Time of peak response in turnover models in pharmacokinetics and pharmacodynamics

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June 16, 2003

1 Introduction

To understand the effects of a drug and the further response of the body, it is very important to realize what these effects can be and how they can be measured. Therefore a thorough study is usually conducted. In general this concerns *in vivo* experiments on laboratory animals mostly rats but sometimes domestic cats or other animals [1]. The effects of the drugs on these animals can be various and are often measured by considering side-effects such as change in body temperature, contraction of an eye muscle or reflexes of the tail that occur under the influence of the drug. Furthermore the concentration of the drug in the blood is being examined regularly to determine data like the half-life of the drug. However to integrate these data into a dynamic model is not easy. Therefore lately the use of mathematical models has increased. In general these models consist of two components: a *pharmacokinetic* component and a *pharmacodynamic* one.

1.1 Kinetics

Pharmacokinetics concern the process of the drug in the body, starting with the description of the drug administration, followed by the course of the drug concentration in the blood. Drugs often work on a receptor, so we need to consider the effect of the drug and its concentration on such a receptor. Through regular blood tests the concentration of the drug is being determined, starting right after the administration, which can occur in two possible ways: either the drug is administered as a *bolus*, this means that the whole quantity enters the body at the same time, for example by taking a pill, or it is administered by *infusion*, which means that the dose enters the body over a longer period of time.
However, it is not true that the drug stays in the blood until its elimination. In a more realistic model the function of organs like the liver should be considered as well. In the beginning, when the drug concentration in the blood is very high, part of it is absorbed by the liver, which thus forms another important element of the process. At a later stage, when the drug concentration in the blood declines, the liver slowly secretes the drugs it is containing into the bloodstream until the elimination is complete and the situation of the body goes back to the initial state before the administration of the drug. Furthermore the effect of the drug on the receptor clearly depends on the concentration.

1.2 Dynamics

Pharmacodynamics concern the dynamic behaviour of the interaction between the receptor and possible body mechanisms, which eventually determine the effect of the body. In other words: pharmacodynamics consider the response of the body to the drug. Right after the administration of the drug the body starts to respond through the effect of the drug on the receptor, which produces a hormone or some other substance. This hormone then causes a certain response of the body: the *Dynamic Response*. To measure this response we need to choose a so-called *marker* like for example the body temperature [2], [3] which changes - depending on the sort of drug administered it goes up or down. After a certain amount of time the response reaches its peak and starts to decline. Eventually - after complete elimination of the drug in the body - the response is reduced to zero and the body returns to its initial state.

One can distinguish two kinds of models: **Direct Response Models** and **Indirect Response Models**.

1. *Direct Response Model.* In this model the administration of the drug is considered, followed by a stimulus of the body and a direct response. This means that the drug alerts a receptor, which causes a stimulus $S(c)$ depending on the concentration c. This stimulus then influences the body and causes a certain effect $E(S)$ which directly depends on the stimulus S. Hence, the response of the body R depends directly on the concentration c:

$$R(t) = E(S(c(t))).$$

2. *Indirect Response Model.* In this model - formulated by Dayneka, Garg and Jusko [4] - the process starts with the drug administration, which causes an effect on the secondary processes in the body like the elimination and the stimulation. Throughout this paper we will denote the effect by $H(c)$, where c denotes the concentration of the drug in the blood. Regarding the basic equation for this kind of model

$$\frac{dR}{dt} = k_{in} - k_{out}R,$$

where k_{in} describes the influence of the drug on the production of the response, and k_{out} on the rate constant for loss of response. The effect H can either influence k_{in} or k_{out}; in other words it can have a stimulating or an eliminating effect. The function H thus indicates where the drug operates. The form of $H(c)$ describes the relation between the impact of the drugs and its concentration. The main difference between the direct and the indirect response model lies in the delay: in the direct model the drug causes a direct response without any delay, while in the indirect model H does cause a delay. In the research process of a drug it is often difficult to know what kind of model to use, direct or indirect. Therefore the difference in response is an important criterion. The object of this study is the investigation of the delay and its dependence on the amount of drugs administered, as well as of the body response and its possible maximum in relation to changing initial drug doses. It is especially interesting to consider the time at which maximal body response takes place and to try and discover its dependence on the amount of drugs administered.

