dose $D$ and the elimination rate $k$. It is then useful to introduce dimensionless variables. By doing so we achieve two objectives:

- Different constants combine into a smaller number of dimensionless parameters, each endowed with a physiological meaning.
- The resulting equations are simpler and thereby more transparent.

Let us introduce the following dimensionless variables:

$$t^* = kt, \qquad R^* = \frac{R}{R_0} = \frac{k_{\text{out}}}{k_{\text{in}}} R \qquad \text{and} \qquad \kappa = \frac{k_{\text{out}}}{k} \tag{11}$$

Thus, the new dimensionless time $t^*$ compares physical time with the characteristic time $(1/k)$ of the elimination of the drug, and the new dimensionless response $R^*(t)$ compares the response $R(t)$ to the equilibrium response $R_0$ in the absence of a drug. Finally, the new dimensionless parameter $\kappa$ compares the decay rate $k_{\text{out}}$ of the response in the absence of a drug, to the elimination rate $k$ of the plasma concentration.

We also scale the concentration, and set

$$C^* = \frac{C}{IC_{50}} \qquad \text{or} \qquad C^* = \frac{C}{EC_{50}} \tag{12}$$

depending on whether the drug inhibits or stimulates. In terms of these new variables, equations (2a) and (2b) become

$$\frac{dR^*}{dt^*} = \kappa\big\{H^*(C^*) - R^*\big\} \tag{13a}$$

$$\frac{dR^*}{dt^*} = \kappa\big\{1 - H^*(C^*)R^*\big\} \tag{13b}$$

where $H^*(C^*) = I^*(C^*)$ or $H^*(C^*) = S^*(C^*)$, and the new drug mechanism functions $I^*$ and $S^*$ are given by

$$I^*(C^*) = 1 - \alpha\frac{C^*}{1+C^*} \qquad \text{and} \qquad S^*(C^*) = 1 + \alpha\frac{C^*}{1+C^*} \tag{14a}$$

in which $\alpha = I_{\max}$ in $I^*$ and $\alpha = E_{\max}$ in $S^*$. When the drug mechanism functions are linear they become

$$I^*(C^*) = 1 - \alpha C^* \qquad \text{and} \qquad S^*(C^*) = 1 + \alpha C^* \tag{14b}$$

The initial value of the response $R$, and the drug function $C$ have become

$$R^*(0) = 1 \qquad \text{and} \qquad C^*(t^*) = D^* e^{-t^*} \tag{15}$$

where we have scaled $D$ like we scaled $C$ in Eq. (12), i.e., $D^* = D/IC_{50}$ or $D^* = D/EC_{50}$.

Thus, we have now reduced the original problem to one in which the relevant parameters are the relative turnover rate $\kappa$, the constant $\alpha$ in the drug mechanism functions, and the drug dose $D^*$, i.e., these three parameters completely determine the dynamics of the turnover model. This implies in particular that the dynamics is not so much determined by the drug dose alone, but by its relation to $I_{\max}$ or $E_{\max}$, i.e., if $I_{\max}$ or $E_{\max}$ is small then even a small drug dose can have a large impact.

**Pharmacodynamic properties**

We are now ready to formulate a series of general properties of the dynamics of the response $R(t)$. In Properties A-E we impose only global conditions on the drug function $C(t)$. In Property F we assume that $C(t)$ is given by Eq. (6).

**Property A:** When the plasma concentration $C(t)$ vanishes as $t \to \infty$, then the response returns to the baseline value:

$$R(t) \to R_0 \qquad \text{as} \qquad t \to \infty$$

This means that there will be no residual effect, i.e., when the drug leaves the body, the body returns to its original state. We prove that the turnover models I - IV all have this property.

**Property B:** Suppose that the drug function $C(t)$ is either *decreasing*, or first *increasing* and then *decreasing*, and the drug mechanism functions $I(C)$ and $S(C)$ are given by Equations (3) and (4) or (5), then the graph of $R(t)$ has precisely one critical point: a minimum in models I and IV, and a maximum in models II and III.

**Property C:** Let $C(t)$ be an arbitrary drug function. When the drug mechanism functions $I(C)$ and $S(C)$ are nonlinear, and given by Equations (3) or (4), we have the following bounds, which are independent of the drug dose:

| | | | |
|---|---|---|---|
| $R(t;D) > R_0\{1 - I_{\max}(1 - e^{-k_{\text{out}}t})\}$ | for | model I | $0 < I_{\max} \leq 1$ |
| $R(t;D) < \dfrac{R_0}{1 - I_{\max}}(1 - I_{\max}e^{-(1-I_{\max})k_{\text{out}}t})$ | for | model II | $0 < I_{\max} < 1$ |
| $R(t;D) < R_0(1 + k_{\text{out}}t)$ | for | model II | $I_{\max} = 1$ |
| $R(t;D) < R_0\{1 + E_{\max}(1 - e^{-k_{\text{out}}t})\}$ | for | model III | $E_{\max} > 0$ |
| $R(t;D) > \dfrac{R_0}{1 + E_{\max}}(1 + E_{\max}e^{-(1+E_{\max})k_{\text{out}}t})$ | for | model IV | $E_{\max} > 0$ |

**Property D:** When the drug mechanism functions $I(C)$ and $S(C)$ are linear, and the drug function is of the form $C(t) = Dc(t)$, where $c(t)$ does not depend on $D$, then in the models I and III the peak time $T_{\max}(D)$ is constant, i.e. it does not change when $D$ varies.

**Property E:** When the drug mechanism functions $I(C)$ and $S(C)$ are nonlinear and $I_{\max} < 1$, then in all four models,

$$T_{\max}(D) \to \infty \qquad \text{as} \qquad D \to \infty$$

and the rate of growth is at least logarithmic, i.e. there exists a constant $c_0 > 0$ such that

$$T_{\max} > c_0 \log(D) \qquad \text{for large values of} \quad D$$

The Properties A-E are not all new. We mention in particular the references (10-15) and (23), where many of them were established. In these studies essential use was made of the fact that it is possible to solve the equations for $R(t)$ explicitly. A drawback of this method is that the resulting expressions can get very involved, especially when the drug function becomes complex. In such cases the explicit solution yields little qualitative insight into the dynamics of the process. Another limitation of this method is that it is mainly restricted to linear equations.

In this paper we adopt a different approach and prove the properties **A, B, C, D** and **E** by using *qualitative*, and *geometric* arguments which are familiar in the theory of dynamical systems. Such an approach is conceptually attractive since it readily gives insight in the dynamics of the problem. In addition, this approach can be used to study linear and nonlinear problems alike.

In a similar spirit, we derive simple expressions for $R(t)$ and $T_{\max}$ when the dose is either small or large. In order to keep the formulas transparent we will phrase the following results in terms of the *dimensionless variables* introduced in Eqs. (11) and (12). However to avoid a plethora of asterisks, we will retain the original notation.

From now on we assume that $C(t)$ is given by Eq. (6), i.e., in dimensionless variables, by

$$C(t) = De^{-t}$$

**Small doses**. We note that when we expand the nonlinear functions $I(C)$ and $S(C)$ in powers of $C$, we find that

$$I(C) = 1 - \alpha C + O(C^2) \qquad \text{and} \qquad S(C) = 1 + \alpha C + O(C^2)$$

i.e., the first two terms on the expansion agree with the linear drug mechanism functions. [1] In fact, we find that for all the four turnover models I-IV – whether nonlinear or linear – the peak time $T_{\max}$ converges to the same positive value as the drug dose becomes small:

$$T_{\max}(D) \to T_0 \qquad \text{as} \qquad D \to 0 \tag{16a}$$

The limiting value $T_0$ is given by

$$T_0 = T_0(\kappa) \stackrel{\text{def}}{=} \begin{cases} \dfrac{\log(\kappa)}{\kappa - 1} & \text{if} \quad \kappa \neq 1 \\ 1 & \text{if} \quad \kappa = 1 \end{cases} \tag{16b}$$

[1] For the definition of the symbol $O$, see the list of symbols at the end of this paper

Recall that when $\kappa = 1$ the decay rate $k$ of the drug function is the same as the fractional turnover rate $k_{\text{out}}$.

In the question as to whether the peak time is delayed, advanced or unchanged when a small amount of the drug is given, the models differ. This question can be answered by computing the slope with which the graph of $T_{\max}(D)$ intersects the vertical axis $D = 0$: if the slope is positive then $T_{\max}(D)$ increases with increasing drug dose, whilst if the slope is negative it decreases with increasing drug dose (cf. Figures 5, 6 and 7). We find the following expression when $I$ and $S$ are nonlinear:

$$\frac{dT_{\max}}{dD}(D) \to \left\{ \begin{array}{ll} +L_1 & \text{in models I and III} \\ L_1 + \alpha L_2 & \text{in model II} \\ L_1 - \alpha L_2 & \text{in model IV} \end{array} \right\} \qquad \text{as} \qquad D \to 0 \qquad (17)$$

The constants $L_1 = L_1(\kappa)$ and $L_2 = L_2(\kappa)$ are given by

$$L_1(\kappa) = \begin{cases} \dfrac{1}{\kappa - 2}(2e^{-T_0} - 1) & \text{if} \quad \kappa \neq 2 \\ \log(2) - \dfrac{1}{2} & \text{if} \quad \kappa = 2 \end{cases}$$

and

$$L_2(\kappa) = \begin{cases} \dfrac{\kappa}{\kappa - 2} - \dfrac{\kappa + 2}{\kappa - 2}e^{-T_0} & \text{if} \quad \kappa \neq 2 \\ \dfrac{3}{2} - 2\log(2) & \text{if} \quad \kappa = 2 \end{cases}$$

Note that $L_1$ and $L_2$ only depend on the value of $\kappa = k/k_{\text{out}}$. It turns out that

$$L_1(\kappa) > 0 \quad \text{and} \quad L_2(\kappa) > 0 \qquad \text{for all} \qquad \kappa > 0.$$

Thus we have established the following property:

**Property F:** In the models I, II and III the peak time *increases* whilst in the model IV the peak time *decreases* for small increasing drug dose, provided $E_{\max}$, or $\alpha$, is large enough. Specifically, we then require

$$\alpha > \frac{L_1(\kappa)}{L_2(\kappa)}.$$

**Remark.** Note that equation Eq. (17) states that in the models I and III, at $D = 0$ the slope of the graph of the function $T_{\max}(D)$ only depends on the value of $\kappa$ and not on the value of $\alpha$. This was observed before in (11) and (12).

When $I(C)$ and $S(C)$ are linear, then from Property **D** we conclude that in the models I and III $dT_{\max}/dD(D) = 0$ for all $D > 0$. For the models II and IV we show that:

$$\frac{dT_{\max}}{dD}(D) \to \left\{ \begin{array}{ll} +\alpha L_2 & \text{in model II} \\ -\alpha L_2 & \text{in model IV} \end{array} \right\} \qquad \text{as} \qquad D \to 0^+ \qquad (18)$$

Thus, in model IV the peak time comes earlier, whilst in model II it comes later when a small dose is given.

For details of the derivation of these limits, we refer to the section on asymptotics.

