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COMPTES RENDUS MATHEMATIQUE

Ordinary Differential Equations/Dynamical Systems

Monotonicity of the peak time in turnover models

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Abstract

We prove that in three of the classical turnover models in pharmacodynamics the time to maximal response increases with increasing drug dose when the concentration of the drug in the blood plasma decreases exponentially with time. ***To cite this article: H.-M. Nguyen, L.A. Peletier, C. R. Acad. Sci. Paris, Ser. I 347 (2009).***

Résumé

Monotonie du temps de réponse maximal dans des modèles turnovers. Nous démontrons que dans des trois modèles turnovers classiques en pharmacodynamique le temps de réponse maximal augmente en fonction de la dose de drogue lorsque la concentration du médicament dans le plasma sanguin diminue exponentiellement en temps. ***Pour citer cet article : H.-M. Nguyen, L.A. Peletier, C. R. Acad. Sci. Paris, Ser. I 347 (2009).***

Version française abrégée

Dans cette Note, nous présentons des résultats récents sur la façon dont le *Temps de Réponse Maximal* dépend de la dose de drogue dans des systèmes décrits par les quatre modèles turnovers classiques en pharmacodynamique (voir, par exemple, [1,9,2]). Dans des modèles turnovers, la réponse R est décrite par une équation différentielle ordinaire linéaire du premier ordre :

$$\frac{\mathrm{d}R}{\mathrm{d}t} = k_{\mathrm{in}} H_1\big(C(t)\big) - k_{\mathrm{out}} H_2\big(C(t)\big) R,$$

où k_{in} et k_{out} sont constantes. Ici $C(t)$ est la concentration du médicament dans le plasma, H_1 et H_2 sont fonctions qui décrivent l'effet de la dose de drogue D. Elles peuvent être stimulantes ($H(C) = S(C)$) ou inhibitrices ($H(C) = I(C)$). Dans cette Note, les fonctions S, I, et C sont données par :

$$S(C) = 1 + \frac{S_{\max} C}{SC_{50} + C}, \quad I(C) = 1 - \frac{I_{\max} C}{IC_{50} + C} \quad \text{et} \quad C(t) = C_0 D e^{-k_{\mathrm{el}} t},$$

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où $S_{\max}$, SC_{50}, $I_{\max}$, IC_{50}, C_0, et k_{el} sont constantes pharmacocinétiques.

D'après Dayneka, Garg et Jusko [2], nous notons ces modèles I, II, III et IV, comme expliqués dans le schéma de la Fig. 1.

Une caractéristique importante des modèles turnovers est qu'un certain temps s'écoule avant que la réponse R établise sa valeur maximale $R_{\max}$. L'instant où ce maximum est atteint est considéré comme le *Temps de Réponse Maximal* et il est noté par $T_{\max}$. Une question essentielle dans l'analyse des données pharmacodynamiques est la manière dont le temps de réponse maximal dépend de la dose de drogue (voir par exemple [13] et [8]).

Dans cette Note, nous établissons les résultats suivants :

Théorème 0.1. *Dans les Modèles* I *et* III*, le temps de réponse maximal* $T_{\max}(D)$ *est une fonction croissante de la dose* D*, pour tout* $k_{\mathrm{in}} > 0$*,* $k_{\mathrm{out}} > 0$*,* $k_{\mathrm{el}} > 0$*, et* $0 < I_{\max} \leqslant 1$ (*Modèle* I) *ou* $S_{\max} > 0$ (*Modèle* III)*.*

Théorème 0.2. *Dans le Modèle* II*, le temps de réponse maximal* $T_{\max}(D)$ *est une fonction croissante de la dose* D*, pour tout* $k_{\mathrm{in}} > 0$*,* $k_{\mathrm{out}} > 0$*,* $k_{\mathrm{el}} > 0$ *et* $0 < I_{\max} \leqslant 1$*, si*

$$I_{\max} k_{\mathrm{out}} \leqslant k_{\mathrm{el}} \quad \textit{ou} \quad I_{\max} \leqslant \frac{1}{2}.$$

Théorème 0.3. *Pour tout* $0 < I_{\max} < 1$*, il existe* $\kappa_{I_{\max}} > 0$ *tel que si* $\frac{k_{\mathrm{out}}}{k_{\mathrm{el}}} > \kappa_{I_{\max}}$*, alors le temps de réponse maximal* $T_{\max}(D)$ *dans le Modèle* II *est une fonction croissante de la dose* D*.*

