Differential and Integral Equations Volume 22, Numbers 1–2 (2009), 1–26

MONOTONICITY OF TIME TO PEAK RESPONSE WITH RESPECT TO DRUG DOSE FOR TURNOVER MODELS

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Abstract. In this paper we analyze the monotonicity of the time to peak response $T_{\max}$ with respect to the drug dose D for the four different turnover models I - IV, as introduced by Dayneka *et al.* [2]. We do this for the situation when the drug is supplied through an initial bolus, and eliminated according to a single exponential function and stimulation or inhibition takes place through a Hill function. We show that in Models I and III, in which the drug impacts the production term, the function $T_{\max}(D)$ is increasing for all values of the system- and the drug parameters. For Model II (inhibition of the loss term) the situation is more delicate. Here we prove monotonicity of $T_{\max}(D)$ for a substantial range of values of the rate- and drug constants, but leave the question of monotonicity open for some values. Finally, in Model IV (stimulation of the loss term) the function $T_{\max}(D)$ is known not to be monotone for some values of the rate constants and $I_{\max}$ [12].

1. Introduction

Turnover models provide an important instrument for pharmacodynamicists in gaining an understanding of the dynamics of the physiological effects of drugs (cf. Ackerman *et. al.* [1], Dayneka *et. al.* [2], Ekblad *et. al.* [3] and Nagashima *et. al.* [11]). They are based on a simple balance equation for the response $R(t)$ involving a zeroth-order production term ($k_{\rm in}$) and a first-order loss term ($k_{\rm out}R$), resulting in the equation

$$\frac{dR}{dt} = k_{\rm in} - k_{\rm out}R. \tag{1.1}$$

Accepted for publication: September 2008.
AMS Subject Classifications: 34C10, 34C60, 92C45.

This equation also forms the basis for a scala of feedback models.

In these models the impact of the drug takes place through changes in the rate constants k_{in} or k_{out} or in both these constants. Since these changes may be inhibitory or stimulatory, this yields four different turnover models. Following Dayneka, Garg and Jusko [2], we number these models I, II, III and IV, as explained in the schematic picture shown in Figure 1. In this paper

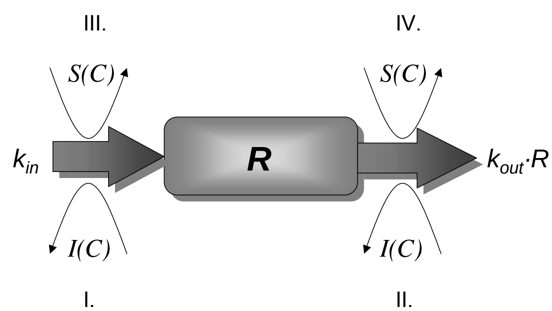


FIGURE 1. Schematic illustration of the four turnover models. Model I and Model III represent inhibition $I(C)$ or stimulation $S(C)$ of the turnover rate k_{in} (production), respectively. Model II and Model IV represent inhibition $I(C)$ or stimulation $S(C)$ of the fractional turnover rate k_{out} (loss), respectively.

we shall always assume that the drug mechanism functions for inhibition $I(C)$ and stimulation $S(C)$ are given by the standard functions

$$I(C) = 1 - I_{\max}\frac{C}{IC_{50} + C} \qquad \text{and} \qquad S(C) = 1 + S_{\max}\frac{C}{SC_{50} + C} \tag{1.2}$$

in which $I_{\max}$, IC_{50}, $S_{\max}$ and SC_{50} denote the maximum inhibition, the potency of the inhibitory effect, the maximum stimulation and the corresponding potency.

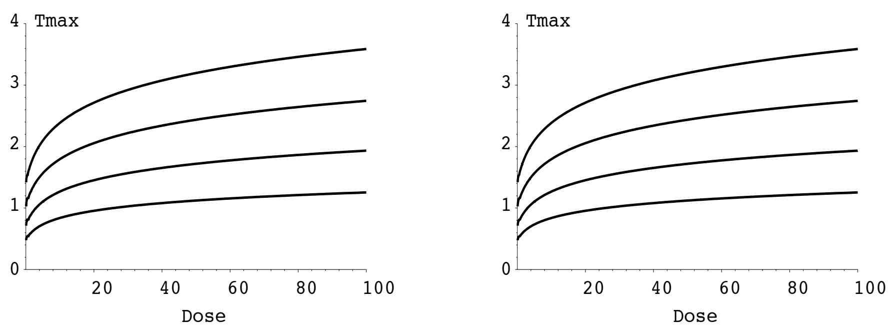
Turnover models, also referred to as indirect response models, have been successful in modeling a diversity of pharmacological responses (cf. Gabrielsson *et al.* [4] and the review paper by Mager *et al.* [9]). They have been the subject of detailed mathematical studies. In particular, we mention the papers by Sharma and Jusko, [13], Krzyzanski and Jusko [5], [6] and [7], Krzyzanski [8], Majumdar [10] and Peletier *et al.* [12].

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 $R_{\max}$. It is generally perceived that this delay, the "time to peak response" $T_{\max}$, increases with the drug dose. This delay of the response plays a role in model selection (cf. Wakelkamp [14]).

In an earlier study [12], analytical and numerical arguments were used to obtain insight into the behavior of $T_{\max}$ with respect to the drug dose when the kinetics is that of an instantaneous infusion into a single compartment. The plasma concentration $C(t)$ is then given by

$$C(t) = C_0 D e^{-k_{\mathrm{el}} t}, \tag{1.3}$$

where C_0 is a positive constant which depends on the model, D the drug dose and k_{el} the elimination rate. In Figures 2 and 3 we give typical sample curves for the four models.



Model I

Model III

FIGURE 2. Peak time $T_{\max}$ *versus* drug dose D for Models I and III. Here $\kappa = k_{\mathrm{out}}/k_{\mathrm{el}}$ takes the values 0.5 (top), 1, 2 and 3 (bottom). The graphs are the same in both models and independent of α.

In [12] it is shown that in Models I - III, regardless of the parameter values, the graph of the function $T_{\max}(D)$ is increasing when D is small and when D is large. Numerical studies warrant the conjecture that this is so for all values of the parameters. In contrast, it is proved that in Model IV there exist rate constants for which $T_{\max}(D)$ is decreasing for small D and increasing for large D. In this paper we prove some of these conjectures.

We shall show that in general the peak time $T_{\max}$ depends on three parameters: the drug dose D, the pharmacokinetic parameter $I_{\max}$ or $S_{\max}$,

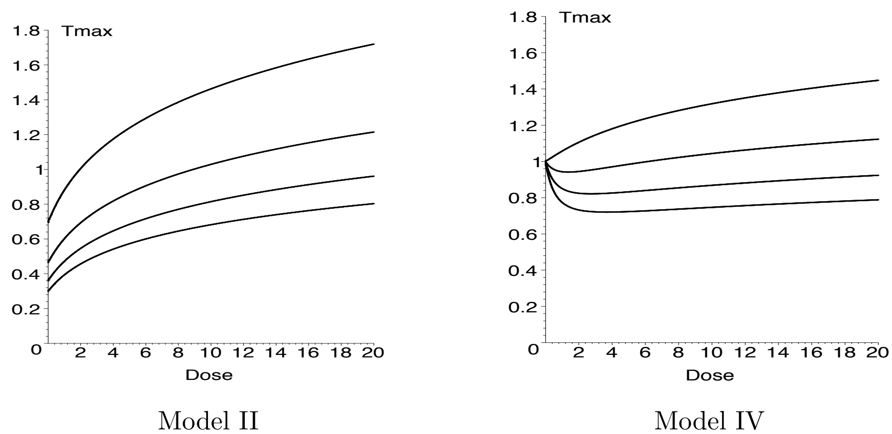


FIGURE 3. Peak time $T_{\max}$ *versus* drug dose D for Models II and IV. In Model II we have taken $\kappa = k_{\rm out}/k_{\rm el} = 2$, 4, 6 and 8 (going down) and $\alpha = 0.5$. In Model IV we took $\kappa = k_{\rm out}/k_{\rm el} = 1$ and $\alpha = 2$, 3, 6 and 8 (going down).

depending on the model, and the ratio κ of the loss rate $k_{\rm out}$ and the elimination rate of the drug $k_{\rm el}$:

$$\kappa = \frac{k_{\rm out}}{k_{\rm el}}.$$

We here recall the well-known facts (e.g. see [12]) that

$$T_{\max}(D)\Big|_{\text{Model I}} = T_{\max}(D)\Big|_{\text{Model III}} \qquad \text{for all} \quad D > 0 \tag{1.4}$$

and that in these models $T_{\max}$ does not depend on $I_{\max}$ (Model I) or $S_{\max}$ (Model III).