**Large doses**. Here, there is an important difference between the nonlinear and the linear drug mechanism functions.

**Nonlinear drug mechanism functions.** We shall see in the section on qualitative analysis that in each of the four models, for fixed $t$:

$$R(t;D) \to \overline{R}(t) \qquad \text{as} \qquad D \to \infty$$

where $\overline{R}(t)$ denotes the lower bound (in models I and II) or the upper bound (in models III and IV) defined in Property C. It is a strictly monotone function: decreasing in the models I and IV and increasing in the models II and III. This means that in each model $T_{\max}(D) \to \infty$ as $D \to \infty$. Specifically, we prove that

$$T_{\max}(D) \sim K(\kappa,\alpha)\log(D) \qquad \text{as} \qquad D \to \infty \tag{19}$$

where $K(\kappa,\alpha)$ is a positive constant, which depends on $\kappa$ and $\alpha$, and on the model. A qualitative argument shows that $K(\kappa,\alpha) \le 1$ for all $\kappa > 0$ and $\alpha > 0$ ($\alpha \le 1$ in the models I and II) [2].

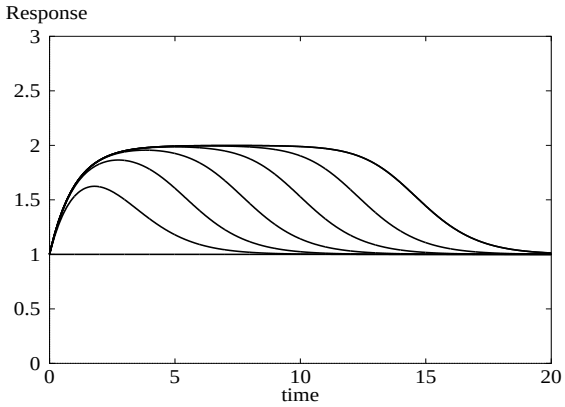



Figure 3: The *Wave*: Response curves $R(t)$ of model III with nonlinear drug mechanism function, for $\kappa = 10$, $\alpha = 1$ and $D = 10^n,\ n = 0, 1, \ldots, 6$

In Figure 3 we show the response curves for increasing values of the drug dose, andwe see what looks like a progressing wave: the maximum of the response no longerincrease, and approaches the value $1 + \alpha$, but the duration of the response grows with a rate which is proportional to $\log(D)$. In the section on qualitative analysis we shall show that in the limit, the shape of this wave no longer changes in suitably moving coordinates.

[2]For the definition of the symbol $\sim$, see the list of symbols at the end of the paper

Figure 3 suggests we transform to a coordinate frame which shifts as $D$ changes and introduce the new variable $s$,

$$t = \log(D) + s$$

We then show that for fixed $s$,

$$R(\log(D) + s; D) \to \Phi(s) \qquad \text{as} \qquad D \to \infty \tag{20}$$

where $\Phi(s)$ is a monotone function defined on $s \in (-\infty, \infty)$: decreasing in the models II and III and increasing in the models I and IV. In Qualitative Analysis we prove Equations (19) and (20), and we give an expression for the limiting shape $\Phi(s)$.

In the special case, when in model II we take $\alpha = 1$, the upper bound $\overline{R}(t)$ is not a bounded function, but one that grows linearly as $t \to \infty$. For this case we find a different type of wave phenomenon, which is shown in Figure 4.

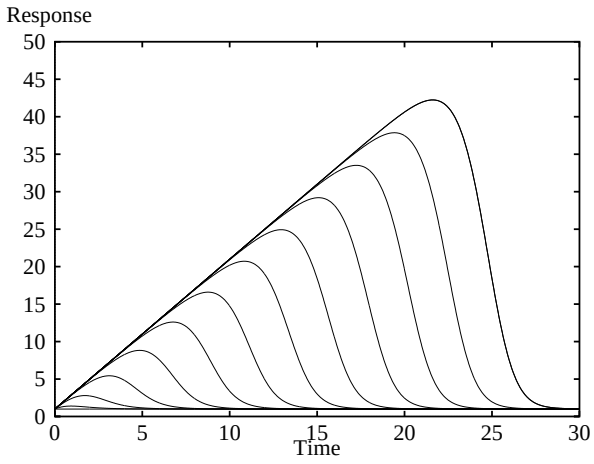



Figure 4: The *Tsunami*: Response curves $R(t)$ of model II with nonlinear drug mechanism function, when $\alpha = 1$. Here $\kappa = 2$ and $D = 10^n,\ n = 0, 1, \ldots, 11$

**Linear drug mechanism functions.** In the linear models there are no comparable uniform upper or lower bounds for the response:

• In models I and III, in which the gain is either stimulated or inhibited, the magnitude of the response is proportional to $D$, and $T_{\max}$ does not move.

• In model IV, in which the loss is stimulated, the response always stays positive, and we find that $T_{\max}$ *decreases* with increasing drug dose. Specifically we show that

$$T_{\max}(D) \sim \frac{2}{\alpha\kappa}\frac{\log(D)}{D} \qquad \text{as} \quad D \to \infty \tag{21}$$

In model II the concentration is restricted, since we require that $I(C) = 1 - \alpha C \geq 0$. Hence, this model is of no practical interest for large drug doses.

Details of the small and the large dose asymptotics are given in the section on asymptotics.

## NUMERICAL RESULTS

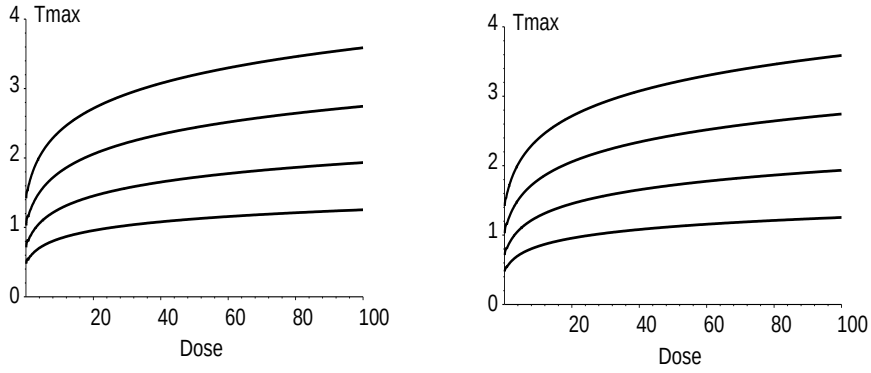
In order to gain further insight into the question of monotonicity we have computed $T_{\max}(D)$ numerically in the four models, when $I(C)$ and $S(C)$ are nonlinear (hyperbolic) and for the models II and IV when $I(C)$ and $S(C)$ are linear. The results of these computations are shown in this section.

The graphs in this section have been made by means of Maple 9 (19). We substituted the explicit expression for $R(t; D)$ into the right hand side of the differential equation. Since $R' = 0$ at the peak time $T_{\max}$, we obtain an implicit relation between $T_{\max}$ and $D$. For models I and III, this relation becomes

$$H(De^{-T_{\max}}) - R(T_{\max}; D) = 0 \tag{22}$$

Maple 9 is then used to plot $T_{\max}$ versus $D$. For the models II and IV a similar relation is found.

**Case I: $I(C)$ and $S(C)$ are nonlinear.** In this case $I(C)$ and $S(C)$ are given by Equations (3) and (4), or, in dimensionless variables, in Eq. (14a). In Figure 5 we show graphs of $T_{\max}$ for the models I and III.




model I model III

Figure 5: Dependence of $T_{\max}$ on the drug dose $D$ when the drug affects the gain term, as in models I and III, and $H(C)$ is nonlinear. Here $\kappa$ takes the values 0.5 (top), 1, 2 and 3 (bottom). The graphs are the same in both models and independent of $\alpha$

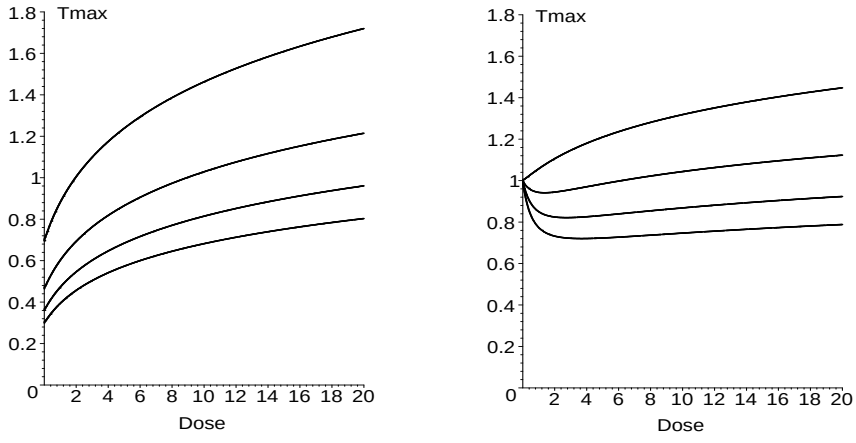
We see that in the models I and III, the peak time $T_{\max}$ increases with the drug dose $D$ and drops with increasing $\kappa$.

The graphs in Figure 5 look the same, and indeed, they are the same. To see this one substitutes the explicit solution of Eq. (13a) into Eq. (22). One then finds that the constant $\alpha$ factors out, so that $T_{\max}$ does not depend on $\alpha$. Because the

models I and III only differ by the sign in front of $\alpha$ it follows that

$$T_{\max}(D)\Big|_{\text{model I}} = T_{\max}(D)\Big|_{\text{model III}} \qquad \text{for all} \qquad D > 0$$

In Figure 6 we show analogous graphs for models II and IV. Here we see demon-




model II model IV

Figure 6: Dependence of $T_{\max}$ on the dose $D$ when the drug affects the loss term, as in models II and IV, and $H(C)$ is nonlinear. In model II, we have taken $\kappa = 2, 4, 6$ and 8 (going down) and $\alpha = 0.5$. In model IV we took $\kappa = 1$ and $\alpha = 2, 3, 6$ and 8 (going down)

strated what we found in Eq. (17) for model IV: if $\alpha$ is small, then $T_{\max}$ *increases* for small doses, whilst if $\alpha$ is larger, it will first *decrease* with increasing doses. In all four models, we see that eventually the peak time becomes larger as the dose $D$ is increases. Similar trends in experimental data have also been reported in the literature when the drug is acting on the loss of response (24).

**Case II: $I(C)$ and $S(C)$ are linear.** Now, $I(C)$ and $S(C)$ are given by Eq. (5) or Eq. (14b). As we saw in Property D, in models I and III the peak time $T_{\max}$ does not change when $D$ varies. In Figure 7 we show the graph of $T_{\max}$ for the model IV when $\kappa = 2$ and $\alpha = 1$. In the linear model II we require that $\alpha D < 1$ for it to make sense, i.e., we need $D < 1/\alpha$. Large values of $D$ are therefore uninteresting in this model.

We observe that in the **linear** model IV, the peak time $T_{\max}(D)$ is monotonically decreasing for **all** $D > 0$, in contrast to what we see in model IV when the drug mechanism function is **nonlinear**. In that case we know from Property E that $T_{\max}(D)$ will be eventually be increasing again when $D$ becomes large.

## QUALITATIVE ANALYSIS

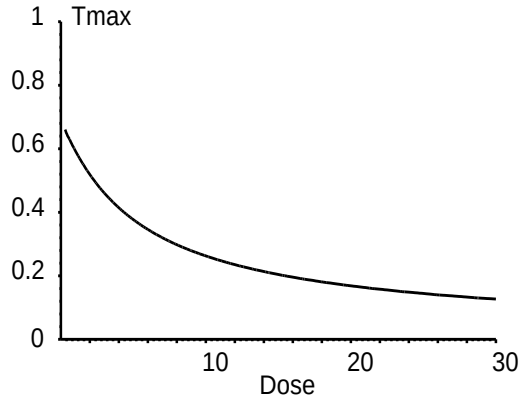



Figure 7: Dependence of $T_{\max}$ on the dose $D$ in model IV when $H(C)$ is linear. Here $\kappa = 2$ and $\alpha = 1$

In this section we prove Properties A-F of the response function $R(t)$ and the Peak time $T_{\max}$. We shall do this by a careful analysis of the basic differential Eqs. (2a) and (2b), in which we view the solution $R(t)$ as a *curve* or *orbit* in the $(t, R)$-plane, parametrized by the time variable $t$. We denote this curve by $\gamma$ and write it as:

$$\gamma = \{(t, R(t)) : 0 \leq t < \infty\}$$

Since $t > 0$ and $R > 0$ this orbit $\gamma$ will lie in the first quadrant. Figure 8 shows examples of orbits in the four different models. It is our objective in this section to investigate their characteristic shapes and their dependence on the parameters $D$, $\kappa$ and $\alpha$.