Théorème 0.4. *Dans le Modèle* II *le temps de réponse maximal* $T_{\max}(D)$ *est une fonction croissante de dose* D *pour tout* $k_{\mathrm{in}} > 0$*,* $k_{\mathrm{out}} > 0$*,* $k_{\mathrm{el}} > 0$ *et* $0 < I_{\max} < 1$ *si* D *est assez grand.*

1. Introduction

In this Note we present recent results about how the *Time of Maximal Response*, $T_{\max}$, depends on the drug dose in systems described by the classical four turnover models in pharmacodynamics (cf. [1,9,2]). It is shown that in three of these models $T_{\max}$ increases with increasing drug dose when the drug is administered through an initial bolus dose. The drug concentration in blood plasma is then assumed to drop off following a first order rate constant.

In turnover models the response R of a pharmacodynamic system is described by a linear first order ordinary differential equation of the form:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = k_{\mathrm{in}} H_1\big(C(t)\big) - k_{\mathrm{out}} H_2\big(C(t)\big) R, \tag{1}$$

in which k_{in} and k_{out} are rate constants. The function $C(t)$ denotes the drug concentration in the plasma and the functions H_1 and H_2 the *drug mechanism functions* which model the effect of the drug. They can be stimulating ($H(C) = S(C)$) or inhibiting ($H(C) = I(C)$). In this paper the functions $S(C)$ and $I(C)$ will be given by the Hill functions:

$$S(C) = 1 + \frac{S_{\max} C}{SC_{50} + C}, \quad I(C) = 1 - \frac{I_{\max} C}{IC_{50} + C} \quad \text{and} \quad C(t) = C_0 D e^{-k_{\mathrm{el}} t}, \tag{2}$$

where $S_{\max}$, SC_{50}, $I_{\max}$ and IC_{50} denote the maximum stimulation, the potency of the stimulating effect, the maximum inhibition and the corresponding potency, whilst C_0 is an appropriate constant, D the drug dose and k_{el} the elimination rate of the drug. Turnover models have been very successful in modelling a wide range of pharmacodynamic processes (cf. [3] and the review paper [7]). Their mathematical properties have also been actively studied (cf. [12,4–6,8,11]).

Following Dayneka, Garg and Jusko [2], we number these models I, II, III and IV, as explained in the schematic picture shown in Fig. 1.

An important feature of turnover models is that they incorporate a delay of the response, i.e., after the administration of the drug, some time elapses before the response R builds up to its maximum value $R_{\max}$. The time this maximum is reached is referred to as the *Time of Maximal Response* or *Peak Time* and is denoted by $T_{\max}$. A central question in pharmacodynamic data analysis is the way the peak time depends on the drug dose (cf. e.g. [13] and [8]).

We establish the following monotonicity theorems for the peak time as it varies with the drug dose:

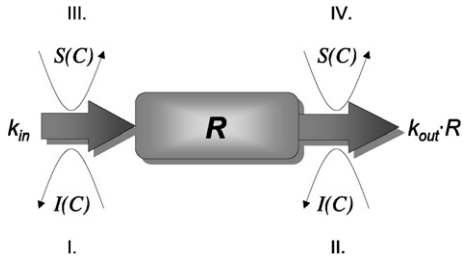

Fig. 1. Schematic illustration of the four turnover models.

Theorem 1.1. *In Models* I *and* III *the peak time* $T_{\max}(D)$ *is an increasing function of the drug dose* D *for any* $k_{\text{in}} > 0$, $k_{\text{out}} > 0$ *and* $k_{\text{el}} > 0$, *and any* $0 < I_{\max} \leqslant 1$ (*Model* I) *or* $S_{\max} > 0$ (*Model* III).