In this paper we establish the following monotonicity theorems.

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 $k_{\rm in} > 0$, $k_{\rm out} > 0$ and $k_{\rm el} > 0$, and any $0 < I_{\max} \leq 1$ (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 $k_{\rm in} > 0$ and for any $k_{\rm out} > 0$, $k_{\rm el} > 0$ and $0 < I_{\max} \leq 1$, if*

$$I_{\max} k_{\rm out} \leq k_{\rm el}. \tag{1.5}$$

Theorem 1.3. *In Model II the peak time $T_{\max}(D)$ is an increasing function of the drug dose D for any $k_{\rm in} > 0$ and for any $k_{\rm out} > 0$, $k_{\rm el} > 0$ and*

$0 < I_{\max} \leq 1$, *if*

$$I_{\max} k_{\text{out}} > k_{\text{el}} \qquad \text{and} \qquad I_{\max} \leq \tfrac{1}{2}. \tag{1.6}$$

If (1.5) and (1.6) are violated, 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 $k_{\text{in}} > 0$ and for any $k_{\text{out}} > 0$, $k_{\text{el}} > 0$ and $0 < I_{\max} < 1$, provided D is large enough.*

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

In order to prove Theorem 1.4 we need to refine the asymptotic estimate for the peak time $T_{\max}(D)$ as the drug dose D tends to infinity, which was established in [12]. This improved estimate is given in the next theorem.

Theorem 1.5. *For any $I_{\max} \in (0, 1)$, $k_{\text{in}} > 0$ and $\kappa = k_{\text{out}}/k_{\text{el}} > 0$ we have for Model II, as $D \to \infty$,*

$$T_{\max}(D) = \frac{1}{1 + \kappa(1 - I_{\max})} \ln(D) + \frac{\ln[(1 - I_{\max})\{1 + \kappa(1 - I_{\max})\}]}{1 + \kappa(1 - I_{\max})} + o(1). \tag{1.7}$$

Thus, for Models I and III the peak time $T_{\max}$ is *always* increasing with drug dose. For Model II, the situation is more complex and we still need to impose certain restrictions on the parameters involved. They are shown graphically in Figure 4, where we depict the $(\kappa, I_{\max})$-plane for this model.

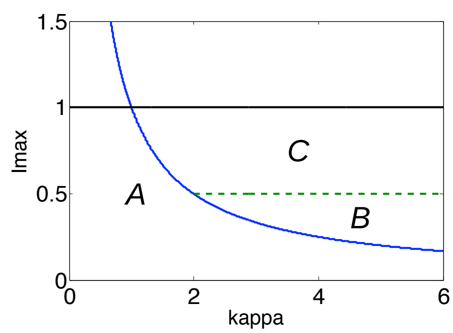


FIGURE 4. The $(\kappa, I_{\max})$-plane for Model II: Strict monotonicity of $T(D)$ is proved in regions A and B and conjectured in Region C.

We conjecture that $T_{\max}(D)$ is an increasing function for all $D > 0$ for any pair of values of κ and $I_{\max}$ in the entire half-strip $\{(\kappa, I_{\max}) : \kappa > 0,\ 0 < I_{\max} < 1\}$.

For notational convenience, we shall often write

$$\alpha = \begin{cases} I_{\max} & \text{in Models I and II,} \\ S_{\max} & \text{in Models III and IV.} \end{cases}$$

2. Dimensionless variables

The scheme shown in Figure 1 translates into the following modification of the differential equation (1.1):

$$\frac{dR}{dt} = k_{\mathrm{in}} H_1(C) - k_{\mathrm{out}} H_2(C) R, \tag{2.1}$$

where $H_1(C)$ and $H_2(C)$ are referred to as drug mechanism functions: $H_1 = I$, $H_2 = 1$ for Model I, $H_1 = 1$, $H_2 = I$ for Model II, $H_1 = S$, $H_2 = 1$ for Model III, $H_1 = 1$, $H_2 = S$ for Model IV. Since $I(0) = 1$ and $S(0) = 1$, it follows that for all four models the baseline of (2.1) is given by

$$R_0 = \frac{k_{\mathrm{in}}}{k_{\mathrm{out}}}. \tag{2.2}$$

Throughout we shall assume that, prior to the administration of the drug, the system is in the baseline state; i.e.,

$$R(0) = R_0. \tag{2.3}$$

In order to identify the parameters which determine the dynamics of the systems, and also make the equation more transparent, we introduce dimensionless variables. We scale 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}. Thus, we introduce the variables

$$t^* = k_{\mathrm{el}} t, \qquad R^* = \frac{R}{R_0} \qquad \text{and} \qquad \kappa = \frac{k_{\mathrm{out}}}{k_{\mathrm{el}}}, \tag{2.4}$$

and the scaled drug mechanism functions become

$$\begin{aligned} I^*(C^*) &= 1 - \alpha \frac{C^*}{1 + C^*}, \qquad C^*(t^*) = \frac{C(t)}{IC_{50}}, \qquad \alpha = I_{\max}, \\ S^*(C^*) &= 1 + \alpha \frac{C^*}{1 + C^*}, \qquad C^*(t^*) = \frac{C(t)}{SC_{50}}, \qquad \alpha = S_{\max}. \end{aligned} \tag{2.5}$$

Henceforth we shall omit the asterisk again.

Substituting these scaled variables into equation (2.1) we obtain

$$\left.\begin{aligned} \frac{dR}{dt} &= \kappa\{H(C(t)) - R\} \qquad \text{for} \qquad \text{Models I and III} \\ \frac{dR}{dt} &= \kappa\{1 - H(C(t))R\} \qquad \text{for} \qquad \text{Models II and IV} \end{aligned}\right., \tag{2.6}$$

where $H(C)$ stands for $I(C)$ or $S(C)$, $C(t) = De^{-t}$ and the constant C_0 has been chosen appropriately. These equations are non-autonomous in that they depend explicitly on the time t, and they contain three parameters: D, α and κ. The initial value of the response in these scaled variables becomes:

$$R(0) = 1. \tag{2.7}$$

In [12] it has been shown that the graph of the solution $R(t)$ of Problem (2.6), (2.7) has precisely one critical point $T_{\max}$, where the system reaches its maximal response $R_{\max}$. Thus, for each of these four models the time to peak response $T_{\max}$ is well defined.

In the next section we present some known results about the function $T_{\max}$ and in the subsequent sections we prove the monotonocity properties formulated in Theorems 1.1 - 1.4.

3. Preliminary results about $T_{\max}$

In this section we cite results about $T_{\max}$ for small and for large values of the drug dose D which were established in [12].