Throughout this section we use dimensionless variables, and, in order to keep the analysis simple and transparent, we assume that the drug function is given by Eq. (6), i.e., in dimensionless variables,

$$C(t) = De^{-t} \tag{23}$$

In the section on Genaralizations we shall discuss more general drug functions, including the Bateman function Eq. (7).

**The shape for the response curve**

To be specific, we study the *shape* of the function $R(t)$ for model III. For the other models the analysis is similar. The basic differential equation for this model is

$$\frac{dR}{dt} = \kappa\{S(C(t)) - R\} \tag{24}$$

For any given point in the $(t, R)$-plane, we can compute the sign of the right hand side of equation (24) and so decide whether at this point the orbit goes *up* or *down*, i.e., what the direction is of the orbit. When the right hand side vanishes, the orbit goes neither up nor down, but has a horizontal tangent. For convenience, we define

the composite function

$$\varphi(t) \stackrel{\text{def}}{=} S(C(t))$$

Then we see that at points in the $(t, R)$-plane where $R$ and $t$ satisfy the equation

$$R = \varphi(t)$$

the orbit has a horizontal tangent. The curve of these points is called the *Nullcline* and we denote it by $\Gamma$:

$$\Gamma \stackrel{\text{def}}{=} \{(t, R) : t > 0 : R = \varphi(t)\} \tag{25}$$

In Figure 8 we have drawn the nullcline of Eq. (24) when the drug function is given by Eq. (23) as well as four orbits, each starting at $R(0) = 1$, and each with a different value of $\kappa$. We deduce from the differential equation (24) that:

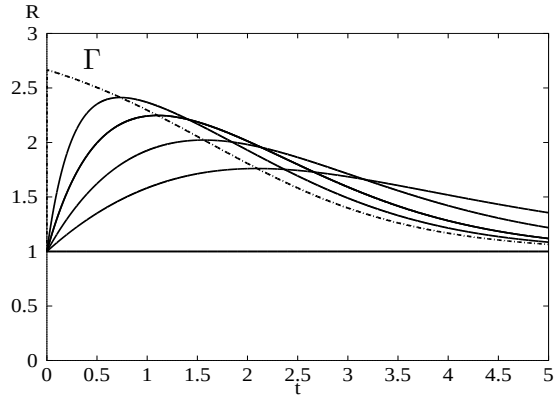



Figure 8: The nullcline $\Gamma$ (dashed) and four orbits for model III, when $D = 4$, $\alpha = 2$ and $\kappa = 0.5$ (bottom) , 1, 2, 4 (top)

*Below* $\Gamma$*, orbits move* **up** *and above* $\Gamma$*, orbits move* **down**

It follows from the Chain Rule that

$$\frac{d\varphi}{dt} = \frac{dS}{dC}\,\frac{dC}{dt} \tag{26}$$

Hence, because $S(C)$ – as defined by Eq. (14a) or Eq. (14b) – is increasing i.e., $dS/dC > 0$, the sign of $d\varphi/dt$ is the same as the sign of $dC/dt$. Thus, for the drug function defined by Eq. (23),

$$\frac{d\varphi}{dt} < 0 \tag{27}$$

We now follow the orbit which starts with initial value $R(0) = 1$, i.e., at the point $(t, R) = (0, 1)$ in the $(t, R)$-plane. Because

$$\varphi(0) = S\left(C(0)\right) = S(D) > 1,$$

the orbit starts at a point which lies below $\Gamma$. Therefore, initially the orbit goes up. It will continue to do so as long as it lies below $\Gamma$, and so eventually it must hit the nullcline $\Gamma$, and cross it, say at time $t = T$. Once it lies above $\Gamma$ it will go down again, and the question is: can it cross $\Gamma$ a second time? The answer is no.

Suppose, by way of contradiction, that it does cross $\Gamma$ again at some later time $t_0$. Then

$$R(t) - \varphi(t) > 0 \quad \text{for} \quad T < t < t_0 \qquad \text{and} \qquad R(t_0) - \varphi(t_0) = 0$$

This means that

$$\frac{d}{dt}\{R(t) - \varphi(t)\}\Big|_{t=t_0} \leq 0$$

Because $dR/dt = 0$ on $\Gamma$ and hence at $t_0$, this implies that

$$-\frac{d\varphi}{dt}(t_0) \leq 0$$

This contradicts Eq. (27), and we may conclude that the orbit does not intersect the nullcline $\Gamma$ a second time. Thus, it has to stay above $\Gamma$ forever. We conclude that

*The graph of $R(t)$ first goes up and then comes down again and decreases monotonically as $t \to \infty$;*

Thus, we have shown that there exists a time $T > 0$ when the orbit crosses $\Gamma$ and that for all $t > T$, the orbit will be decreasing. Since it is bounded below by the line $R = 1$ it follows that $R(t)$ tends to a limit, say $L$, i.e. $R(t) \to L$ as $t \to \infty$. It is clear that $L \geq 1$. Suppose that $L > 1$. Then Eq. (23) implies that

$$\frac{dR}{dt}(t) \to \kappa(1 - L) < 0 \qquad \text{as} \qquad t \to \infty$$

which, in turn, implies that $R(t) \to -\infty$ as $t \to \infty$, a contradiction. Therefore, $L = 1$, and we conclude that

$$R(t) \to 1 \qquad \text{as} \qquad t \to \infty \tag{28}$$

**Conclusion:** *There exist a time $T_{\max} > 0$ such that $R(t)$ increases on $(0, T_{\max})$ and decreases on $(T_{\max}, \infty)$, and $R(t) \to 1$ as $t \to \infty$.*

This establishes the Properties A and B for the drug function given by Eq. (6).

A different proof of the above Conclusion was given in (12).

### Bounds of the response

We derive bounds for the response $R(t)$. Since the nonlinear drug mechanism functions $I(C)$ and $S(C)$ level off, and saturate, whilst the linear drug mechanism functions are unbounded for large doses, we obtain different types of bounds.

**I. Nonlinear drug mechanism functions.** In this case we obtain bounds which are independent of the drug dose $D$. We consider model III in some detail and quote the bounds for the other models. In model III, the response $R$ is governed by the equation

$$R' = \kappa\{S(C) - R\} \qquad \text{where} \qquad R' = \frac{dR}{dt}$$

Since

$$S(C) = 1 + \alpha\frac{C}{1+C} < 1 + \alpha \qquad \text{for all} \qquad C > 0$$

it follows that

$$R' < \kappa(1 + \alpha - R)$$

Let $\overline{R}(t)$ be the solution of the problem

$$R' = \kappa(1 + \alpha - R), \qquad R(0) = 1$$

Then, by a standard comparison lemma (17) (see also Appendix B),

$$R(t) < \overline{R}(t) = 1 + \alpha(1 - e^{-\kappa t}) \qquad \text{for} \qquad t > 0 \tag{29}$$

In Figure 9 we show a family of response curves for different drug doses, as well as the upper bound $\overline{R}(t)$.

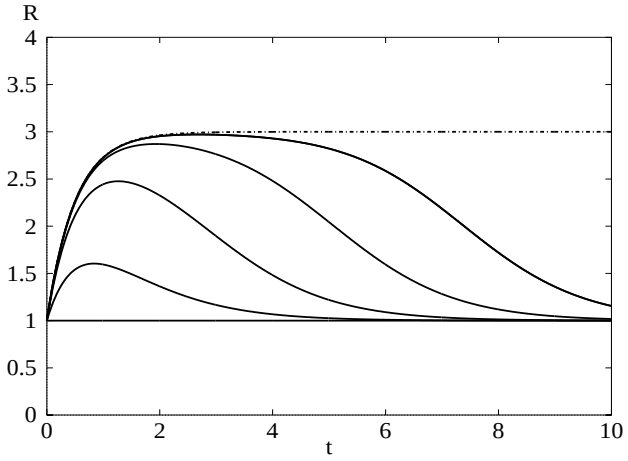



Figure 9: Response curves $R(t)$ for model III for $\kappa = 2$, $\alpha = 2$ and $D = 1,\ 10,\ 100,\ 1000$, and the upper bound $\overline{R}(t)$ (dashed)

The corresponding bounds for the models I, II, IV are

$$R(t) > 1 - \alpha(1 - e^{-\kappa t}) \qquad \text{model I} \tag{30}$$

$$R(t) < \frac{1}{1-\alpha}\left\{1 - \alpha e^{-(1-\alpha)\kappa t}\right\} \quad (0 < \alpha < 1) \quad \text{model II} \tag{31}$$

$$R(t) > \frac{1}{1+\alpha}\left\{1 + \alpha e^{-(1+\alpha)\kappa t}\right\} \qquad \text{model IV} \tag{32}$$

In model II we have assumed that $0 < \alpha < 1$ and used the inequality

$$1 - \alpha\frac{C}{1+C} > 1 - \alpha.$$

When $\alpha = 1$, then in model II we can only say that

$$R' < \kappa \qquad \text{and} \qquad R(0) = 1$$

which means that

$$R(t) < 1 + \kappa t \qquad \text{for all} \qquad t > 0 \tag{33}$$

Similar bounds were given by Krzyzanski and Jusko (12).

**Remark.** Note that in the derivation of these bounds the particular form of the drug function has played no role.

**II. Linear drug mechanism functions.** If $I(C)$ or $S(C)$ depend linearly on $C$, the response in the models I and III depends linearly on $D$. To see this, we introduce a new dependent variable $r(t)$:

$$R(t) = 1 + \alpha D r(t) \tag{34}$$

We find that $r(t)$ is a solution of the problem

$$r' = \kappa(e^{-t} - r), \qquad r(0) = 0$$

which can be given explicitly by

$$r(t) = \frac{\kappa}{\kappa - 1}(e^{-t} - e^{-\kappa t}) \qquad \text{if} \quad \kappa \neq 1$$

Hence the response $R(t)$ is given by

$$R(t) = 1 + \alpha D\frac{\kappa}{\kappa - 1}(e^{-t} - e^{-\kappa t}) \qquad \text{if} \quad \kappa \neq 1$$

It is clear that in these models the peak time does not depend on $D$. In the next section we shall show that

$$T_{\max} = \frac{\log \kappa}{\kappa - 1} \quad \text{if} \quad \kappa \neq 1 \quad \text{and} \quad T_{\max} = 1 \quad \text{if} \quad \kappa = 1 \tag{35}$$

**Remark.** The analysis above reveals that in models I and III $T_{\max}$ does not depend on $\alpha$ either if the drug mechanism functions are linear.

For the models II and IV we can establish bounds for $R(t)$ as before; they are:

$$R(t) < \frac{1}{1-\alpha D}\left\{1 - \alpha D e^{-(1-\alpha D)\kappa t}\right\} \qquad (\alpha < 1/D) \quad \text{model II} \tag{36}$$

$$R(t) > \frac{1}{1+\alpha D}\left\{1 + \alpha D e^{-(1+\alpha D)\kappa t}\right\} \qquad \text{model IV} \tag{37}$$

Note that these bounds depend on the drug dose $D$.