The basic model described above, which we will consider further in this paper, is a very simple one. More recently, variations on this model have been developed. They include a feed back mechanism. We mention two of them:

I.

$$\begin{cases} \frac{dR}{dt} &= k_{in}H - k_{out}M \\ \frac{dM}{dt} &= k_{tol}R - k_{tol}M \end{cases}$$

Here k_{tol} denotes the tolerance development [1], while the effect function H can work on k_{in}, k_{out} or k_{tol}. The function R is counter-regulated by the moderator function M. It is clear that this system - under influence of the effect function H - will go to an equilibrium state as R decreases for increasing M and increases for decreasing M, while M increases for increasing R and decreases for decreasing R. The function M thus keeps the process close to its equilibrium state, which it will reach eventually. As the function H influences k_{in} it has a stimulating action on the production of response. The model is developed to

describe the body response on the hormone adrenocorticotropin (ACTH), with the goal to obtain a dose-response-time dataset displaying feedback regulation at constant drug exposure.

II.

$$\begin{cases} \frac{dT}{dt} &= k_{in} - k_{out} T X^{-\gamma} \\ \frac{dX}{dt} &= a\{T_{SP} - T\}. \end{cases}$$

Here T denotes the temperature, which is considered as an indirect response and X denotes the thermostat signal [2]. The model describes the effect of $5 - HT_{1A}$ agonists on body temperature. As the agonist binds to its receptor, a stimulus is generated. This stimulus causes certain physiological processes that lower the body temperature. During the process, the body temperature is compared to a set-point temperature T_{SP} which depends on the drug concentration c:

$$T_{SP} = T_0[1 - f(c)],$$

where T_0 denotes the set-point value in the absence of any drug. The function

$$f(c) = \frac{S_{max} c^n}{c_{50}^n + c^n},$$

with S_{max} the maximal stimulus the drug can produce, c the drug concentration, c_{50}^n the concentration required to produce 50 % of the maximal stimulus, and n a slope vector determining the steepness of the curve, corresponds with our function $H(c)$ and describes the stimulus, determined by the interaction between the drug and the receptor. The change in the thermostat signal X is driven by the difference between this set-point temperature T_{SP} and the body temperature T. When the set-point value is lowered, the body temperature becomes too high and X is lowered. As body temperature and set-point temperature are interdependent, a feedback loop is created causing oscillatory behaviour. Under certain conditions damped oscillations around the equilibrium point occur; for a relatively large stimulus however no such things take place. It turns out that for a maximal stimulus S_{max} close or equal to zero there are no oscillations, while for S_{max} between 0 and 1 there are.

In this paper we will consider the basic model. In our analysis our main focus will be on the relation between the time at which the peak in the body response occurs and the initial dose of the drug. This kind of mathematical modeling is called **Modeling of Dose-Response-Time Data** and the model is often referred to as the **Turnover Model**.

We will consider two different cases of the Turnover model. In the first model the function H is in the first term, while in the second model the function H is in the second term. In other words, in the first model H acts as a stimulation, while in the second model H acts in an eliminating function.

Furthermore we will consider two different forms of the function H: in Chapter 4 we will discuss a linear one, while in Chapter 5 we will discuss a logistic one. If $H(c)$ is linear, the effect is linearly dependent on the concentration, what means it increases and decreases with the amount of drugs in the body. This means the effect function $H(c)$ is unbounded; the effect thus is unlimited.

In Chapter 5 we discuss a non-linear version of $H(c)$. Especially the lack of a bound of the

Figuur 1: Linear and nonlinear function $H(c)$.

effect for the linear function is not realistic. It is far more logic to assume that for increasing concentration the effect will reach a limit. Therefore we choose a logistic function for $H(c)$. Then the effect will change rapidly with the initial increase of concentration, but for larger concentrations it will reach its limit.