Proposition 3.1. *For Models I-IV we have for any admissible value of α and κ that*

$$\lim_{D\to 0} T_{\max}(D) = T_0 := \begin{cases} \dfrac{\ln(\kappa)}{\kappa - 1} & \text{if} \quad \kappa \neq 1, \\ 1 & \text{if} \quad \kappa = 1, \end{cases} \tag{3.1}$$

and for the derivative $T'_{\max} = dT_{\max}/dD$ in Models I and III,

$$\lim_{D\to 0} T'_{\max}(D) = \begin{cases} \dfrac{1}{\kappa - 2}(2e^{-T_0} - 1) & \text{if} \quad \kappa \neq 2, \\ \ln 2 - \dfrac{1}{2} & \text{if} \quad \kappa = 2. \end{cases} \tag{3.2}$$

For the large dose behavior it was shown that

$$T_{\max}(D) \sim K(\alpha, \kappa)\log(D) \qquad \text{as} \qquad D \to \infty, \tag{3.3}$$

where

$$K(\alpha,\kappa)=\begin{cases}\dfrac{1}{1+\kappa} & \text{Models I and III,}\\ \dfrac{1}{1+\kappa(1-\alpha)} & \text{Model II}\quad (0<\alpha\le 1),\\ \dfrac{1}{1+\kappa(1+\alpha)} & \text{Model IV.}\end{cases} \tag{3.4}$$

4. MODELS I AND III: PROOF OF THEOREM 1.1

Since $T_{\max}$ is the same for Models I and III, we focus on one of them, Model III, and consider the problem

$$\frac{dR}{dt}=\kappa\{S(C)-R\},\qquad R(0)=1 \tag{4.1}$$

in which

$$S(C)=1+\alpha\frac{C}{1+C}\qquad\text{and}\qquad C(t,D)=De^{-t}. \tag{4.2}$$

We write

$$R(t)=1+\alpha r(t).$$

Then

$$\frac{dr}{dt}=\kappa\{\varphi(t,D)-r\},\quad r(0)=0, \tag{4.3}$$

where

$$\varphi(t,D)=\frac{De^{-t}}{1+De^{-t}}. \tag{4.4}$$

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

$$r(t)=\kappa\int_0^t \varphi(s,D)e^{\kappa(s-t)}\,ds.$$

Since $T=T_{\max}$ is the unique zero of dR/dt and hence of dr/dt, we conclude from (4.3) that

$$\varphi(T,D)e^{\kappa T}=\kappa\int_0^T \varphi(s,D)e^{\kappa s}\,ds, \tag{4.5}$$

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

The identity (4.5) defines the function $T(D)$ implicitly. In Appendix A we shall show that this function is continuously differentiable.

In the following lemma we establish an identity which involves $T'(D)=dT/dD$.

Lemma 4.1. *We have*

$$\varphi_t(T,D)e^{\kappa T}T'(D) = \kappa \int_0^T \varphi_D(s,D)e^{\kappa s}\,ds - \varphi_D(T,D)e^{\kappa T}, \tag{4.6}$$

where $\varphi_t = \partial\varphi/\partial t$ *and* $\varphi_D = \partial\varphi/\partial D$.

Proof. Differentiation of (4.5) yields

$$\begin{aligned}
&\varphi(T,D)e^{\kappa T}T' + \int_0^T \varphi_D(s,D)e^{\kappa s}\,ds \\
&= \frac{1}{\kappa}\{\varphi_t(T,D) + \kappa\varphi(T,D)\}e^{\kappa T}T' + \frac{1}{\kappa}\varphi_D(T,D)e^{\kappa T}
\end{aligned}$$

or

$$\int_0^T \varphi_D(s,D)e^{\kappa s}\,ds = \frac{1}{\kappa}\varphi_t(T,D)e^{\kappa T}T' + \frac{1}{\kappa}\varphi_D(T,D)e^{\kappa T}.$$

Rearranging the terms we obtain (4.6). □

Next, we give a technical lemma in which we collect a few useful properties of the function $\varphi(t,D)$ defined in (4.4):

$$\varphi(t,D) = \frac{De^{-t}}{1+De^{-t}}.$$

Lemma 4.2. *We have*

$$\varphi_t(t,D) = -\frac{\varphi(t,D)}{1+De^{-t}} \quad \textit{and} \quad \varphi_D(t,D) = \frac{\varphi(t,D)}{D(1+De^{-t})}.$$

Therefore,

$$\varphi_D(t,D) = -\frac{1}{D}\varphi_t(t,D).$$

Plainly, we have

$$\varphi_t(t,D) < 0 \quad \textit{and} \quad \varphi_D(t,D) > 0 \quad \textit{for all} \quad t>0,\ D>0.$$

Proof. The proof follows from a simple computation. The details are left to the reader. □

We denote the right-hand side of (4.6) by X:

$$X = \kappa \int_0^T \varphi_D(s,D)e^{\kappa s}\,ds - \varphi_D(T,D)e^{\kappa T}, \tag{4.7}$$

and we prove the following.

Lemma 4.3. *We have*

$$X = \frac{\kappa}{D}\int_0^T \varphi(s,D)e^{\kappa s}\mathcal{L}(s,T,D)\,ds,$$

where

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

Proof. We write

$$X = X_1 - X_2, \tag{4.8}$$

where

$$X_1 = \kappa\int_0^{T_1} \varphi_D(s,D)e^{\kappa s}\,ds \qquad \text{and} \qquad X_2 = \varphi_D(T,D)e^{\kappa T}.$$

Using Lemma 4.2 we can write X_1 as

$$X_1 = \kappa\int_0^T \varphi(s,D)e^{\kappa s}\frac{1}{D(1+De^{-s})}\,ds \tag{4.9}$$

and X_2 as

$$X_2 = \frac{1}{D(1+De^{-T})}\varphi(T,D)e^{\kappa T}.$$

When we use (4.5) we can write X_2 as

$$X_2 = \frac{\kappa}{D(1+De^{-T})}\int_0^T \varphi(s,D)e^{\kappa s}\,ds. \tag{4.10}$$

Putting the expressions (4.9) and (4.10) for, respectively, X_1 and X_2 into (4.8), we end up with

$$X = \frac{\kappa}{D}\int_0^T \varphi(s,D)e^{\kappa s}\left(\frac{1}{1+De^{-s}} - \frac{1}{1+De^{-T}}\right)ds,$$

which is the expression we set out to prove. □

We are ready to complete the proof of Theorem 1.1.

Proof of Theorem 1.1. Plainly

$$\frac{1}{1+De^{-s}} < \frac{1}{1+De^{-T}} \qquad \text{for} \qquad 0<s<T.$$

Therefore,

$$\mathcal{L}(s,T,D) < 0 \qquad \text{for} \qquad 0<s<T.$$

Thus, since $\varphi(s,D)>0$, it follows from Lemma 4.3 that $X<0$ and hence, by Lemma 4.1, that

$$\varphi_t(T,D)e^{\kappa T}T'(D) < 0.$$

Remembering from Lemma 4.2 that $\varphi_t < 0$ we conclude that $T'(D) > 0$ for any $D > 0$. $\square$

5. MODEL II: PROOF OF THEOREM 1.2

We consider the problem

$$\frac{dR}{dt} = \kappa\{1 - I(C)R\}, \qquad R(0) = 1 \tag{5.1}$$

in which

$$I(C) = 1 - \alpha\frac{C}{1+C} \qquad \text{and} \qquad C(t, D) = De^{-t}. \tag{5.2}$$

We write

$$R(t) = 1 + r(t).$$

Then

$$\frac{dr}{dt} = \kappa[\{1 - i(t, D)\} - i(t, D)r], \qquad r(0) = 0, \tag{5.3}$$

where

$$\varphi(t, D) = \frac{De^{-t}}{1 + De^{-t}} \qquad \text{and} \qquad i(t, D) = 1 - \alpha\varphi(t, D). \tag{5.4}$$

This problem can be solved explicitly, and the solution is found to be

$$r(t) = \kappa\int_0^t \{1 - i(t, D)\}e^{-\kappa\int_s^t i(\xi,D)\,d\xi}\,ds. \tag{5.5}$$

Therefore, when the response is maximal, i.e., when $t = T_{\max}$ and $dR/dt = 0$ and hence $dr/dt = 0$, then we deduce from equation (5.3) that

$$\int_0^T \{1 - i(s, D)\}e^{-\kappa\int_s^T i(\xi,D)\,d\xi}\,ds = \frac{1 - i(T, D)}{\kappa i(T, D)}, \qquad T = T_{\max}(D). \tag{5.6}$$

Since $0 < \alpha \le 1$ and $\varphi(T, D) < 1$ for any $T > 0$ and $D > 0$, the right-hand side of (5.6) is well defined.