**Bounds of the Peak Time**

The bounds obtained above also yield lower bounds for the peak time $T_{\max}$. To see this, we return to the discussion of model III.

Let us denote the orbit which corresponds to the upper bound $\overline{R}(t)$ by $\overline{\gamma}$. Since $\overline{\gamma}$ runs from the point $(t, R) = (0, 1)$ to the point $(\infty, 1+\alpha)$ in the $(t, R)$-plane, and the nullcline $\Gamma$ runs from the point $(0, S(0))$ to the point $(\infty, 1)$, and $S(0) > 1$, it follows that the two curves must intersect. Since they are both monotone, $\overline{\gamma}$ increasing and $\Gamma$ decreasing, there exists precisely one point of intersection, say at $t = \overline{T}$. Because $\gamma$ lies below $\overline{\gamma}$, it follows that

$$T_{\max}(D) > \overline{T}(D) \qquad \text{for} \qquad D > 0 \tag{38}$$

We find that this lower bound also holds for the other models. In each of these models $\overline{T}(D)$ is defined as the unique time at which the orbit $\overline{\gamma}$ intersects the nullcline $\Gamma$.

By studying the behavior of $\overline{R}(t)$ and $H(C(t))$ for large values $t$ and $D$, we obtain the following limiting behavior of the function $\overline{T}(D)$ when $H(C)$ is nonlinear:

$$\overline{T}(D) \sim \frac{1}{\kappa+1}\log(D) \qquad \text{as} \quad D \to \infty \qquad \text{models I and III} \tag{39}$$

Similarly for the models II and IV, we find that as $D \to \infty$,

$$\overline{T}(D) \sim \begin{cases} \dfrac{1}{1+(1-\alpha)\kappa}\log(D) & \text{in} \quad \text{model II} \quad (0 < \alpha \leq 1) \\ \dfrac{1}{1+(1+\alpha)\kappa}\log(D) & \text{in} \quad \text{model IV} \end{cases} \tag{40}$$

Thus, we readily obtain lower bounds for the behavior of $T_{\max}(D)$ as $D \to \infty$. In the next section we shall see that these bounds are actually sharp.

**A wave phenomenon**

The solution graphs depicted in Figure 3 exhibit a wave-like phenomenon: when the drug dose is increased, the decreasing part of the response curve translates to the right but essentially preserves its shape. The shift appears to be proportional to $\log(D)$.

To explain this phenomenon we inspect the equation for the response in model III:

$$R' = \kappa\Big\{1 + \alpha\frac{De^{-t}}{1 + De^{-t}} - R\Big\}, \qquad 0 < t < \infty \tag{41}$$

The observations of Figure 3 and Eq. (41) suggest we introduce a new temporal variable $s$ which shifts with increasing drug dose $D$:

$$s = t - \log(D) \qquad \text{and} \qquad \phi_D(s) = R(t; D)$$

In terms of these variables, Eq. (41) becomes

$$\phi_D' = \kappa\Big\{1 + \alpha\frac{e^{-s}}{1 + e^{-s}} - \phi_D\Big\}, \qquad -\log(D) < s < \infty \tag{42}$$

One can prove that in the limit as $D \to \infty$,

$$\phi_D(s) \to \Phi(s) \qquad \text{as} \quad D \to \infty \tag{43}$$

for every fixed $s \in (-\infty, \infty)$, where $\Phi$ is the solution of the problem

$$\begin{cases} \Phi' = \kappa\Big\{1 + \alpha\dfrac{e^{-s}}{1 + e^{-s}} - \Phi\Big\}, \qquad -\infty < s < \infty \\ \Phi(-\infty) = 1 + \alpha \qquad \text{and} \qquad \Phi(+\infty) = 1 \end{cases} \tag{44}$$

The details of the proof of this result are given in Lemma D.1 of Appendix D. There it is also shown that $\Phi(s)$ is a decreasing function i.e.,

$$\Phi'(s) < 0 \qquad \text{for} \qquad -\infty < s < \infty \tag{45}$$

The fact that $\Phi(s)$ is decreasing can be shown to imply that

$$T_{\max}(D) - \log(D) \to -\infty \qquad \text{as} \quad D \to \infty \tag{46}$$

For the proof of Eq. (46) we refer to Lemma D.2 of Appendix D.

The limiting behavior for $R(t; D)$, obtained in (43), enables us to determine how the *Area Under the Curve*, $AUC_R$, which is defined by

$$AUC_R(D) \stackrel{\text{def}}{=} \int_0^\infty \{R(t; D) - 1\}\, dt$$

grows as $D \to \infty$. Figure 3 suggests that $AUC_R$ expands on the right where the response curve shifts to larger values of $t$, and this part of the curve is well approximated by the function $\Phi(t - \log(D))$. Using this property one can show that

$$AUC_R(D) \sim \alpha \log(D) \qquad \text{as} \qquad D \to \infty \tag{47}$$

The details of the proof can be found in Lemma D.3 in Appendix D.

In the other models we encounter similar wave phenomena. They involve the following transitions:

$$\begin{array}{lcll} R = 1-\alpha & \nearrow & R=1 & \text{model I} \\ R = \dfrac{1}{1-\alpha} & \searrow & R=1 & \text{model II} \quad (0<\alpha<1) \\ R = \dfrac{1}{1+\alpha} & \nearrow & R=1 & \text{model IV} \end{array} \tag{48}$$

The corresponding behavior of the *Area Under the Curve*, is given by

$$AUC_R(D) \sim \begin{cases} -\,\alpha \log(D) & \text{model I} \\ +\,\dfrac{\alpha}{1-\alpha}\log(D) & \text{model II} \quad (0<\alpha<1) \\ -\,\dfrac{\alpha}{1+\alpha}\log(D) & \text{model IV} \end{cases} \qquad \text{as} \qquad D \to \infty \tag{49}$$

A special case is model II with $\alpha = 1$. As we saw in Figure 4, there is also a wave like phenomenon here, but it is different from what we saw in Figure 3. In particular, we see that

$$R_{\max}(D) \to \infty \qquad \text{as} \qquad D \to \infty$$

We find that in this case the shape of $R(t)$ tends to that of a triangle which grows like $\log(D)$ as $D \to \infty$. From this limiting behavior of the response profiles we can conclude that in this case

$$T_{\max}(D) \sim \log(D) \qquad \text{and} \qquad R_{\max}(D) \sim \kappa \log(D) \qquad \text{as} \qquad D \to \infty \tag{50}$$

and that

$$AUC_R(D) \sim \frac{1}{2}\kappa \left\{\log(D)\right\}^2 \qquad \text{as} \qquad D \to \infty \tag{51}$$

The proofs of these limits are given in the final part of Appendix D.

**Conclusion.** In the four nonlinear models, I, II ($0 < \alpha < 1$), III and IV, $AUC_R(D)$ grows linearly with $\log(D)$ when $D$ is large, and when $\alpha = 1$ in model II, $AUC_R(D)$ grows quadratically with $\log(D)$. From the expressions above we see that we can determine the value of $\alpha$ from the rate of growth of $AUC_R(D)$, i.e., from the limiting slope of the graph of $AUC_R(D)$ versus $\log(D)$, (when $0 < \alpha < 1$ in model II) . These results were also established, by different means in (12) and (14).

**Remark.** When in model III, the drug mechanism function is linear, then it follows at once from Eq. (33) that $AUC_R(D)$ increases linearly with $D$.

### Dependence on $\kappa$ and $\alpha$

Although the prime focus in this paper is on the dependence of $T_{\max}$ on the drug dose $D$, we make a few observations about the dependence of $T_{\max}$ on the ratio $\kappa$

of the fractional turnover rate $k_{\text{out}}$ and the elimination rate $k$ in the drug function, and how it depends on the parameter $\alpha$, which stands for $I_{\max}$ or $E_{\max}$.

**Dependence on** $\kappa$. We see from the fundamental equations (13a) and (13b) that if $\kappa$ is small, then $R(t)$ will vary slowly with time. This implies the following property:

**Property G1:** Let $D$ and $\alpha$ be fixed. Then

$$T_{\max}(\kappa) \to \infty \qquad \text{as} \qquad \kappa \to 0$$

To see this we consider Eq. (13a) for model III, i.e., with $H(C) = S(C)$. Since $R > 1$ it follows that

$$R'(t) < \kappa\{S(C(t)) - 1\} < \kappa\{S(D) - 1\}$$

and hence

$$R(t) < 1 + \kappa\{S(D) - 1\}t$$

At $t = T = T_{\max}$ we therefore have

$$S(C(T)) = R(T) < 1 + \kappa\{S(D) - 1\}T$$

so that

$$T > \frac{1}{\kappa}\frac{S(De^{-T}) - 1}{S(D) - 1}$$

which implies that $T \to \infty$ as $\kappa \to 0$, as asserted. □

On the other hand, when $\kappa$ is large we have:

**Property G2:** Let $D$ and $\alpha$ be fixed. Then

$$T_{\max}(\kappa) \to 0 \qquad \text{as} \qquad \kappa \to \infty$$

We explain this for the models I and III, and write Eq. (13a) as

$$\varepsilon R' = H(C(t)) - R, \qquad \text{where} \qquad \varepsilon = 1/\kappa$$

Note that initially, the right hand side is given by

$$H(C(0)) - R(0) = H(D) - 1 < 0 \text{ (model I)} \quad \text{and} \quad > 0 \text{ (model III)}$$

When $\varepsilon = 1/\kappa$ is small, this implies that $R(t)$ jumps quickly from its initial value $R(0) = 1$ to the value $H(D)$ and then follows the monotone graph of $H(C(t))$. This means that $T_{\max}$ will be small when $\kappa$ is large, and tends to 0 as $\kappa \to \infty$. □

For the models II and IV the argument is similar.

**Dependence on** $\alpha$. We have seen that in the models I and III, $T_{\max}$ does not depend on $\alpha$.

As to the models II and IV, if $H(C)$ is *linear*, then $\alpha$ appears as a factor of $D$. Hence, in this case

$$T_{\max}(D;\alpha) = T_{\max}(\alpha D;1)$$

This means that if $\alpha$ increases, then the graph of $T_{\max}(D;\alpha)$ shifts to the left, i.e., for a given value of $D$, the peak time $T_{\max}$ will become larger when the graph of $T_{\max}$ is increasing and it will become smaller when the graph of $T_{\max}$ is decreasing.

If $H(C)$ is *nonlinear*, the influence of $IC_{50}/EC_{50}$ or $\alpha$ on $T_{\max}$ is more complex. However, we see from Eq. (17) and Eq. (18) that when $\alpha$ increases, then $T_{\max}$ will become smaller, both for small and for large values of the dose $D$.

## ASYMPTOTIC ANALYSIS

Whereas in the previous section we discussed a series of mainly *qualitative* properties of the response curve $R(t)$ and the peak time $T_{\max}$, in this section we establish *quantitative* results about the peak time, for small and large drug doses. For small doses $D$, we use a standard perturbation argument (26), expanding $R(t;D)$ and the drug mechanism function $H(C)$ in a series of increasing powers of $D$, while for large doses, we use an asymptotic analysis of the explicit solution of the differential equations underlying the different models.

Throughout this section we use the dimensionless variables introduced in Eq. (11) and we assume that the drug function $C(t)$ is given by Eq. (6).