We will thus discuss two models with two different functions $H(c)$ each, what means that altogether we consider four different cases, all this to facilitate the comparison of the experimental data with the model. For example: does it take more time until the body response is maximal if the initial dose is increased or does this depend on other circumstances as well? This is an important question and we hope that we will be able to answer it after the construction and examination of the four models which we will introduce in the following chapters. At the end of the paper we hope to be able to make clear statements about the existence and uniqueness of a time at which the response is maximal, as well as the dependence of this time on the initial dose.
The main question however we will discuss in this paper concerns the time at which a possible maximum in the body response takes place. Therefore we define

$$R_{max} = \sup\{R(t) : \quad t \geq 0\}.$$

R_{max} will be achieved at some positive time T_{max}. For $H(c)$ a monotonous function we will find that T_{max} exists and is unique. We will try and find out whether this function $T_{max}(D)$, with D the initial drug dose, is an increasing or decreasing function.
Where possible we will answer this question in an analytic way - sometimes for all D, sometimes only for very small and very large values of D. Where needed we will use numerical computations and plots as well.
Only in one case - H stimulating and linear - we will find that T_{max} does not depend on the initial dose D and we will be able to determine T_{max} explicitly.
For the three other cases - $H(c)$ linear and eliminating, $H(c)$ logistic and stimulating and $H(c)$ logistic and eliminating - we will find that the peaktime T_{max} does depend on the initial dose D and that for very small as for very large initial doses D we have $\frac{dT_{max}}{dD} > 0$,

Figuur 2: In this figure the two functions $H(c(t)) = 1 + \alpha c(t)$ and $H(c(t)) = 1 + \alpha \frac{c(t)}{1+c(t)}$, where $c(t) = De^{-t}$ with which we will work troughout this paper, are plotted for constant $\alpha = 0.3$ and initial dose $D = 10$. Notice that the difference between the two versions of $H(c)$ at the beginning is quite large: the one corresponding to the Hill function stays much closer to 1 than the linear version of H. For larger values of t however, they are not far apart. If we consider the asymptotic behaviour of both functions, we see that for very small values of t the linear version goes to $1 + \alpha D$, while the non-linear one goes to $1 + \alpha \frac{D}{1+D}$; for very large values of t both versions of $H(c)$ go to 1.

what suggests that the peaktime T_{max} will increase for increasing dose D. Unfortunately we will not be able to prove analyticly that $\frac{dT_{max}}{dD} > 0$ for all initial doses D, or in other words that the peaktime T_{max} increases for increasing initial dose D. The numerical results however suggest that this indeed is the case.

2 Development of the model

We develop the model in two steps. First we give a model for the time course of the concentration of the drug in the blood, and then we model the response of the body.

2.1 Concentration of the drug in the blood

Let us start with the development of the model by considering the concentration of the drug in the blood. Time will be denoted by t and the concentration by $c(t)$. We can assume that right after the administration of the drug its concentration in the blood is known and we denote it by D. Furthermore the concentration will change in time with a rate proportionate to the drug concentration in the blood. This yields the following relation:

$$\frac{dc}{dt} = -kc \qquad \text{and} \qquad c(0) = D, \tag{2.1}$$

in which k is a proportionality constant. We set $t = 0$ at the end of the administration of the drug. The dose in the blood at that time is equal to D. Solving Problem (2.1) we obtain

$$c(t) = De^{-kt}, \qquad t \geq 0. \tag{2.2}$$

Figuur 3: In the first plot we see the concentration $c(t) = De^{-kt}$ of the drug in the blood versus the time t for initial dose $D = 4$, and constant $k = 1$. In the second plot the logarithm of the concentration is plotted versus the time t.

It follows that the drug concentration in the blood $c(t)$ decreases monotonously with time.