This identity defines the function $T(D)$ implicitly. We shall show in Appendix A that it is continuously differentiable.

We proceed as in the previous section and first derive an intermediate identity which is comparable to the one in Lemma 4.1.

Lemma 5.1. *Let $0 < \alpha \le 1$ and $\kappa > 0$. Then*

$$\frac{i_t(T, D)}{\kappa i^2(T, D)}T'(D) = -\frac{i_D(T, D)}{\kappa i^2(T, D)} + Y_1 + Y_2, \tag{5.7}$$

where

$$Y_1 = \int_0^T i_D(s,D) e^{-\kappa \int_s^T i(\xi,D)\,d\xi}\, ds,$$
$$Y_2 = \int_0^T \{1 - i(s,D)\} e^{-\kappa \int_s^T i(\xi,D)\,d\xi} \left(\kappa \int_s^T i_D(\xi,D)\,d\xi \right) ds.$$

Proof. When we differentiate (5.6) with respect to D we obtain

$$\begin{aligned}
&\{1 - i(T,D)\}T' - \int_0^T i_D(s,D) e^{-\kappa \int_s^T i(\xi,D)\,d\xi}\, ds \\
&- \int_0^T \{1 - i(s,D)\} e^{-\kappa \int_s^T i(\xi,D)\,d\xi} \left(\kappa i(T,D)T' + \kappa \int_s^T i_D(\xi,D)\,d\xi \right) ds \\
&= -\frac{1}{\kappa i^2(T,D)} \left\{ i_t(T,D)T' + i_D(T,D) \right\}.
\end{aligned}$$

Thanks to the identity (5.6), two terms cancel and we are left with

$$\begin{aligned}
&\int_0^T i_D(s,D) e^{-\kappa \int_s^T i(\xi,D)\,d\xi}\, ds \\
&+ \int_0^T \{1 - i(s,D)\} e^{-\kappa \int_s^T i(\xi,D)\,d\xi} \left(\kappa \int_s^T i_D(\xi,D)\,d\xi \right) ds \\
&= \frac{1}{\kappa i^2(T,D)} \left\{ i_t(T,D)T' + i_D(T,D) \right\}.
\end{aligned}$$

Rearranging the terms we obtain (5.7).

Before stating the final expression for $T'(D)$, we list a few properties of the function $i(t,D)$.

Lemma 5.2. *For any $D > 0$ and any $t > 0$,*

$$i_D(t,D) = -\frac{\alpha e^{-t}}{(1 + De^{-t})^2} = -\frac{1 - i(t,D)}{D(1 + De^{-t})}$$

and

$$i_t(t,D) = -D\, i_D(t,D) = \frac{1 - i(t,D)}{1 + De^{-t}}.$$

In particular,

$$i_t(t,D) > 0 \quad \text{and} \quad i_D(t,D) < 0 \quad \text{for all } t > 0,\ D > 0.$$

We use these properties of the function $i(t,D)$ to rewrite the integrand in Y_1 and Y_2 in terms of $i(t,D)$ only. This results in the following lemma.

Lemma 5.3. *Let $0 < \alpha \le 1$ and $\kappa > 0$. Then*

$$\frac{i_t(T,D)}{i^2(T,D)}T'(D) = \frac{\kappa}{D}\int_0^T \{1 - i(s,D)\}e^{-\kappa\int_s^T i(\xi,D)\,d\xi}\mathcal{M}(s,T,D)\,ds, \tag{5.8}$$

where

$$\mathcal{M}(s,t,D) = \frac{1}{(De^{-t}+1)i(t,D)} - \frac{1}{De^{-s}+1} - \kappa i(t,D) + \kappa i(s,D)$$

for any $s, T, D > 0$.

Proof. Using the expression for $i_D(t,D)$ from Lemma 5.2 we can write Y_1 as

$$Y_1 = -\frac{1}{D}\int_0^T \frac{1 - i(s,D)}{1 + De^{-s}}e^{-\int_s^T \kappa i(\xi,D)\,d\xi}\,ds. \tag{5.9}$$

In order to eliminate $i_D(t,D)$ from Y_2, we use the identity

$$i_D(t,D) = -\frac{1}{D}i_t(t,D)$$

from Lemma 5.2 and write

$$\int_s^T i_D(\xi,D)\,d\xi = -\frac{1}{D}\int_s^T i_t(\xi,D)\,d\xi = -\frac{1}{D}\{i(T,D) - i(s,D)\}.$$

Putting this into the expression for Y_2 we obtain

$$Y_2 = \frac{1}{D}\int_0^T \{1 - i(s,D)\}e^{-\int_s^T \kappa i(\xi,D)\,d\xi}\{-\kappa i(T,D) + \kappa i(s,D)\}\,ds. \tag{5.10}$$

Finally, by Lemma 5.2 we can write the first term on the right-hand side of (5.7) as

$$\frac{i_D(T,D)}{\kappa i^2(T,D)} = -\frac{1}{D}\frac{1 - i(T,D)}{\kappa i^2(T,D)(1 + De^{-T})}.$$

Using the identity (5.6) this yields

$$\frac{i_D(T,D)}{\kappa i^2(T,D)} = -\frac{1}{D}\frac{1}{i(T,D)(1 + De^{-T})}\int_0^T \{1 - i(s,D)\}e^{-\int_s^T \kappa i(\xi,D)\,d\xi}\,ds. \tag{5.11}$$

Putting (5.9), (5.10) and (5.11) into (5.7), we obtain the desired expression (5.8). $\square$

Proof of Theorem 1.2. The proof of Theorem 1.2 is a consequence of Lemma 5.3. Indeed, observe that since $i(T,D) < 1$,

$$\mathcal{M}(s,T,D) > \frac{1}{1 + C(T)} - \kappa I(C(T)) - \frac{1}{1 + C(s)} + \kappa I(C(s)), \qquad C(t) = De^{-t}.$$

Write

$$F(C) = \frac{1}{1+C} - \kappa I(C).$$

Then

$$F'(C) = \frac{\alpha\kappa - 1}{(1+C)^2}.$$

Hence, if $\alpha\kappa \le 1$, then $F'(C) \le 0$ for $C \ge 0$ and it follows that, since $C(T) \le C(s)$ if $0 \le s \le T$,

$$\mathcal{M}(s,T,D) > F(C(T)) - F(C(s)) \ge 0 \qquad \text{for} \qquad 0 \le s \le T. \tag{5.12}$$

Thus, if $\alpha\kappa \le 1$, then (5.12) holds, and the integral in (5.8) is positive. Remembering that $i_t(t,D) > 0$ for all $t > 0$ and $D > 0$ we conclude that, if $\alpha\kappa \le 1$, then $T'(D) > 0$ for all $D > 0$.