### Small doses

We have seen that for all the models I – IV, nonlinear as well as linear,

$$T(D) \to T_0(\kappa) = \begin{cases} \dfrac{\log(\kappa)}{\kappa - 1} & \text{if} \quad \kappa \neq 1 \\ 1 & \text{if} \quad \kappa = 1 \end{cases} \tag{52}$$

We give a proof of this limit for the nonlinear model III. For the other models the proof can be given in a similar manner.

We expand the function $R(t;D)$ and the function $S(C)$ in increasing powers of $D$. Since if $D = 0$, then $R$ is given by the equilibrium state $R = 1$, this expansion must be of the form

$$R(t,D) = 1 + Dr_1(t) + D^2 r_2(t) + \dots \tag{53}$$

For the drug mechanism function (see (3.4a)) we obtain

$$H(C(t)) = S(C(t)) = 1 + \alpha D e^{-t} - \alpha D^2 e^{-2t} + \dots \tag{54}$$

We substitute these expansions into Eq. (2a) for $R$:

$$Dr_1'(t) + D^2 r_2'(t) + \cdots = \kappa\{\alpha D e^{-t} - \alpha D^2 e^{-2t} + \dots\} - \kappa\{Dr_1(t) + D^2 r_2(t) + \dots\}$$

or

$$D\{r_1' + \kappa r_1 - \alpha\kappa e^{-t}\} + D^2\{r_2' + \kappa r_2 + \alpha\kappa e^{-2t}\} \cdots = 0$$

where primes denote differentiation with respect to time $t$. Equating the coefficients of $D$ and $D^2$ to zero we obtain

$$r_1' + \kappa r_1 - \alpha\kappa e^{-t} = 0 \tag{55a}$$

$$r_2' + \kappa r_2 + \alpha\kappa e^{-2t} = 0 \tag{55b}$$

Remembering that $R(0, D) = 1$, and hence $r_1(0) = 0$ and $r_2(0) = 0$, we find for $r_1$ and $r_2$:

$$r_1(t) = \frac{\alpha\kappa}{\kappa - 1}\left(e^{-t} - e^{-\kappa t}\right) \quad \text{if} \quad \kappa \neq 1 \qquad \text{and} \qquad r_1(t) = \alpha t e^{-t} \quad \text{if} \quad \kappa = 1 \tag{56a}$$

and

$$r_2(t) = -\frac{\alpha\kappa}{\kappa - 2}\left(e^{-2t} - e^{-\kappa t}\right) \quad \text{if} \quad \kappa \neq 2 \qquad \text{and} \qquad r_2(t) = 2\alpha t e^{-2t} \quad \text{if} \quad \kappa = 2 \tag{56b}$$

At the time $T_{\max}$ of maximal response, we have

$$R'(T_{\max}(D); D) = D r_1'(T_{\max}) + D^2 r_2'(T_{\max}) + \cdots = 0 \tag{57}$$

Hence, in the limit as $D \to 0$, we have $r_1'(T_{\max}(0)) = 0$. We can use (56a) to compute $T_{\max}(0)$, and we find that $T_{\max}(0) = T_0$, where $T_0$ is given in (52).

To determine whether $T_{\max}(D)$ increases or decreases when a small dose is administered, we expand $T_{\max}(D)$ in powers of $D$, writing

$$T_{\max}(D) = T_0 + D T_1 + \ldots \tag{58}$$

Plainly, if $T_1 > 0$ then a small dose increases $T_{\max}$ and if $T_1 < 0$ a small dose leads to a drop in $T_{\max}$.

We continue with the analysis of the nonlinear model III and substitute the expansion Eq. (58) into Eq. (57). This yields

$$D r_1'(T_0) + D^2 T_1 r_1''(T_0) + D^2 r_2'(T_0) + O(D^3) = 0$$

Since $r_1'(T_0) = 0$, this implies that

$$T_1 r_1''(T_0) + r_2'(T_0) = 0$$

From (56a) we deduce that $r_1''(T_0) \neq 0$, so that we may conclude that

$$T_1 = -\frac{r_2'(T_0)}{r_1''(T_0)} \tag{59}$$

With the expressions for $r_1(t)$ and $r_2(t)$ from (56) we can now compute $T_1$, and we find that

$$T_1 = L_1(\kappa) = \begin{cases} \dfrac{1}{\kappa - 2}(2e^{-T_0} - 1) & \text{if} \quad \kappa \neq 2 \\ \log(2) - \dfrac{1}{2} & \text{if} \quad \kappa = 2 \end{cases}$$

where $T_0 = T_0(\kappa)$ has been defined in Eq. (52). We find that $L_1(\kappa) > 0$ for all $\kappa > 0$, so that irrespective of the value of $\kappa$, the response is delayed when a small dose is given. For the nonlinear model I we find the same value of $T_1$.

For the nonlinear models II and IV we find

$$T_1 = L_1(\kappa) \pm \alpha L_2(\kappa), \qquad \text{where} \qquad L_2(\kappa) = \begin{cases} \dfrac{\kappa}{\kappa-2} - \dfrac{\kappa+2}{\kappa-2} e^{-T_0} & \text{if} \quad \kappa \neq 2 \\ \dfrac{3}{2} - 2\log(2) & \text{if} \quad \kappa = 2 \end{cases}$$

Here the plus sign applies to model II and the minus sign to model IV. We find that $L_2(\kappa) > 0$ for all $\kappa > 0$.

For the linear models I and III, $T_1 = 0$, and for the linear models II and IV we find exactly as in the nonlinear models,

$$T_1 = \pm \alpha L_2(\kappa)$$

the plus sign for model II and the minus sign for model IV.

**Large doses**

We first discuss the case when $H(C)$ is nonlinear, and then when it is linear.

**I. Nonlinear drug mechanism function.** We recall from the lower bounds derived in Section 5.3 that in all four models

$$T_{\max}(D) > K \log(D) \qquad \text{if} \qquad D > D_0$$

for some positive constants $K$ and $D_0$. However, in Section 5.4, and in Lemma D.2 in Appendix D, we saw that

$$T_{\max}(D) - \log(D) \to -\infty \qquad \text{as} \qquad D \to \infty \tag{60}$$

This means that $K \leq 1$.

In this subsection, we derive more precise estimates, and we first consider model III. We use the explicit expression for the solution, which is found to be

$$\begin{aligned} R(t;D) &= e^{-\kappa t} + \kappa e^{-\kappa t} \int_0^t e^{\kappa s} S(C(s))\, ds \\ &= 1 + \alpha\kappa e^{-\kappa t} \int_0^t \frac{e^{\kappa s}\, ds}{1+\varepsilon e^s}, \qquad\qquad \varepsilon = \frac{1}{D} \end{aligned}$$

Since $R'(T_{\max}) = 0$, we obtain upon substitution into the differential equation

$$\frac{e^{\kappa T}}{1+\varepsilon e^T} = \kappa \int_0^T \frac{e^{\kappa s}\, ds}{1+\varepsilon e^s} \tag{61}$$

where we have written $T = T_{\max}$. In what follows we shall often omit the subscript "max". Because of our preliminary estimate Eq. (60), we have

$$\varepsilon e^{T(D)} = e^{T(D)-\log(D)} \to 0 \qquad \text{as} \qquad D \to \infty$$

Therefore, we may expand the integrand in Eq. (61) to obtain

$$\frac{e^{\kappa T}}{1+\varepsilon e^{T}} = \kappa \int_0^T e^{\kappa s}\big\{1 - \varepsilon e^{s} + O\big((\varepsilon e^{s})^2\big)\big\}\, ds \tag{62}$$

Expanding the left hand side as well, we end up to leading order,

$$\varepsilon e^{(\kappa+1)T} = 1 + \frac{\varepsilon\kappa}{\kappa+1}\, e^{(\kappa+1)T}$$

Thus

$$\frac{1}{\kappa+1} e^{(\kappa+1)T} \sim \frac{1}{\varepsilon} \qquad \text{as} \qquad \varepsilon \to 0$$

or, since $D = 1/\varepsilon$,

$$T_{\max}(D) \sim \frac{1}{\kappa+1}\log(D) \qquad \text{as} \qquad D \to \infty \tag{63}$$

In model I the function $T_{\max}(D)$ is the same as in model III (cf. Section 4).

In models II and IV the line of reasoning is the same, but the formulas are a little more complex. For these two models we find that as $D \to \infty$,

$$T_{\max}(D) \sim \begin{cases} \dfrac{1}{1+\kappa(1-\alpha)}\log(D) & \text{in} \quad \text{model II} \quad (0 < \alpha \le 1) \\ \dfrac{1}{1+\kappa(1+\alpha)}\log(D) & \text{in} \quad \text{model IV} \end{cases} \tag{64}$$

**II. Linear drug mechanism function.** Since in the case of inhibition, when $H(C) = 1 - \alpha C$, the concentration is bounded above by $1/\alpha$, we need only discuss model IV. In this model we have

$$R' = \kappa\{1 - (1 + \alpha D e^{-t})R\}, \qquad R(0) = 1 \tag{65}$$

We scale the variables and write

$$s = \alpha D t, \qquad \rho(s) = \alpha D R(t), \qquad \varepsilon = \frac{1}{\alpha D} \tag{66}$$

Equation (6.14) then becomes

$$\rho' = \kappa\{1 - (\varepsilon + e^{-\varepsilon s})\rho\} = 0, \qquad \rho(0) = \frac{1}{\varepsilon} \tag{67}$$

This initial value problem can be solved explicitly, and we find that

$$\rho(s) = e^{-\kappa A(s)} \left\{ \frac{1}{\varepsilon} + \kappa \int_0^s e^{\kappa A(t)}\, dt \right\} \tag{68}$$

where

$$A(s) = \int_0^s a(t)\, dt \qquad \text{and} \qquad a(s) = \varepsilon + e^{-\varepsilon s} \tag{69}$$

We write $S = \alpha D T_{\max}$. Since $\rho'(s) = R'(t)$ it follows that $\rho'(S) = 0$, and hence, by (67), that

$$a(S)\rho(S) = 1$$

or

$$1 + \varepsilon\kappa \int_0^S e^{\kappa A(t)}\, dt = \varepsilon\, \frac{e^{\kappa A(S)}}{a(S)} \tag{70}$$

Expanding both sides of Eq. (70) in powers of $\varepsilon$, we finally end up with

$$1 = \varepsilon^2 e^{\kappa S} + O(\varepsilon^3) \qquad \text{as} \quad \varepsilon \to 0$$

which implies that

$$S(\varepsilon) \sim \frac{2}{\kappa} \log\left(\frac{1}{\varepsilon}\right) \qquad \text{as} \quad \varepsilon \to 0$$

Returning to the original variables we find that

$$T_{\max}(D) \sim \frac{2}{\alpha\kappa} \frac{\log(D)}{D} \qquad \text{as} \quad D \to \infty \tag{71}$$

Thus, in the *linear* model IV, in contrast to the other models, $T_{\max}(D) \to 0$ as $D \to \infty$.

## GENERALIZATIONS

We present two generalizations of the turnover model discussed in the earlier sections.

(a) We generalize the drug function $C(t)$ to a function which is no longer monotone. Specifically we discuss the *Bateman function*

$$C(t) = D(e^{-kt} - e^{-k_a t}), \qquad k_a > k \tag{7}$$

(b) We investigate a turnover model which involves a nonlinear elimination term which is bounded:

$$\frac{dR}{dt} = k_{\text{in}} - k_{\text{out}} \frac{R}{R_{50} + R} \tag{10}$$

as discussed in (21) and (22).

For both generalizations we investigate the implications for Property A and Property B.