Theorem 1.2. *In Model* II *the peak time* $T_{\max}(D)$ *is an increasing function of the drug dose* D *for any* $k_{\text{in}} > 0$, $k_{\text{out}} > 0$, *and* $k_{\text{el}} > 0$ *and any* $0 < I_{\max} \leqslant 1$, *if*

$$\text{either } I_{\max} k_{\text{out}} \leqslant k_{\text{el}} \quad \text{or} \quad I_{\max} \leqslant \frac{1}{2}. \tag{3}$$

Theorem 1.3. *For any* $0 < I_{\max} < 1$ *there exits* $\kappa_{I_{\max}} > 0$ *such that if* $\frac{k_{\text{out}}}{k_{\text{el}}} > \kappa_{I_{\max}}$, *then the peak time* $T_{\max}(D)$ *in Model* II *is an increasing function of the drug dose* D.

Thus, for Models I and III the peak time $T_{\max}$ is *always* increasing with the drug dose. For Model II, the situation is more complex and we still need to impose some restrictions on the parameters involved. Nonetheless, it is conjectured that also in Models II, $T_{\max}$ is *always* increasing with the drug dose.

If neither of the conditions in Theorems 1.2 and 1.3 is satisfied, we can still prove the following asymptotic result for large drug doses which is valid for all reaction rates and any $I_{\max} \in (0, 1)$:

Theorem 1.4. *In Model* II *the peak time* $T_{\max}(D)$ *is an increasing function of the drug dose* D *for any* $k_{\text{in}} > 0$, $k_{\text{out}} > 0$ *and* $k_{\text{el}} > 0$ *and any* $0 < I_{\max} < 1$, *provided* D *is large enough.*

Apart from being interesting in its own right, Theorem 1.4 supplies an important ingredient in the proof of Theorems 1.2 and 1.3.

In [11] it is shown that in Model IV there exist values of the rate constants and $S_{\max}$ for which $T(D)$ is not increasing for all $D > 0$.

2. Sketch of the proofs

We introduce dimensionless variables by scaling time with the elimination rate k_{el}, the response with the baseline response R_0 and the plasma concentration with the potencies IC_{50} and SC_{50}:

$$t^* = k_{\text{el}} t, \quad R^* = \frac{R}{R_0} = \frac{k_{\text{in}}}{k_{\text{out}}} \quad \text{and} \quad \kappa = \frac{k_{\text{out}}}{k_{\text{el}}}, \tag{4}$$

and the scaled drug mechanism functions become,

$$\begin{aligned} I^*(C^*) &= 1 - \alpha \frac{C^*}{1 + C^*}, \quad C^*(t^*) = \frac{C(t)}{IC_{50}}, \quad \alpha = I_{\max}, \\ S^*(C^*) &= 1 + \alpha \frac{C^*}{1 + C^*}, \quad C^*(t^*) = \frac{C(t)}{SC_{50}}, \quad \alpha = S_{\max}. \end{aligned} \tag{5}$$

Henceforth we shall omit the asterisk again. This yields the dimensionless equation,

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \kappa \big\{ H_1\big(C(t)\big) - H_2\big(C(t)\big) R \big\}, \quad C(t) = De^{-t}, \tag{6}$$

where, depending on the model, H_1 and H_2 are given by the functions $I(C)$ and $S(C)$ defined in (5) and D is the *drug dose*.

2.1. Sketch of the proof of Theorem 1.1

Since $T_{\max}$ is the same for Models I and III (cf. [11]), it suffices to prove monotonicity for one of them; we do it for Model III. Thus, we consider the problem:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \kappa\big\{S\big(C(t)\big) - R\big\}, \quad R(0) = 1, \quad C(t) = De^{-t}, \tag{7}$$

where $S(C)$ is given in (5). Plainly, $R = 1$ is the base line. Writing $R(t) = 1 + \alpha r(t)$, and using the expressions for $S(C)$ and $C(t)$, we obtain:

$$\frac{\mathrm{d}r}{\mathrm{d}t} = \kappa\big\{\varphi(t, D) - r\big\}, \quad r(0) = 0, \quad \text{where } \varphi(t, D) = \frac{De^{-t}}{1 + De^{-t}}. \tag{8}$$

This problem can readily be solved explicitly, and we find that the solution is given by

$$r(t) = \kappa \int_0^t \varphi(s, D) e^{\kappa(s-t)}\,\mathrm{d}s. \tag{9}$$

Since $T = T_{\max}$ is the unique zero of $\mathrm{d}R/\mathrm{d}t$ (cf. [11]) and hence of $\mathrm{d}r/\mathrm{d}t$, we conclude from (8) and (9) that

$$\varphi(T, D)e^{\kappa T} = \kappa \int_0^T \varphi(s, D) e^{\kappa s}\,\mathrm{d}s, \tag{10}$$

where, for notational ease, we have written T in place of $T(D)$.