This concludes the proof of Theorem 1.2. □

6. Two technical lemmas

In this section we derive a convenient expression for $T'(D)$ and a necessary and sufficient condition for $T''(D)$ to be positive when $T'(D) = 0$.

Lemma 6.1. *Let $0 < \alpha \le 1$ and $\kappa > 0$ in Model II. Then*

$$T'(D) = \frac{\kappa i^2(T,D)}{D i_t(T,D)} \left(\frac{i_t(T,D)}{\kappa i^2(T,D)} - \{1 - i(0,D)\} e^{-\int_0^T \kappa i(\xi,D)\,d\xi} \right).$$

Proof. We start from the expression (5.7) in Lemma 5.1. Using Lemma 5.2 we write

$$Y_1 = -\frac{1}{D} \int_0^T i_t(s,D) e^{-\kappa \int_s^T i(\xi,D)\,d\xi}\,ds$$

and integrate by parts. This yields

$$Y_1 = -\frac{1}{D} \Big\{ i(T,D) - i(0,D) e^{-\kappa \int_0^T i(\xi,D)\,d\xi} - \kappa \int_0^T i^2(s,D) e^{-\kappa \int_s^T i(\xi,D)\,d\xi}\,ds \Big\}. \tag{6.1}$$

For Y_2 we obtain, invoking the identity (5.6) along the way,

$$\begin{aligned} Y_2 &= -\frac{1}{D} \int_0^T \{1 - i(s,D)\} e^{-\kappa \int_s^T i(\xi,D)\,d\xi} \left(\kappa \int_s^T i_t(\xi,D)\,d\xi \right) ds \\ &= -\frac{\kappa}{D} \int_0^T \{1 - i(s,D)\} e^{-\kappa \int_s^T i(\xi,D)\,d\xi} \{ i(T,D) - i(s,D) \}\,ds. \\ &= -\frac{\kappa}{D} i(T,D) \frac{1 - i(T,D)}{\kappa i(T,D)} + \frac{\kappa}{D} \int_0^T i(s,D) \{1 - i(s,D)\} e^{-\kappa \int_s^T i(\xi,D)\,d\xi}\,ds. \end{aligned}$$

Thus, we obtain the expression

$$Y_2 = -\frac{1}{D} + \frac{1}{D} i(T,D) + \frac{\kappa}{D}\int_0^T i(s,D)\{1-i(s,D)\}e^{-\kappa\int_s^T i(\xi,D)\,d\xi}\,ds. \quad (6.2)$$

Putting the new expressions (6.1) and (6.2) for respectively Y_1 and Y_2 into (5.7) we obtain

$$\begin{aligned}
\frac{Di_t(T,D)}{\kappa i^2(T,D)}T'(D) &= \frac{i_t(T,D)}{\kappa i^2(T,D)} - i(T,D) + i(0,D)e^{-\int_0^T \kappa i(\xi,D)\,d\xi} \\
&\quad + \int_0^T \kappa i^2(s,D)e^{-\int_s^T \kappa i(\xi,D)\,d\xi}\,ds \\
&\quad - 1 + i(T,D) + \int_0^T \kappa i(s,D)\{1-i(s,D)\}e^{-\int_s^T \kappa i(\xi,D)\,d\xi}\,ds \\
=&\frac{i_t(T,D)}{\kappa i^2(T,D)} + i(0,D)e^{-\int_0^T \kappa i(\xi,D)\,d\xi} - 1 + \int_0^T \kappa i(s,D)e^{-\int_s^T \kappa i(\xi,D)\,d\xi}\,ds.
\end{aligned}$$

On the other hand,

$$\int_0^T \kappa i(s,D)e^{-\int_s^T ki(\xi,D)\,d\xi}\,ds = \int_0^T d\left(e^{-\int_s^T \kappa i(\xi,D)\,d\xi}\right) = 1 - e^{-\int_0^T \kappa i(\xi,D)\,d\xi}.$$

Hence,

$$\frac{Di_t(T,D)}{\kappa i^2(T,D)}T'(D) = \frac{i_t(T,D)}{ki^2(T,D)} + \{i(0,D)-1\}e^{-\int_0^T \kappa i(\xi,D)\,d\xi}.$$

This implies that

$$T'(D) = \frac{\kappa i^2(T,D)}{Di_t(T,D)}\left(\frac{i_t(T,D)}{\kappa i^2(T,D)} + \{i(0,D)-1\}e^{-\int_0^T \kappa i(\xi,D)\,d\xi}\right),$$

as required. □

Lemma 6.2. *Let $0 < \alpha \le 1$ and let $\kappa > 0$. Assume that $T'(D) = 0$. Then*

$$T''(D) > 0 \iff \frac{1}{D+1} - \frac{2(1-\alpha)e^{-T}}{1+(1-\alpha)De^{-T}} - \frac{\kappa\alpha(1-e^{-T})}{(D+1)(1+De^{-T})} > 0. \quad (6.3)$$

Proof. Using the expression for $T'(D)$ derived in Lemma 6.1 we write

$$T'(D) = g(T,D)f(T,D),$$

where

$$g(t,D) = \frac{\kappa i^2(t,D)}{i_t(t,D)}[1+(1-\alpha)De^{-t}]^{-2}\frac{\alpha D}{D+1}$$
$$f(t,D) = \frac{e^{-t}}{\kappa}(D+1) - [1+(1-\alpha)De^{-t}]^2 e^{-\int_0^t \kappa i(\xi)\,d\xi}.$$

This factorization has been chosen so that $g(t,D) > 0$ for all $t > 0$ and $D > 0$. Thus, $T'(D) = 0$ if and only if $f(T,D) = 0$. It follows that, if $T'(D) = 0$, then

$$T'' = (gf)_t T' + (gf)_D = (gf)_D = g_D f + g f_D = g f_D \tag{6.4}$$

so that it suffices to determine the sign of $f_D(T,D)$.

Plainly,

$$\begin{aligned} f_D(t,D) =& \frac{e^{-t}}{\kappa} - 2(1-\alpha)e^{-t}[1+(1-\alpha)De^{-t}]e^{-\int_0^t \kappa i(\xi)\,d\xi} \\ &+ \kappa[1+(1-\alpha)De^{-t}]^2 e^{-\int_0^t \kappa i(\xi)\,d\xi}\Big(\int_0^t i_D(\xi,D)\,d\xi\Big). \end{aligned}$$

Since $T'(D) = 0$, it follows from Lemma 6.1 that

$$e^{-\int_0^T \kappa i(\xi,D)\,d\xi} = \frac{(D+1)e^{-T}}{\kappa[1+(1-\alpha)De^{-T}]^2},$$

and since, by Lemma 5.2, $i_D = -i_t/D$ we have

$$\int_0^t i_D(\xi,D)\,d\xi = -\frac{1}{D}\{i(t,D) - i(0,D)\}.$$

Using these expressions we can write $f_D(T,D)$ as

$$\begin{aligned} f_D(T,D) = & \frac{e^{-T}}{\kappa} - 2(1-\alpha)e^{-T}[1+(1-\alpha)De^{-T}]\frac{(D+1)e^{-T}}{\kappa[1+(1-\alpha)De^{-T}]^2} \\ &- \frac{\kappa}{D}[1+(1-\alpha)De^{-T}]^2 \frac{(D+1)e^{-T}}{\kappa[1+(1-\alpha)De^{-T}]^2}\{i(T,D)-i(0,D)\}, \end{aligned}$$

which can be simplified to

$$\frac{1}{D+1}\kappa e^T f_D(T,D) = \frac{1}{D+1} - \frac{2(1-\alpha)e^{-T}}{1+(1-\alpha)De^{-T}} - \frac{\kappa}{D}\{i(T,D)-i(0,D)\}.$$