**The drug function**

Since the drug function defined in Eq. (7) satisfies the conditions of Property A, we may focus on Property B. We shall show that this property continues to hold. As with many of our results, this is was known (cf. (13)), but here we present a different proof. We give it for model III, but for the other models it is the similar.

We study the initial value problem

$$\frac{dR}{dt} = k_{\text{in}} S(C(t)) - k_{\text{out}} R, \qquad R(0) = R_0 = \frac{k_{\text{in}}}{k_{\text{out}}} \tag{72}$$

The nullcline $\Gamma$ is given by

$$R = \varphi(t) = R_0 S(C(t))$$

Since $C(0) = 0$ and $C(t) \to 0$ as $t \to \infty$, it follows that

$$\varphi(0) = R_0 \qquad \text{and} \qquad \varphi(t) \to R_0 \quad \text{as} \quad t \to \infty$$

Moreover,

$$\frac{d\varphi}{dt} = R_0 \frac{dS}{dC} \frac{dC}{dt}$$

Thus, since $dS/dC > 0$ and $C(t)$ increasing and then decreasing, so is $\varphi$.

As regards the orbit, we have

$$R(0) = R_0 \qquad \text{and} \qquad R(t) \to R_0 \quad \text{as} \quad t \to \infty$$

where we have used Property A. An elementary computation shows that

$$\frac{dR}{dt}\Big|_{t=0} = 0 \qquad \text{and} \qquad \frac{d\varphi}{dt}\Big|_{t=0} > 0$$

Hence, the orbit starts out below the nullcline $\Gamma$. The vector field is such that the orbit will go up as long it lies below the nullcline. Because we know that the orbit eventually drops down to the initial value again, it has to cross $\Gamma$. This can only happen at a point where $\varphi(t) \leq 0$. Once it has crossed $\Gamma$, the orbit must stay above $\Gamma$ and the proof is completed as in Section 5. □

**Remark.** In the proof of Property B given above, we have only used the fact that $C(t)$ first increases and then decreases. Thus, it is clear, that Property B holds for any drug function, which is either decreasing or first increasing and then decreasing.

**A nonlinear turnover model**

As an example of a nonlinear turnover model we consider the equation

$$\frac{dR}{dt} = k_{\text{in}} S(C(t)) - k_{\text{out}} \frac{R}{R_{50} + R} \tag{73}$$

i.e., we consider a nonlinear generalisation of model III, where $S(C)$ is defined in Eq. (4). To keep the analysis transparent we use the simple drug function defined in Eq. (6).

As a first step, we look for a stationary solution. In the absence of a drug, we expect the system to be at a rest state $R_1$. We deduce from Eq. (73) that $R_1$ must be a root of the equation

$$k_{\text{in}} - k_{\text{out}} \frac{R}{R_{50} + R} = 0$$

where we have used the fact that $S(0) = 1$. An elementary computation shows that

$$R_1 = R_0 \frac{R_{50}}{1 - R_0} \qquad\qquad R_0 = \frac{k_{\text{in}}}{k_{\text{out}}}$$

It is evident that $R_1$ needs to be positive. Therefore we must require that

$$R_0 < 1 \tag{74}$$

Assuming that prior to administration of the drug, the system is at rest, we impose the initial condition:

$$R(0) = R_1 \tag{75}$$

Proceeding as in the proof of Property A given in Section 5, we can prove the following analogue of this property:

**Property A*:** Let $R(t)$ be the solution of Problem (73), (75) and let $C(t)$ be given by Eq. (6). Then

$$R(t) \to R_1 \qquad \text{as} \qquad t \to \infty$$

Next, let us turn to Property B which deals with the shape of the graph of $R(t)$. Again, a key role is played by the nullcline $\Gamma$, i.e. the curve along which $dR/dt = 0$. Here it is given by the equation

$$k_{\text{in}} S(C(t)) - k_{\text{out}} \frac{R}{R_{50} + R} = 0$$

which yields

$$R = \psi(t) \stackrel{\text{def}}{=} R_0 \frac{R_{50} S(C(t))}{1 - R_0 S(C(t))}$$

Because $R$ needs to be positive, the nullcline is well defined as long as $R_0 S(C(t)) < 1$. We distinguish two cases:

**Case A:** $R_0 S(D) \leq 1$. Because $C(t) < D$ for all $t > 0$ it follows that in this case $R_0 S(C(t)) < 1$ for all $t > 0$, so that $\Gamma$ is defined for all $t > 0$.

**Case B:** $R_0 S(D) > 1$. Since $C(t) \to 0$ monotonically, and $R_0 S(0) = R_0 < 1$, there exists a unique time $\tau > 0$ such that $R_0 S(C(\tau)) = 1$. Then $R_0 S(C(t)) < 1$ on the interval $\tau < t < \infty$, on which $\Gamma$ is now well defined. Note that $\psi(t) \to \infty$ as $t \to \tau$.

Differentiating the expression for $\psi$ we find that

$$\frac{d\psi}{dt} = \frac{R_0 R_{50}}{\{1 - R_0 S(C(t))\}^2} \frac{dS}{dC} \frac{dC}{dt} < 0 \qquad \text{for} \qquad \tau < t < \infty$$

because $dS/dC > 0$ and $dC/dt < 0$. Thus the nullcline is a strictly decreasing curve.

Let us now follow the orbit $\gamma$. At the starting point $t = 0$, we have

$$C(0) = D, \qquad S(D) > S(0) = 1 \qquad \text{and} \qquad R_1 = R_0 \frac{R_{50}}{1 - R_0} < R_0 \frac{R_{50} S(D)}{1 - R_0 S(D)}$$

if $R_0 S(D) < 1$. Thus, in Case A the orbit starts below $\Gamma$ i.e., at a point where $dR/dt > 0$. As in the linear turnover model, $\gamma$ hits the nullcline and will cross it precisely once. In Case B, any orbit will go up in the interval $0 \leq t \leq \tau$, and eventually hit the nullcline, cross it and drop down without crossing it a second time. Thus, in both cases $\gamma$ has precisely one critical point, as asserted in Property B. □

**Remark** By similar arguments Properties A and B can be established for systems of the form

$$\frac{dR}{dt} = k_{\text{in}} S(C(t)) - k_{\text{out}} f(R) \tag{76}$$

as long as the function $f(R)$ is increasing for all $R > 0$.

## DISCUSSION AND CONCLUSIONS

Pharmacodynamic analysis coupled to the the concentration-time course of drugs in plasma, tissues or urine, has become a common approach/means in the drug discovery/development process. Both, industry and regulators appreciate the merit of not only documenting the pharmacokinetic characteristics of a new compound, but also the onset, intensity and duration of its response. In certain situations compounds with non-optimal pharmacokinetics can often be "rescued" by good pharmacodynamic properties. An example of this is the proton-pump inhibitor *omeprazole*, with a plasma half-life of less than an hour, but a half-life of response in the range of 15-20 hours in man (25).

In order to make accurate and precise predictions of the *onset*, *intensity* and *duration* of the response one needs to understand the intrinsic behavior of the proposed model. Knowing the constraints of the model characteristics, it is also possible to design experiments accordingly, in order to challenge the model(s). In an attempt to elucidate the behavior of the basic turnover model, we have analytically studied the effect of different "shapes" of the drug mechanism functions ($I(C)$ and $S(C)$) – both nonlinear (saturating) and linear – on the response-time profile.

In particular we studied the effect of the drug function on the peak shift. Our analysis confirms that when the drug function $I(C)$ or $S(C)$ is *nonlinear*, then $T_{\max}$

increases with increasing doses in all the four models we studied, with the exception of model IV. In this model the peak time $T_{\max}$ *drops* for small doses when $E_{\max}$ is large enough, and then increases as the doses become larger. If the drug function is *linear*, $T_{\max}$ will either be independent of the dose (models I and III), decrease with increasing doses (model II) ($\alpha D < 1$) or decrease with increasing doses (model IV).

By a qualitative study of the fundamental equation of the Indirect Response Model, we establish a priori bounds on the response function $R(t)$, on the peak time $T_{\max}$, and on the area under the curve $AUC_R$. We also show that in the nonlinear models $T_{\max}$ and $AUC_R$ increase with increasing doses, in proportion to the logarithm of the drug dose. In all nonlinear models ($0 < \alpha < 1$ in model II), we find that $AUC_R(D)$ increases linearly with $\log(D)$ when $D$ is large. The parameter $\alpha$ in the drug mechanism function can be determined from the slope of the graph of $AUC_R(D)$ versus $\log(D)$. We also establish how $T_{\max}$ is affected by $E_{\max}$ and $I_{\max}$ and by the ratio of $k_{\text{out}}$ and the elimination rate constant $k$ of the drug plasma concentration.

We find that this qualitative approach, based on ideas from the theory of dynamical systems offers a powerful and conceptually attractive method for analyzing the four Indirect Reponse Models and conjecture that it will be an important tool in the analysis of more complex pharmacodynamic models.

The overall conclusion we can draw from this analysis is that the cause of the peak shift with changing drug doses lies in the drug mechanism function ($I(C)$ or $S(C)$), rather than the turnover function in its *basic* form, such as $-k_{\text{out}}R$. This may be of some help in discriminating between drug effects and system effects and for deciding between *distributional* and *turnover* models.

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## APPENDICES

# A Symbols and definitions

**Pharmacokinetic constants and functions:**

$C$ = Plasma concentration of the drug
$Dose$ = Amount of drug administered
$D$ = $Dose/EC_{50}$ (stimulus) or $Dose/IC_{50}$ (inhibition)
$k$ = Elimination-rate constant of drug in plasma (cf. (2.6))
$H(C)$ = General drug mechanism function
$I(C)$ = Drug mechanism function for inhibition
$I_{\max}$ = Maximal drug induced inhibition
$IC_{50}$ = Concentration at 50 percent of maximal drug induced inhibition
$S(C)$ = Drug mechanism function for stimulation
$E_{\max}$ = Maximal drug induced stimulation
$EC_{50}$ = Concentration at 50 percent of maximal drug induced stimulus
$\alpha$ = $IC_{50}$, respectively $EC_{50}$, in the capacity limited drug mechanism functions and factor of $C$ in the linear drug mechanism functions

**Pharmacodynamic constants and functions:**

$k_{\text{in}}$ = Production rate of pharmacological response
$k_{\text{out}}$ = Fractional turnover rate of pharmacological response
$\kappa$ = $k_{\text{out}}/k$; scaled/normalized fractional turnover rate of pharmacological response for plasma kinetics
$R_0$ = $k_{\text{in}}/k_{\text{out}}$; equilibrium response
$t$ = Time and dimensionless time
$R(t)$ = Response and dimensionless response
$T_{\max}$ = Time of maximal change in drug induced response; peak time
$T_0$ = Limit of $T_{\max}(D)$ as $D \to 0$
$^*$ = Superscript indicating a dimensionless variable

**Mathematical symbols, constants and functions:**

$L_1$ and $L_2$ = Constants in the limit of $dT_{\max}(D)/dD$ as $D \to 0$
$r_1(t)$ and $r_2(t)$ = Terms in the asymptotic expansion of $R(t)$ as $D \to 0$
$s$ = Scaled or shifted time-like variable
$\phi_D(s)$ = Response in terms of shifted time coordinate
$\Phi(s)$ = Limit of $\phi_D(s)$ as $D \to \infty$
$\rho(s)$ = Scaled response
$'$ (prime) = Differentiation with respect to $t$: $d/dt$
$(t, R)$-plane = Plane with a coordinate frame in which $t$ is measured along the horizontal axis and $R$ along the vertical axis
$\gamma$ = Orbit in the $(t, R)$-plane
$\Gamma$ = Nullcline in the $(t, R)$-plane along which $dR/dt = 0$