If at a later stage we would like to refine this model, it is possible to consider the function of the liver for example, which absorbs part of the drug. We then have the following situation: after the administration of the drug into the body its concentration in the blood is denoted by $c_1(t)$. In the first model we only needed to consider the elimination of the drug with constant k. In this case however we have to deal with the liver as well, the drug concentration in which we will be denote by $c_2(t)$. The change in drug concentration

in the blood caused by the transportation of the drug from the blood into the liver is described by the constant k_2, the change in drug concentration in the blood caused by the transportation the other way round, from the liver into the blood, is described by the constant k_2 as well, as we can assume that these constants are equal. The elimination of the drug is decribed by the constant k_1. This leads to the following model:

$$\begin{cases} \frac{dc_1}{dt} &= -k_1c_1 - k_2c_1 + k_2c_2 \\ \frac{dc_2}{dt} &= k_2c_1 - k_2c_2. \end{cases}$$

The model describing this situation is called the *two compartments model*. Solving this differential equation we obtain

$$\phi(t) = av_1e^{\lambda_1 t} + bv_2e^{\lambda_2 t},$$

where

$$\phi(t) = \begin{pmatrix} c_1(t) \\ c_2(t) \end{pmatrix},$$

$\lambda_1 = -\frac{1}{2}k_1 - k_2 + \frac{1}{2}\sqrt{k_1^2 + 4k_2^2}$ and $\lambda_2 = -\frac{1}{2}k_1 - k_2 - \frac{1}{2}\sqrt{k_1^2 + 4k_2^2}$ the eigenvalues of the matrix

$$A = \begin{pmatrix} -k_1 - k_2 & k_2 \\ k_2 & -k_2 \end{pmatrix},$$

v_1 and v_2 the corresponding eigenvectors and constants a and b that satisfy

$$av_1 + bv_2 = \begin{pmatrix} D \\ 0 \end{pmatrix}.$$

For $k_1 = 3$ and $k_2 = 2$ for example the solution becomes

$$\begin{cases} c_1(t) &= \frac{1}{5}De^{-t} + \frac{4}{5}De^{-6t} \\ c_2(t) &= \frac{2}{5}De^{-t} - \frac{2}{5}De^{-6t}. \end{cases}$$

In this paper however we will restrict ourselves to the less complicated *one compartment model*.

2.2 Response of the body

We start with the basic *indirect response model* of Dayneka, Garg and Jusko [4], which describes the response $R(t)$ by means of the equation

$$\frac{dR}{dt} = k_{in} - k_{out}R. \tag{2.3}$$

In equilibrium, this yields the response

$$R_0 = \frac{k_{in}}{k_{out}}.$$

Figuur 4: Plot of the two compartment model for the drug concentration in the blood. Here $c_1(t)$ and $c_2(t)$ are plotted for $k_1 = 3$ and $k_2 = 2$. The behaviour of $c_1(t)$ is not very different from that of $c(t)$ in the one compartment model. The decay of the drug in the blood is exponential. From the plot of $c_2(t)$ becomes quite clear that at first the drug concentration in the liver increases largely until it is equal to the drug concentration in the blood. Then, after a small peak it decreases more slowly then the concentration in the blood. After quite some time, there is no substantial difference between the drug concentration in the blood and that in the liver: both are almost reduced to zero.

However this leaves us with the mechanisms which cause the return of the response to the initial state. Let us introduce the function H for this purpose. It is obvious that at $t = 0$ there is no stimulus, so $H(0) = 1$. Furthermore the function $H(c)$ can be of influence during the stimulation process, or during the elimination. For the model this means that in the first case H influences k_{in} and in the second case the function influences k_{out}. Therefore it is necessary to rewrite Problem (2.3) into two new problems:

$$\frac{dR}{dt} = k_{in}H(c) - k_{out}R, \qquad R(0) = R_0 \tag{2.4}$$

and

$$\frac{dR}{dt} = k_{in} - k_{out}H(c)R, \qquad R(0) = R_0. \tag{2.5}$$

From now on Problem (2.4) will be considered in the section *Stimulation* of the following chapters and Problem (2.5) in the section *Elimination*.
Now we need to consider the function H in itself. Obviously H depends on the drug concentration $c(t)$ and is equal to 1 when the drug concentration is zero. A logical choice for H thus are the two functions H_+ and H_-:

$$H_+(c) = 1 + h(c) \tag{2.6}$$

in case H is of influence during the admission of the drug, and

$$H_-(c) = 1 - h(c) \tag{2.7}$$

in case H is of influence during its elimination, where $h(c)$ is a function of the drug concentration c.
In a first attempt to model the problem we take $h(c)$ as simple as possible:

$$h(c) = \alpha c, \qquad \text{with} \qquad \alpha \in (0,1) \qquad \text{a constant.}$$