Using the formula for $i(t,D)$ this results in

$$\frac{1}{D+1}\kappa e^{T} f_D(T,D) = \frac{1}{D+1} - \frac{2(1-\alpha)e^{-T}}{1+(1-\alpha)De^{-T}} - \frac{\kappa\alpha(1-e^{-T})}{(D+1)(1+De^{-T})}. \tag{6.5}$$

By (6.4) and the positivity of $g(T,D)$, we have $\operatorname{sign}(T'') = \operatorname{sign}(f_D)$, so that we may conclude from (6.5) that

$$T''(D) > 0 \iff \frac{1}{D+1} - \frac{2(1-\alpha)e^{-T}}{1+(1-\alpha)De^{-T}} - \frac{\kappa\alpha(1-e^{-T})}{(D+1)(1+De^{-T})} > 0,$$

which is what we set out to prove. □

7. THE CASE $\alpha\kappa > 1$ - PROOF OF THEOREM 1.3

The proof of Theorem 1.3 proceeds in steps. We first prove that $T'(D) > 0$ for $D > 2/(1-\alpha)$ and κ large enough. Then we expand this result to all $D > 0$, but still for κ large enough. Finally, by a continuation argument we extend the values of α and κ to the region $\alpha\kappa > 1$ and $0 < \alpha \le \frac{1}{2}$.

Lemma 7.1. *For any $\alpha \in (0,1)$ there exists a constant $\kappa_\alpha > 0$ such that, if $\kappa > \kappa_\alpha$, then*

$$T'(D) > 0 \qquad \text{for all} \qquad D > \frac{2}{1-\alpha}.$$

Proof. Fix $\alpha \in (0,1)$. Suppose to the contrary that there exists a sequence $\{\kappa_j\}$ tending to infinity as $j \to \infty$ such that for each $j \ge 1$ there exists a drug dose $D_j > 2/(1-\alpha)$ such that $T'(D_j,\kappa_j) \le 0$. Because we know from Theorem 1.4 that, for each κ_j, $T'(D) > 0$ for D large enough, we may choose the sequence $\{D_j\}$ such that

$$T'(D_j,\kappa_j) = 0 \qquad \text{and} \qquad T''(D_j,\kappa_j) \ge 0 \qquad \text{for every} \quad j \ge 1.$$

From Lemma 6.2 we deduce that

$$\frac{1}{D+1} - \frac{2(1-\alpha)e^{-T}}{1+(1-\alpha)De^{-T}} \ge 0 \quad \text{and} \quad \frac{1}{D+1} - \frac{\kappa\alpha(1-e^{-T})}{(D+1)(De^{-T}+1)} \ge 0, \tag{7.1}$$

where we have dropped the subscript j and $T = T(D)$. These inequalities can be simplified to, respectively,

$$e^{T} \ge D(1-\alpha) + 2(1-\alpha) \tag{7.2}$$

and

$$D + e^{T} \ge \kappa\alpha(e^{T}-1). \tag{7.3}$$

Eliminating D between them, we obtain

$$\Big(1 + \frac{1}{1-\alpha}\Big)e^T \geq \kappa\alpha(e^T - 1) + 2. \tag{7.4}$$

Since $D > 2/(1-\alpha)$ it follows from (7.2) that $e^T > D(1-\alpha) > 2$. Therefore, for j, and hence κ_j, large enough we obtain a contradiction. □

Lemma 7.2. *Fix $\alpha \in (0,1)$. Then, for every $D > 0$, we have*
(a) $T(D,\kappa) \to 0$ *as* $\kappa \to \infty$ *and*
(b) $\kappa T(D,\kappa) \to \infty$ *as* $\kappa \to \infty$.
Both limits are uniform with respect to $D \geq 0$ on compact intervals.

Proof. The starting point of the proof is (5.6):

$$\int_0^T \{1 - i(s,D)\} e^{-\kappa \int_s^T i(\xi,D)\,d\xi}\,ds = \frac{1 - i(T,D)}{\kappa i(T,D)}, \qquad T = T_{\max}(D,\kappa). \tag{7.5}$$

Part (a): $T(D,\kappa) \to 0$ *as* $\kappa \to \infty$. Let $D_0 > 0$. Then we have, for $0 \leq D \leq D_0$ and $0 < s < T$,

$$\frac{1 - i(s,D)}{1 - i(T,D)} = \frac{D + e^T}{D + e^s} \tag{7.6}$$

and it follows that

$$\begin{aligned} &\frac{1}{1 - i(T,D)} \int_0^T \{1 - i(s,D)\} e^{-\kappa \int_s^T i(\xi,D)\,d\xi}\,ds \\ &= (D + e^T) \int_0^T \frac{1}{D + e^s} e^{-\kappa \int_s^T i(\xi,D)\,d\xi}\,ds. \end{aligned} \tag{7.7}$$

Moreover, because $i_t(t,D) > 0$, by Lemma 5.2,

$$i(t,D) < i(T,D) \qquad \text{for} \qquad 0 < t < T,$$

so that

$$\int_0^T \frac{1}{D + e^s} e^{-\kappa \int_s^T i(\xi,D)\,d\xi}\,ds > \int_0^T \frac{1}{D + e^s} e^{-\kappa i(T,D)(T-s)}\,ds.$$

Integrating by parts, one has

$$\begin{aligned} &\int_0^T \frac{1}{D + e^s} e^{-\kappa i(T,D)(T-s)}\,ds \\ &= \frac{e^{-\kappa i(T,D)T}}{\kappa i(T,D)} \left(\frac{e^{\kappa i(T,D)T}}{D + e^T} - \frac{1}{D+1} + \int_0^T \frac{e^{\kappa i(T,D)s} e^s}{(D + e^s)^2}\,ds \right). \end{aligned}$$

This implies

$$\int_0^T \frac{1}{D+e^s} e^{-\kappa i(T,D)(T-s)}\,ds \tag{7.8}$$
$$= \frac{1}{\kappa i(T,D)(D+e^T)} + \frac{e^{-\kappa i(T,D)T}}{\kappa i(T,D)} \left(\int_0^T \frac{e^{\kappa i(T,D)s} e^s}{(D+e^s)^2}\,ds - \frac{1}{D+1} \right).$$

Combining (7.5), (7.7) and (7.8), we obtain the inequality

$$\int_0^T \frac{e^{\kappa i(T,D)s} e^s}{(D+e^s)^2}\,ds < \frac{1}{D+1},$$

from which we conclude that

$$\lim_{\kappa\to\infty} T(D) = 0.$$

Moreover, the limit is uniform with respect to $D < D_0$.
Part (b): $\kappa\, T(D,\kappa) \to \infty$ *as* $\kappa \to \infty$. Since

$$i(t,D) > i(0,D) = \frac{1+(1-\alpha)D}{1+D} \qquad \text{and} \qquad 1 - i(t,D) < \alpha \frac{D}{1+D}$$

for $t > 0$, we have

$$\int_0^T \{1 - i(s,D)\} e^{-\kappa \int_s^T i(\xi,D)\,d\xi}\,ds \tag{7.9}$$
$$< \frac{\alpha D}{1+D} \int_0^T e^{-\kappa \frac{1+(1-\alpha)D}{1+D}(T-s)}\,ds = \frac{\alpha}{\kappa} \frac{D}{1+(1-\alpha)D} \left(1 - e^{-\kappa \frac{1+(1-\alpha)D}{1+D} T}\right).$$

Also

$$\frac{1 - i(T,D)}{\kappa i(T,D)} = \frac{\alpha}{\kappa} \frac{D}{e^T + (1-\alpha)D}. \tag{7.10}$$

Substituting (7.9) and (7.10) into (7.5), we obtain the inequality

$$\frac{\alpha}{\kappa} \frac{D}{e^T + (1-\alpha)D} < \frac{\alpha}{\kappa} \frac{D}{1+(1-\alpha)D} \left(1 - e^{-\kappa \frac{1+(1-\alpha)D}{1+D} T}\right)$$

or

$$\frac{1+(1-\alpha)D}{e^T + (1-\alpha)D} < 1 - e^{-\kappa \frac{1+(1-\alpha)D}{1+D} T}$$

or

$$e^{-\kappa T} < e^{-\kappa \frac{1+(1-\alpha)D}{1+D} T} < \frac{e^T - 1}{e^T + (1-\alpha)D} < 1 - e^{-T}. \tag{7.11}$$

Since $T(D,\kappa) \to 0$ as $\kappa \to \infty$ uniformly with respect to D on compact sets, it follows that the right-hand side of (7.11) tends to zero as $\kappa \to \infty$, and hence we conclude that $\kappa T(D,\kappa) \to \infty$ as $\kappa \to \infty$ uniformly with respect to D in compact intervals. $\square$

Using Lemmas 7.1 and 7.2, one can prove the following.