The identity (10) defines the function $T(D)$ implicitly. It can be shown that this function is continuously differentiable.

Differentiation of the identity in (10) with respect to the drug dose D yields after a lengthy computation the following expression for $T' = \mathrm{d}T/\mathrm{d}D$:

$$\varphi_t(T, D)e^{\kappa T} T'(D) = \frac{\kappa}{D} \int_0^T \varphi(s, D) e^{\kappa s} \mathcal{L}(s, T, D)\,\mathrm{d}s, \tag{11}$$

where

$$\mathcal{L}(s, t, D) = \frac{1}{1 + De^{-s}} - \frac{1}{1 + De^{-t}} \quad \text{for all } s, t, D > 0,$$

and φ_t denotes the partial derivative of φ with respect to t. Clearly, $\mathcal{L}(s, T, D) < 0$ for $0 < s < T$ and an elementary computation shows that $\varphi_t(T, D) > 0$. Thus, it follows from (11) that $T'(D) > 0$ for any $D > 0$, as asserted. □

2.2. Sketch of the proof of Theorem 1.2

Case 1: $\alpha\kappa \leqslant 1$. The proof starts out in a similar manner: we write $R(t) = 1 + r(t)$ and obtain the problem,

$$\frac{\mathrm{d}r}{\mathrm{d}t} = \kappa\big[\big\{1 - i(t, D)\big\} - i(t, D)r\big], \quad r(0) = 0, \tag{12}$$

where $i(t, D) = 1 - \alpha\varphi(t, D)$. This problem can also be solved explicitly:

$$r(t) = \kappa \int_0^t \big\{1 - i(t, D)\big\} e^{-\kappa \int_s^t i(\xi, D)\,\mathrm{d}\xi}\,\mathrm{d}s. \tag{13}$$

From (12) and (13) we now obtain the following identity for $T = T_{\max}(D)$:

$$\int_0^T \bigl\{1 - i(s, D)\bigr\} e^{-\kappa \int_s^T i(\xi, D)\,\mathrm{d}\xi}\,\mathrm{d}s = \frac{1 - i(T, D)}{\kappa i(T, D)}, \quad T = T_{\max}(D). \tag{14}$$

Differentiating this identity with respect to D we obtain an expression for $T'(D)$ similar to (11). We find that if $\alpha\kappa \leqslant 1$, the integral on the right of this expression can be shown to be positive for all drug doses. Since i_t is also positive we may then conclude that $T'(D) > 0$ for all $D > 0$.

Case 2: $\alpha\kappa > 1$ and $\alpha \leqslant 1/2$. In order to prove Theorem 2 in this case, we use a continuation argument. Suppose Theorem 1.2 is not true in this case. Since $T'(D) > 0$ for large values of D (by Theorem 1.4), there exist $\alpha \in (0, 1)$, $\kappa > 0$ ($\alpha\kappa > 1$ and $0 < \alpha \leqslant 1/2$) and $D_0 > 0$ such that

$$T'(D_0) = 0 \quad \text{and} \quad T''(D_0) \geqslant 0. \tag{15}$$

(That D_0 is positive follows from a result in [11].)

We now use the proposition:

(1) *If* $\alpha\kappa > 1$ *and* $\alpha \in (0, 1/2]$, *then* (15) *cannot be satisfied.*

This completes the (sketch of the) proof of Theorem 1.2 since we know $T'(D) > 0$ for $0 < \alpha < 1$ and $\kappa > 0$ with $\alpha\kappa \leqslant 1$. □

2.3. Sketch of the proof of Theorem 1.3

We also use a continuation argument in this proof. In addition to Theorem 1.4, in the proof, we also need the following proposition:

(2) *Fix* $\alpha \in (0, 1)$. *Then for every* $D > 0$, *we have, in Model* II,
   (a) $T(D, \kappa) \to 0$ *as* $\kappa \to \infty$;
   (b) $\kappa T(D, \kappa) \to \infty$ *as* $\kappa \to \infty$.
   Both limits are uniform with respect to $D \geqslant 0$ *on compact intervals.*

Details of the proofs of Theorems 1.1–1.4 can be found in [10].

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