Refining the model at a second stage we consider the effect of the drug on the receptor and we choose a function $h(c)$ that is of a form very common in biopharmeceutical analysis: it is usual to postulate the so-called *Hill function* to describe the stimulus of the drug:

$$S(c) = S_{max}\frac{c^n}{c_{50}^n + c^n}$$

in which S_{max} denotes the maximal value of $S(c)$, c_{50} the value of c for which $S(c)$ adopts half of its maximal value and n is a slope factor, which determines the steepness of the curve. These constants are used to fit the function in a specific model. In our case we fit the Hill function taking $n = 1$:

$$h(c) = \alpha\frac{c}{1+c}.$$

2.3 Rescaling

To make the Problems (2.4) and (2.5) a little less complicated, we need to rescale the functions and variables. Notice that there are two time scales involved in the problem:
(a) from the concentration $c(t) = De^{-kt}$ we deduce that the decay rate of the drug is $\frac{1}{k}$,
(b) from equation (2.3) we deduce that the decay rate of the response term is $\frac{1}{k_{out}}$.
This means there are two possible choices for the rescaling: $t^* = kt$ and $t^* = k_{out}t$. We choose the first and start by denoting the equilibrium value of R, when $c = 0$, by R_0, i.e.

$$R_0 = \frac{k_{in}}{k_{out}}.$$

We then introduce the dimensionless variables

$$t^* = kt, \qquad R^* = \frac{R}{R_0}, \qquad \frac{k_{out}}{k} = B.$$

Here we assume that $B = \mathcal{O}(1)$. If B is very large, then we should have chosen the other possibility $t^* = k_{out}t$ to prevent that the interesting behaviour of the solution $R^*(t^*)$ all takes place for very small t^*.
Substituting the new variables gives us

$$c(t) = De^{-kt} = De^{-t^*},$$

and for Problem (2.4)

$$\frac{dR^*}{dt^*} = \frac{1}{kR_0}\frac{dR}{dt} = \frac{k_{in}}{kR_0}H - \frac{k_{out}}{kR_0}R = \frac{k_{out}}{k}H - BR^* = B(H - R^*).$$

For Problem (2.5) we obtain analogously

$$\frac{dR^*}{dt} = B(1 - HR^*). \tag{2.8}$$

The system starts in the equilibrium state, i.e.

$$R(0) = R_0.$$

Thus, in terms of the new variable R^*:

$$R^*(0) = 1. \tag{2.9}$$

In the rest of the paper we will drop the asterisks when considering the function $R^*(t^*)$.

3 Basic Properties

In this chapter we will consider the solution $R(t)$ of the two problems we have derived in the previous chapter concerning

Stimulation:

$$\text{(I)} \qquad R'(t) = B\{H_+(c(t)) - R(t)\}, \qquad R(0) = 1 \tag{3.1}$$

in case the concentration $c(t)$ influences k_{in} and

Elimination:

$$\text{(II)} \qquad R'(t) = B\{1 - H_-(c(t))R(t)\}, \qquad R(0) = 1 \tag{3.2}$$

in case the concentration $c(t)$ influences k_{out}.

In both cases B is a positive constant. The functions H_+ and H_- are defined as follows:

$$H_+(c) = 1 + h(c), \qquad \text{and} \qquad H_-(c) = 1 - h(c),$$

with $h(c)$ a continuous function on $[0, \infty)$. Furthermore we introduce the following hypotheses:

H1: $h(0) = 0$ and $h(c) > 0$ for all $c > 0$.

H2: $h'(c) > 0$ for all $c > 0$.

We have assumed as well that

$$c(t) = De^{-t}.$$

First of all we will consider the existence and the uniqueness of a solution $R(t)$ for Problem I and Problem II for all $t > 0$. Furthermore we will do some qualitative analysis regarding the slope of the solution, with special attention for a possible maximum or minimum.