**Mathematical definitions**

$A \stackrel{\text{def}}{=} B$ = The symbol $A$ is defined by the expression $B$
$f(x) \sim g(x) \quad \text{as} \quad x \to \infty \ (0)$ = $f(x)/g(x) \to 1 \quad \text{as} \quad x \to \infty \quad (x \to 0)$
$f(x) = O(\omega(x)) \quad \text{as} \quad x \to \infty \ (0)$ = There exist constants $K > 0$ and $\xi > 0$ such that $|f(x)| < K|\omega(x)| \quad \text{as} \quad x > \xi \quad (0 < x < \xi)$

## B A comparison theorem

We compare solutions of the following two initial value problems:

$$R' = \kappa\{S(C(t)) - R\}, \qquad R(0) = 1 \tag{B.1}$$

and

$$\overline{R}' = \kappa(1 + \alpha - \overline{R}), \qquad \overline{R}(0) = 1 \tag{B.2}$$

**Theorem B.1** *Let $R(t)$ and $\overline{R}(t)$ be the solutions of respectively (B.1) and (B.2) Then*

$$R(t) < \overline{R}(t) \qquad \textit{for all} \qquad t > 0$$

**Proof** We denote the difference between the two solutions by $u$:

$$u(t) \stackrel{\text{def}}{=} \overline{R}(t) - R(t)$$

Then, by subtractiong (B.1) from (B.2) we find that $u(t)$ is the solution of the following problem

$$u' + \kappa u = \kappa f(t), \qquad u(0) = 0 \tag{B.3}$$

where

$$f(t) = 1 + \alpha - S(C(t)) = \alpha - \alpha\frac{C(t)}{1 + C(t)} = \frac{\alpha}{1 + C(t)} > 0 \qquad \text{for} \quad t > 0$$

Problem (B.3) can be solved explicitly, and we find that

$$u(t) = \kappa e^{-\kappa t} \int_0^t e^{\kappa s} f(s)\, ds \qquad \text{for} \quad t > 0$$

Because $f(s) > 0$ it follows that $u(t) > 0$ for all $t > 0$. This means that $\overline{R}(t) > R(t)$, as asserted. □

## C Proof of Property A

Whereas in Section 5, we proved **Property A** under the assumption that

$$C(t) = De^{-kt}, \qquad k > 0 \tag{2.6}$$

here we shall prove this property assuming only that

$$C(t) \to 0 \qquad \text{as} \qquad t \to \infty \tag{C.1}$$

We shall do this again for model III. For the other models the proof is similar.

Suppose to the contrary that $R(t)$ does not tend to $R_0$ as $t \to \infty$. Since, by comparison, $R(t) > R_0$ for all $t > 0$, this implies that there exists a sequence of points $\{t_n\}$, tending to infinity as $n \to \infty$, and a constant $\delta > 0$ such that

$$R(t_n) > R_0 + \delta \qquad \text{for all} \qquad n \geq 1 \tag{C.2}$$

On the other hand there must be a sequence of points $\{\tau_n\}$, tending to infinity as $n \to \infty$ such that

$$R(\tau_n) < R_0 + \delta \qquad \text{for all} \qquad n \geq 1 \tag{C.3}$$

because if $R(t) > R_0 + \delta$ for $t$ large enough, the differential equation would imply, in view of (C.1), that

$$\limsup_{t\to\infty} R'(t) \leq -\delta$$

which means that $R(t) \to -\infty$ as $t \to \infty$. This contradicts the fact that we know that $R(t) > R_0$ for all $t > 0$.

Thus, the graph of $R(t)$ would cross the line $R = R_0 + \delta$ at a sequence of points $\{\tau_n\}$ which tends to infinity. However, if we put $R = R_0 + \delta$ into the differential equation, we find that

$$\frac{dR}{dt} = k_{\text{in}} S(C(t)) - k_{\text{out}}(R_0 + \delta) \tag{C.4}$$

When we let $t \to \infty$ in this equation we find that

$$\lim_{t\to\infty} \frac{dR}{dt} = k_{\text{in}} - k_{\text{out}}(R_0 + \delta) = -k_{\text{out}}\delta < 0 \tag{C.5}$$

so that the graph of $R(t)$ can only cross the line $R = R_0 + \delta$ in the downward direction. This contradicts our observation that $R(t)$ would be crossing this line an infinite number of times, and so proves the assertion. □

# D Proofs of results in Subsection 5.4

Let $\phi_D(s)$ be the solution of the problem

$$\begin{cases} \phi_D' = \kappa\Big\{1 + \alpha\dfrac{e^{-s}}{1+e^{-s}} - \phi_D\Big\}, & -\log(D) < s < \infty \\ \phi_D(-\log(D)) = 1 + \alpha \qquad \text{and} \qquad \phi_D(+\infty) = 1 \end{cases} \tag{D.1}$$

We shall first prove the following limit:

**Lemma D.1** *For any fixed $s \in (-\infty, \infty)$ we have*

$$\phi_D(s) \to \Phi(s) \qquad \textit{as} \quad D \to \infty, \tag{D.2}$$

*where $\Phi$ is the unique solution of the equation*

$$\Phi' = \kappa\Big\{1 + \alpha\frac{e^{-s}}{1+e^{-s}} - \Phi\Big\}, \qquad -\infty < s < \infty \tag{D.3}$$

*which satisfies the following conditions at $s = \pm\infty$:*

$$\Phi(-\infty) = 1 + \alpha \qquad \textit{and} \qquad \phi(+\infty) = 1 \tag{D.4}$$

*The function $\Phi(s)$ is a strictly decreasing for $-\infty < s < \infty$.*

**Proof** Observe that for any $D > 0$,

$$1 < \phi_D(s) < 1 + \alpha \qquad \text{for} \qquad -\log(D) < s < \infty.$$

Thus the family of solutions $\{\phi_D(s) : D > 0\}$ is bounded above and below by bounds which do not depend on $D$ or $s$, and according to the differential equation, its derivatives $\phi'_D(s)$ and $\phi''_D(s)$ are similarly bounded. It follows by an application of the lemma of Arzela-Ascoli (cf. (27), Theorem 7.23 on page 144 and (28), Theorem C on page 126) that there exists a sequence of values $D_j$ of $D$ such that $D_j \to \infty$ as $j \to \infty$, and a continuously differentiable function $\Phi(s)$, such that for every $s \in \mathbf{R}$,

$$\phi_{D_j}(s) \to \Phi(s) \qquad \text{as} \quad D \to \infty, \tag{D.5}$$

and that $\Phi(s)$ is a solution of equation (D.3) with the bounds

$$1 \le \Phi(s) \le 1 + \alpha \qquad \text{for} \qquad -\infty < s < \infty$$

Next, let us show that $\Phi(s)$ satisfies the limiting conditions (D.4). Let us denote the nullcline by

$$\Phi^*(s) \stackrel{\text{def}}{=} 1 + \alpha \frac{e^{-s}}{1 + e^{-s}}$$

Plainly, if there exists a point $s_0$ such that $\Phi(s) < \Phi^*(s)$ for $s_0 < s < \infty$, then $\Phi(s) \to 1$ as $s \to \infty$. However, if there exists a point $s_1$ such that $\Phi(s_1) \ge \Phi^*(s_1)$, then

$$\Phi(s) > \Phi^*(s) \quad \text{and} \quad \Phi'(s) < 0 \qquad \text{for} \qquad s_1 < s < \infty,$$

where we have used the differential equation (D.3). Thus $\Phi(s)$ is decreasing and bounded below. Therefore, it must tend to a limit as $s \to \infty$, and this limit can only be 1.

A similar argument can be used to prove that $\Phi(s)$ satisfies the limiting condition at $s = -\infty$. In fact, we find that

$$\Phi^*(s) < \Phi(s) < 1 + \alpha \qquad \text{for all} \quad -\infty < s < \infty$$

Using this inequality in equation (D.3) we conclude that

$$\Phi'(s) < 0 \qquad \text{for all} \quad -\infty < s < \infty$$

It remains to show that equation (D.3) has at most one solution which satisfies the boundary condtions (D.4). Suppose, to the contrary, that there are two solutions, $\Phi_1(s)$ and $\Phi_2(s)$, and let us denote the difference by $w(s)$, i.e., $w(s) = \Phi_1(s) - \Phi_2(s)$. Then we see that

$$w' = -\kappa w \quad \text{for} \quad -\infty < s < \infty \qquad \text{and} \qquad w(\pm\infty) = 0$$

It is evident that this implies that $w(s) = 0$ for all $-\infty < s < \infty$, and hence that $\Phi_1 = \Phi_2$.

By a standard argument we can now conclude that $\phi_D \to \Phi$ not just along a sequence $\{D_j\}$ of values of $D$, but for all $D \to \infty$. □

The fact that $\Phi$ is decreasing on $\mathbf{R}$ can be used to prove the following limit:

**Lemma D.2** *We have*

$$T_{\max}(D) - \log(D) \to -\infty \qquad as \qquad D \to \infty$$

**Proof** From Lemma D.1 we know that

$$R(T_{\max}(D), D) \to 1 + \alpha \qquad \text{as} \qquad D \to \infty$$

Hence, since $R$ is strictly decreasing on $(T_{\max}, \infty)$, and $R(\infty) = 1$, there exists a unique time $T_1(D) \in (T_{\max}, \infty)$ such that $R(T_1) = 1 + (\alpha/2)$. Define

$$S_1(D) = T_1(D) - \log(D) \qquad \text{and} \qquad S_{\max}(D) = T_{\max}(D) - \log(D).$$

Then for all $D > 0$,

$$-\infty < S_{\max}(D) < S_1(D)$$

and we wish to prove that $S_{\max}(D) \to -\infty$ as $D \to \infty$.

Suppose to the contrary that there exists a sequence $\{D_j\}$ which tends to infinity as $j \to \infty$, and a constant $S_- > -\infty$ such that

$$S_{\max}(D_j) > S_- \qquad \text{for all} \qquad j = 1, 2, 3, \ldots.$$

Let $\Phi^{-1}$ denote the inverse of the function $\Phi$. Since $\Phi'(s) < 0$ for all $s \in (-\infty, \infty)$ it is well defined. It follows from Lemma D.1 that $S_1(D_j) \to S_+ = \Phi^{-1}(1 + (\alpha/2))$ as $j \to \infty$. Thus the sequence $\{S_{\max}(D_j)\}$ is bounded above and below. Hence, by compactness, there exists a subsequence, which we denote by $\{D_{j'}\}$, along which $S_{\max}(D_{j'})$ tends to a limit, i.e., there exists a constant $S_\infty \in [S_-, S_+]$ such that

$$S_{\max}(D_{j'}) \to S_\infty \qquad \text{as} \qquad j' \to \infty$$

and

$$\phi_{D_{j'}}(S_{\max}(D_{j'})) \to \Phi'(S_\infty) \qquad \text{as} \qquad j' \to \infty$$

However, $\phi_{D_{j'}}(S_{\max}(D_{j'})) = 0$ for all $j'$ and $\Phi'(S_\infty) < 0$. This means that we have arrived at a contradiction, and the assertion is proved. □

**Remark.** Problem (D.1) can be solved explicitly, and alternative proofs of Lemmas D1 and D2 can be given by means of a detailed analysis of the resulting expression for the solution. In nonlinear generalizations of Problem (D.1) such an explicit solution is generally not available. However, for such problems the proofs given above still stand.

From Lemma D.1 we can also deduce the rate of growth of $AUC_R(D)$ as $D \to \infty$.