Proposition 7.1. *For any $\alpha \in (0,1)$, there exists a constant $\kappa_\alpha > 0$ such that, for any $\kappa > \kappa_\alpha$,*

$$T'(D) > 0 \quad \textit{for all} \quad D > 0.$$

Proof. First, by Lemma 7.1, it suffices to prove that there exists a constant κ_α such that

$$T'(D) > 0 \quad \text{for all} \quad D \in (0, 2/(1-\alpha)), \tag{7.12}$$

for any $\kappa > \kappa_\alpha$. In fact, by Lemma 7.2 there is a constant κ_1 such that

$$\Big(1 + \frac{1}{1-\alpha}\Big)e^T < \kappa\alpha(e^T - 1) + 2 \quad \text{for all} \quad D \in (0, 2/(1-\alpha)) \tag{7.13}$$

whenever $\kappa > \kappa_1$. We prove that (7.12) holds when we choose for κ_α the maximum of κ_1 and the constant κ_α of Lemma 7.1.

Suppose to the contrary that (7.12) is not true. Then, since $T'(D) > 0$ for $D \geq 2/(1-\alpha)$ and $\kappa > \kappa_\alpha$ (by Lemma 7.1), there exist values for $\kappa > \kappa_\alpha$ and $D \in (0, 2/(1-\alpha))$ such that

$$T'(D) = 0 \quad \text{and} \quad T''(D) \geq 0.$$

Hence we obtain as in the proof of Lemma 7.1 that

$$\Big(1 + \frac{1}{1-\alpha}\Big)e^T \geq \kappa\alpha(e^T - 1) + 2.$$

This contradicts (7.13) which holds for the value of κ which we have chosen. $\square$

We are now ready to prove Theorem 1.3, which we reformulate in the following proposition.

Proposition 7.2. *Let $0 < \alpha \leq \frac{1}{2}$ and $\kappa\alpha > 1$. Then*

$$T'(D) > 0 \quad \textit{for all} \quad D > 0.$$

Proof. We prove the proposition by contradiction. Since $T'(D) > 0$ for large D (by Theorem 1.4), there exist $\kappa > 0$ and $D > 0$ such that

$$T'(D) = 0 \quad \text{and} \quad T''(D) \geq 0.$$

Using Lemma 6.2, one has

$$[1 + (1-\alpha)De^{-T}](1 + De^{-T}) - 2(1-\alpha)e^{-T}(1+D)(1+De^{-T})$$

$$- \kappa\alpha(1-e^{-T})[1+(1-\alpha)De^{-T}] \geq 0,$$

or equivalently,

$$\begin{aligned}
&1 + De^{-T} + (1-\alpha)De^{-T} + (1-\alpha)D^2e^{-2T} \\
&- 2(1-\alpha)e^{-T}[1+D+De^{-T}+D^2e^{-T}] \\
&- \kappa\alpha[1-e^{-T}+(1-\alpha)De^{-T}-(1-\alpha)De^{-2T}] \geq 0.
\end{aligned}$$

This implies that

$$\begin{aligned}
1-\kappa\alpha + &e^{-T}[\kappa\alpha - 2(1-\alpha)] - De^{-T}[\kappa\alpha(1-\alpha)-\alpha] \\
&+ De^{-2T}(\kappa\alpha-2)(1-\alpha) - D^2e^{-2T}(1-\alpha) \geq 0.
\end{aligned}$$

We write this as

$$X_1 + X_2 > 0, \tag{7.14}$$

where

$$\begin{aligned}
X_1 &= 1-\kappa\alpha + e^{-T}[\kappa\alpha-2(1-\alpha)] \\
X_2 &= -De^{-T}[\kappa\alpha(1-\alpha)-\alpha] + De^{-2T}(\kappa\alpha-2)(1-\alpha) - D^2e^{-2T}(1-\alpha).
\end{aligned}$$

Since $\alpha \leq \frac{1}{2}$ and $\kappa\alpha > 1$, it follows that

$$X_1 = 1-\kappa\alpha + e^{-T}[\kappa\alpha-2(1-\alpha)] = (1-\kappa\alpha)(1-e^{-T}) + e^{-T}(2\alpha-1) < 0.$$

In order to estimate X_2, we handle the cases $\kappa\alpha \geq 2$ and $1 < \kappa\alpha < 2$ separately. If $\kappa\alpha \geq 2$, we have

$$\begin{aligned}
X_2 &< -De^{-T}[\kappa\alpha(1-\alpha)-\alpha] + De^{-2T}(\kappa\alpha-2)(1-\alpha) \\
&\leq -De^{-T}[\kappa\alpha(1-\alpha)-\alpha] + De^{-T}(\kappa\alpha-2)(1-\alpha) \\
&= De^{-T}(3\alpha-2) < 0.
\end{aligned}$$

On the other hand, if $1 < \kappa\alpha < 2$, then

$$X_2 < -De^{-T}[\kappa\alpha(1-\alpha)-\alpha] + De^{-2T}(\kappa\alpha-2)(1-\alpha) < 0,$$

since $\kappa\alpha(1-\alpha)-\alpha > 1-2\alpha \geq 0$. Thus,

$$X_1 + X_2 < 0.$$

This contradicts (7.14) and completes the proof of Theorem 1.3. □

Remark 1. Combining Proposition 7.2 and Theorem 1.2, we have shown that $T'(D) > 0$ for any $\kappa > 0$ and any $\alpha \leq 1/2$.

8. Large dose asymptotics of $T(D)$ in Model II Proof of Theorems 1.4 and 1.5

In order to prove the asymptotic results for large drug doses, we first need to refine the estimate for the asymptotic behavior of $T(D)$ for Model II as D tends to infinity, which was established in [12] and formulated in (3.4). There it was stated that, for Model II, $T(D) \approx \frac{1}{1+k(1-\alpha)} \ln D$ as $D \to \infty$.

We prove the following lemma.

Lemma 8.1. *Let $\alpha \in (0,1)$ and $\kappa > 0$. Then*

$$\frac{1}{D} e^{\{1+\kappa(1-\alpha)\}T(D)} = (1-\alpha)\{1+\kappa(1-\alpha)\}[1+o(1)] \qquad as \quad D \to \infty. \tag{8.1}$$

Proof. We take as starting point the identity (5.6):

$$\int_0^T \{1 - i(s,D)\} e^{-\int_s^T \kappa i(\xi,D)\, d\xi}\, ds = \frac{1 - i(T,D)}{\kappa i(T,D)}, \tag{5.6}$$

and we expand the left- and the right-hand side in powers of the small quantity $\varepsilon = \frac{1}{D}$. Thus, we write

$$1 - i(s,D) = \frac{\alpha D e^{-s}}{1 + D e^{-s}} = \frac{\alpha}{\varepsilon e^s + 1} = \alpha \left\{1 - [1+o(1)]\varepsilon e^s\right\},$$

and hence

$$i(s,D) = 1 - \alpha + [1+o(1)]\alpha\varepsilon e^s$$

for values of s restricted to the interval $(0,T)$. Here $o(1)$ denotes a term which tends to zero as $\varepsilon \to 0$. Because of (3.4) we have

$$\varepsilon e^s \le \varepsilon e^T = O(\varepsilon^\gamma) \quad \text{as} \quad \varepsilon \to 0; \qquad \gamma = 1 - \frac{1}{1+\kappa(1-\alpha)}.$$

Using the expansion for $i(s,D)$ in the integral in the exponent we obtain

$$\begin{aligned} e^{-\int_s^T \kappa i(\xi,D)\, d\xi} &= e^{-\int_s^T \kappa(1-\alpha)\, d\xi} \left\{1 - [1+o(1)] \int_s^T \varepsilon\kappa\alpha e^\xi\, d\xi \right\} \\ &= e^{-\kappa(1-\alpha)(T-s)} \left\{1 - [1+o(1)]\alpha\kappa\varepsilon(e^T - e^s)\right\}. \end{aligned}$$

This implies that

$$\begin{aligned} &\{1 - i(s,D)\} e^{-\int_s^T \kappa i(\xi,D)\, d\xi} \\ &= \alpha e^{-\kappa(1-\alpha)(T-s)} \left\{1 - \varepsilon[e^s + \alpha\kappa(e^T - e^s)][1+o(1)]\right\}. \end{aligned} \tag{8.2}$$

We now integrate the expression we computed in (8.2) over the interval $(0, T)$. Since

$$\int_0^T e^{-\kappa(1-\alpha)(T-s)}\, ds = \frac{1-e^{-\kappa(1-\alpha)T}}{\kappa(1-\alpha)}$$
$$\int_0^T e^{-\kappa(1-\alpha)(T-s)} e^s\, ds = \frac{e^T - e^{-\kappa(1-\alpha)T}}{\kappa(1-\alpha)+1}$$
$$\int_0^T e^{-\kappa(1-\alpha)(T-s)}(e^T - e^s)\, ds = \frac{e^T(1-e^{-\kappa(1-\alpha)T})}{\kappa(1-\alpha)} - \frac{e^T - e^{-\kappa(1-\alpha)T}}{\kappa(1-\alpha)+1},$$

we obtain for the left-hand side (LHS) of (5.6)

$$LHS = \frac{\alpha}{\kappa(1-\alpha)}(1-e^{-\kappa(1-\alpha)T}) - \frac{\varepsilon\alpha e^T}{(1-\alpha)\{\kappa(1-\alpha)+1\}}[1+o(1)].$$

For the right-hand side (RHS) of (5.6) we obtain

$$RHS = \frac{1-i(T,D)}{\kappa i(T,D)} = \frac{\alpha}{\kappa(1-\alpha+\varepsilon e^T)} = \frac{\alpha}{\kappa(1-\alpha)}\Big(1 - \frac{\varepsilon e^T}{1-\alpha}[1+o(1)]\Big).$$

Equating the left- and the right-hand side of (5.6), i.e., putting $LHS = RHS$, we obtain

$$\begin{aligned} &-\frac{\alpha}{\kappa(1-\alpha)}e^{-\kappa(1-\alpha)T} - \frac{\alpha\varepsilon e^T}{(1-\alpha)\{1+\kappa(1-\alpha)\}}[1+o(1)] \\ &= -\frac{\alpha\varepsilon e^T}{\kappa(1-\alpha)^2}[1+o(1)], \end{aligned}$$

which yields

$$\frac{1}{D}e^{\{1+\kappa(1-\alpha)\}T(D)} = (1-\alpha)\{1+\kappa(1-\alpha)\}[1+o(1)] \quad \text{as} \quad D\to\infty. \tag{8.3}$$

This completes the proof of Lemma 8.1. □

Taking the logarithm of the expression in (8.3) we obtain, after some rearrangement,

$$T(D) = \frac{1}{1+\kappa(1-\alpha)}\ln(D) + \frac{\ln[(1-\alpha)\{1+\kappa(1-\alpha)\}]}{1+\kappa(1-\alpha)} + o(1) \quad \text{as} \quad D\to\infty. \tag{8.4}$$

This completes the proof of Theorem 1.5. □

We are now ready to prove Theorem 1.4.

Proof of Theorem 1.4. Since $i_t(T,D) > 0$ we conclude from Lemma 6.1 that $T'(D) > 0$ if and only if

$$\frac{i_t(T,D)}{\kappa i^2(T,D)} > \{1 - i(0,D)\}e^{-\int_0^T \kappa i(\xi,D)\,d\xi}. \tag{8.5}$$

Using the explicit expressions for $i(t,D)$ and $i_t(t,D)$ of Lemma 5.2, and replacing D by $1/\varepsilon$, we can write this inequality as

$$\frac{\varepsilon e^T e^{\int_0^T \kappa i(\xi,D)\,d\xi}}{\{(1-\alpha)+\varepsilon e^T\}^2} > \frac{\kappa}{1+\varepsilon}. \tag{8.6}$$

We readily see that

$$e^{\int_0^T \kappa i(\xi,D)\,d\xi} = e^{\kappa(1-\alpha)T}\big[1 + o(1)\big] \qquad \text{as} \quad D \to \infty.$$

Hence, using (8.3) we can compute the left-hand side of (8.6):

$$\frac{\varepsilon e^T e^{\int_0^T \kappa i(\xi,D)\,d\xi}}{\{(1-\alpha)+\varepsilon e^T\}^2} \to \frac{1+\kappa(1-\alpha)}{1-\alpha} \qquad \text{as} \quad D \to \infty. \tag{8.7}$$

For the limit of the right-hand side of (8.6) we obviously obtain

$$\frac{\kappa}{1+\varepsilon} \to \kappa \qquad \text{as} \quad D \to \infty. \tag{8.8}$$

Because

$$\frac{1+\kappa(1-\alpha)}{1-\alpha} > \kappa,$$

it follows that (8.3) holds for D large enough.

This completes the proof of Theorem 1.4. □

APPENDIX A. DIFFERENTIABILITY OF $T(D)$ IN MODELS I, II AND III

For Model III we start from the implicit definition (4.5) of the function $T_{\max}(D)$:

$$\varphi(T,D)e^{\kappa T} = \kappa \int_0^T \varphi(s,D)e^{\kappa s}\,ds, \tag{4.5}$$

and use the implicit function theorem. Define

$$G(t,D) \stackrel{\text{def}}{=} \kappa \int_0^t \varphi(s,D)e^{\kappa s}\,ds - \varphi(t,D)e^{\kappa t}.$$

Then

$$G_t(t,D) = \kappa\varphi(t,D)e^{\kappa t} - \kappa\varphi(t,D)e^{\kappa t} - \varphi_t(t,D)e^{\kappa t}. \tag{A.1}$$

Hence,

$$G_t(T, D) = -\varphi_t(T, D)e^{\kappa T} > 0$$

because, by Lemma 4.2, $\varphi_t(t, D) < 0$ for all $t > 0$ and $D > 0$. By the implicit function theorem this means that T is differentiable with respect to D. Since $T(D)$ is the same for Models I and III, this also proves the differentiability of $T(D)$ in Model I.

For Model II we start from the definition (5.6) of $T_{\max}(D)$ and proceed likewise. We omit the details.

Acknowledgement. The authors are very grateful to Haïm Brezis for his interest in this problem and the many stimulating conversations during the preparation of this paper.

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