**Lemma D.3** *We have*

$$AUC_R(D) = \alpha \log(D) + O(1) \qquad as \qquad D \to \infty$$

**Proof** In model III we have

$$AUC_R(D) = \int_0^\infty \{R(t,D) - 1\}\, dt = \int_{-\log(D)}^\infty \{\phi_D(s) - 1\}\, ds$$
$$= \int_{-\log(D)}^0 \{\phi_D(s) - 1\}\, ds + \int_0^\infty \{\phi_D(s) - 1\}\, ds = I_1(D) + I_2(D)$$

Plainly,

$$I_2(D) \to \int_0^\infty \{\Phi(s) - 1\}\, ds \qquad \text{as} \qquad D \to \infty$$

We write

$$I_1(D) = I_{1,1}(D) + I_{1,2}(D)$$

where

$$I_{1,1}(D) = \int_{-\log(D)}^0 \{\phi_D(s) - 1 - \alpha\}\, ds$$

and

$$I_{1,2}(D) = \int_{-\log(D)}^0 \{\alpha\}\, ds = \alpha \log(D)$$

By an easy comparison argument,

$$\Phi(s) < \phi_D(s) < 1 + \alpha \qquad \text{for} \qquad -\log(D) < s < 0$$

Hence

$$\int_{-\infty}^0 \{\Phi(s) - 1 - \alpha\}\, ds < \int_{-\log(D)}^0 \{\Phi(s) - 1 - \alpha\}\, ds < I_{1,1}(D) < 0$$

Therefore $I_{1,1}(D)$ remains bounded as $D \to \infty$, so that

$$AUC_R(D) = \alpha \log(D) + O(1) \qquad \text{as} \qquad D \to \infty$$

which we set out to prove. □

**Model II ($\alpha = 1$):** When $\alpha = 1$ in model II, it is known that$R_{\max}(D) \to \infty$ as $D \to \infty$ (14). Therefore a different analysis is required in this case. Problem (D.1) now becomes

$$\begin{cases} \phi_D' = \kappa\Big\{1 - \dfrac{1}{1+e^{-s}}\phi_D\Big\}, & -\log(D) < s < \infty \\ \phi_D(-\log(D)) = 1 \qquad \text{and} & \phi_D(+\infty) = 1 \end{cases} \tag{D.6}$$

We first prove the following upper bounds:

**Lemma D.4** *We have*

$$\phi_D(s) < 1 + \kappa\{s + \log(D)\} \qquad \textit{for} \quad s > -\log(D) \tag{D.7}$$

*and*

$$\phi_D(s) < \overline{\phi}_D(s) \qquad \textit{for} \quad s > 0 \tag{D.8}$$

*where*

$$\overline{\phi}_D(s) = (1 + e^s)^{-\kappa} \left\{ 1 + \kappa \log(D) + \kappa \int_0^s (1 + e^\sigma)^\kappa \, d\sigma \right\} \tag{D.9}$$

**Proof** The first bound, (D.7), follows from the observation that

$$\phi_D' < \kappa \quad \text{for} \quad s > -\log(D) \qquad \text{and} \qquad \phi_D(-\log(D)) = 1$$

To prove (D.8) we observe that by a comparison argument like the one used in Appendix B, (D.8) holds, if we can prove that $\overline{\phi}_D(s)$ is the solution of the problem

$$\overline{\phi}_D' = \kappa \Big\{ 1 - \frac{1}{1 + e^{-s}} \overline{\phi}_D \Big\}, \quad s > 0, \qquad \overline{\phi}_D(0) = \kappa \log(D) \tag{D.10}$$

An elementary computation shows that this is indeed true.

**Remark** Using l'Hôpital's rule, one can show that for any $D > 0$,

$$\overline{\phi}_D(s) \to 1 \qquad \text{as} \qquad s \to \infty$$

We now perform one more transformation, and write

$$s = \sigma \, \log(D) \qquad \text{and} \qquad \phi_D(s) = 1 + \psi_D(\sigma) \, \log(D) \tag{D.11}$$

Then the bound (D.7) becomes

$$\psi_D(\sigma) < \kappa(1 + \sigma) \qquad \text{for} \qquad \sigma > -1$$

and Problem (D.6) becomes

$$\psi_D' = \kappa \Big\{ \frac{1}{1 + e^{\sigma \, \log(D)}} - \frac{\log(D)}{1 + e^{-\sigma \, \log(D)}} \psi_D \Big\}, \quad \sigma > -1, \qquad \psi_D(-1) = 0 \tag{D.12}$$

If we let $D \to \infty$ and keep $\sigma$ fixed and *negative*, then we find that

$$\psi_D(\sigma) \to \Psi(\sigma) \qquad \text{as} \qquad D \to \infty \tag{D.13}$$

where

$$\Psi(\sigma) = \kappa(1 + \sigma) \qquad -1 < \sigma < 0 \tag{D.14}$$

On the other and, it follows from Lemma D.4 that for $\sigma > 0$,

$$\psi_D(\sigma) < \frac{\phi_D(\sigma \log(D)) - 1}{\log(D)} \to 0 \qquad \text{as} \qquad D \to \infty \tag{D.15}$$

We have

$$T_{\max}(D) = \log(D)\{1 + \sigma_{\max}(D)\} \tag{D.16}$$

where $\sigma_{\max}$ is the unique zero of $\psi'_D(\sigma)$ where $\psi_D(\sigma)$ reaches its maximum value. It follows from (D.13), (D.14) and (D.15) that

$$\sigma_{\max}(D) \to 0 \qquad \text{and} \qquad \psi_D(\sigma_{\max}(D)) \to \kappa \qquad \text{as} \quad D \to \infty \tag{D.17}$$

By (D.16) this implies that

$$T_{\max}(D) \sim \log(D) \qquad \text{and} \qquad R_{\max}(D) \sim \kappa \log(D) \qquad \text{as} \qquad D \to \infty \tag{D.18}$$

# REFERENCES


1. E. Ackerman, J.W. Rosevear, and W.F. McGuckin, A mathematical model of the glucose-tolerance test, *Phys. Med. Biol.* **9:**203-213 (1964).
2. R. Nagashima, R.A. O'Reilly and G. Levy, Kinetics of pharmacological effects in man: The anticoagulant action of warfarin. *Clin. Phamacol. Ther.* **10:**22 (1969).
3. E.B.M. Ekblad and V. Licko, A model eliciting transient responses, *Am. J. Physiol.* **246** (Regulatory Integrative Comp. Physiol. 15): R114-R121 (1984).
4. N.L. Dayneka, V. Garg and W.J. Jusko, Comparison of four basic models of indirect pharmacodynamic responses. *J. Pharmacokin. Biopharm.* **21:**457-478 (1993).
5. N.H.G. Holford, J.L. Gabrielsson, L.B. Sheiner, N. Benowitz, and R. Jones, A physiological pharmacologicodynamic model for tolerance to cocaine effects on systolic blood pressure, heart rate and euphoria in human volunteers. Presented at Measurement and Kinetics of in vivo drug effects, 28-30 June, 1990, Noordwijk, The Netherlands.
6. M. Wakelkamp, G. Alvan, J. Gabrielsson and G. Paintaud, Pharmacodynamic modeling of furosemide tolerance after multiple intravenous administration, *Clin. Pharmacol. Ther.* **60**:75–88 (1996).
7. Y.-N. Sun, D.C. DuBois, R.R. Almon, N.A. Pyszczynski and W.J. Jusko, Dose dependence and repeated-dose studies for receptor/gene-mediated pharmacodynamics of methylprednisolone on glucocorticoid receptor down-regulation and Tyrosine Aminotransferase induction in rat liver, *J. Pharmacokin. Biopharm.* **26:**619-648 (1998).
8. K.P. Zuideveld, H.J. Maas, N. Treijtel, J. Hulshof, P.H. van der Graaf, L.A. Peletier and M. Danhof, A set-point model with oscillatory behavior predicts the time-course of 8-OH-DPAT induced hypothermia. *Am J Physiol Regulatory Comp. Physiol.* **281:**R2059-071 (2001).
9. J. Gabrielsson and D. Weiner, Pharmacokinetic/Pharmacodynamic Data Analysis: Concepts and Applications, 2nd and 3rd eds. *Swedish Pharmaceutical Press*, Stockholm, 1997, 2000.

10. D.E. Mager, E. Wyska and W.J. Jusko, Diversity of mechanism-based pharmacodynamic models, *Drug Metab. Dispos.* **31:**510-519 (2003).
11. A. Sharma and W.J. Jusko, Characterization of four basic models of indirect pharmacodynamic responses , *J. Pharmacokin. Biopharm.* **24:** 611-635 (1996).
12. W. Krzyzanski and W.J. Jusko, Mathematical formalism for the properties of four basic models of indirect pharmacodynamic responses. *J. Pharmacokin. Biopharm.* **25:**107-123 (1997).
13. W. Krzyzanski and W.J. Jusko, Mathematical formalism and characteristics of four basic models of indirect pharmacodynamic responses for drug infusions. *J. Pharmacokin. Biopharm.* **26:**385-408 (1998).
14. W. Krzyzanski and W.J. Jusko, Integrated functions for four basic models of indirect pharmacodynamic response, *J. Pharmaceutical Sciences*, **87:**67-72 (1998).
15. W. Krzyzanski, Asymptotics of the total net pharmacological effect for large drug doses. *J. Math. Biol.* **41:**477-492 (2000).
16. M. Wakelkamp, G. Alvan and G. Paintaud, The time of maximum effect for model selection in pharmacokinetic-pharmacodynamic analysis applied to frusemide. [Clinical Trial. Journal Article. Randomized Controlled Trial] *British Journal of Clinical Pharmacology.* **45:**63-70 (1998).
17. P. Blanchard, R.L. Devaney and G.R. Hall, Differential Equations, *Brooks/Cole Publishing Company*, Boston, 1997.
18. G.B. Ermentraut, XPPAUT, `www.math.pitt.edu/ bard/xpp/xpp.html`.
19. Maple 9, Waterloo Maple Inc.
20. A. Rescigno and G. Segre, Drug and Tracer Kinetics. *Blaisdell Publishing Company*, London, 1961, 1966.
21. M. Gibaldiand D. Perrier, Pharmacokinetics, 2nd ed. Revised and Expanded. *Marcel Dekker Inc.*, New York, (1982).
22. L. Finkelstein and E.R. Carson, Mathematical modelling of dynamic biological systems, *Research Studies Press Ltd.*, Letchworth, (1985).
23. A. Majumdar, Characterization of the dose-dependent time of peak effect in Indirect response models, *J. Pharmacokin. Biopharm.* **26:**183-206 (1998).
24. R. Hansen and J.P. Balthasar, Pharmacokinetic/pharmacodynamic modeling of the effects of intravenous immunoglobin on the disposition of antiplatelet antibodies in a rat model of immune thrombocytopenia, *J. Pharmaceutical Sciences*, **92:**1206-1215 (2003).
25. A. Äbelö, U.G. Eriksson, M.O. Karlsson, H. Larsson and J. Gabrielsson, A turnover model of irreversible inhibition of gastric acid secretion by Omeprazole in the dog, *JPET* **295:**662-669 (2000).
26. C.M. Bender and S.A. Orszag, Advanced Mathematical Methods for Scientists and Engineers, *McGraw-Hill International Editions,* Singapore, 1978.
27. W. Rudin, Principles of Mathematical Analysis, *McGraw-Hill,* New York, 1964.

28. G.F. Simmons, Introduction to Topology and Modern Analysis, *McGraw-Hill,* New York, 1963.