3.1 Stimulation

Theorem 3.1 *Problem I has a unique solution $R(t)$ attained for all $t \geq 0$.*

Proof. The differential equation can be written as

$$(e^{Bt}R(t))' = e^{Bt}BH_+(c).$$

Integrating this equation over $(0, t)$ gives us

$$R(t) = e^{-Bt} + Be^{-Bt}\int_0^t e^{Bs}H_+(c(s))ds. \tag{3.3}$$

Lemma 3.1 *Let $R(t)$ be the solution of Problem I in which $H_+(c)$ satisfies hypothesis **H1**. Then*

(a) $R(t) > 1$ *for all* $t > 0$.

(b) $R(t) \to 1$ *as* $t \to \infty$.

Proof. **(a)** Let us define $r(t) := R(t) - 1$. Then consider the differential equation

$$r'(t) = B\{h(c(t)) - r(t)\}$$

or

$$r'(t) + Br(t) = Bh(c(t)) > 0.$$

This yields

$$(e^{Bt}r(t))' = e^{Bt}Bh(c(t))$$

and by integration

$$e^{Bt}r(t) = B\int_0^t e^{Bs}h(c(s))ds > 0,$$

so for all $t \in (0, \infty)$

$$r(t) > 0 \qquad \Leftrightarrow \qquad R(t) > 1.$$

(b) Write

$$R(t) = e^{-Bt} + B\frac{\int_0^t e^{Bs}H_+(c(s))ds}{e^{Bt}}.$$

As

$$\lim_{t\to\infty} \frac{\int_0^t e^{Bs}H_+(c(s))ds}{e^{Bt}} = \lim_{t\to\infty} \frac{e^{Bt}H_+(c(t))}{Be^{Bt}} = \frac{1}{B}$$

we obtain the desired result.

As we have already explained earlier, our main interest regarding the first differential equation goes out to the time T_{max} at which the response $R(t)$ reaches its maximum value:

$$R(T_{max}) = R_{max} = \sup\{R(t) : t > 0\}.$$

Lemma 3.2 ***(a)*** *If* ***H1*** *holds, then there exists a time $T_{max} \in (0, \infty)$ such that*

$$R'(T_{max}(D), D) = 0 \qquad \textit{and} \qquad R''(T_{max}(D), D) \leq 0.$$

(b) *If* ***H1*** *and* ***H2*** *hold, then T_{max} is unique.*

Proof. **(a)** We know that $R(0) = 1$ and $R'(0) = B\{H(c(0)) - R(0)\} = Bh(D) > 0$. As we have seen in Lemma 3.1, $R(\infty) = 1$ as well, so there has to be a maximum.

(b) Now let T be a critical point of $R(t)$. Then

$$R''(T) = Bh'(c(T))c'(T) < 0$$

i.e. T has to be an isolated maximum. Therefore it has to be unique.

3.2 Elimination

Theorem 3.2 *Problem II has a unique solution $R(t)$ for all $t \geq 0$.*

Proof. The differential equation can be written as

$$(e^{A(t)}R(t))' = Be^{A(t)}.$$

Integrating this equation over $(0, t)$ gives us the solution

$$R(t) = e^{-A(t)}\left\{1 + B\int_0^t e^{A(s)}ds\right\}, \tag{3.4}$$

with

$$A(t) = \int_0^t BH_-(c(\tau))d\tau. \tag{3.5}$$

Lemma 3.3 *Let $R(t)$ be the solution of Problem II in which $H_-(c)$ satisfies **H1**. Then*
(a) $R(t) > 1$ *for all* $t > 0$,
(b) $R(t) \to 1$ *as* $t \to \infty$.

Proof. **(a)** We know that $R(0) = 1$ and

$$R'(0) = B\{1 - (1 - h(D))R(0)\} = Bh(D) > 0$$

by **H1**. Hence $R(t) > 0$ for $0 < t < \tau$ for some $\tau > 0$. Now suppose that $R(t) \leq 1$ for $t \geq t^*$ for some $t^* > 0$. Then $R(t^*) = 1$ and $R'(t^*) \leq 0$. However, the differential equation gives us

$$R'(t^*) = B\{1 - H_-(c(t^*))R(t^*)\} = Bh(c(t^*)) > 0$$

by **H1**, which is a contradiction.

(b) Write

$$R(t) = e^{-A(t)} + B\frac{\int_0^t e^{A(s)}ds}{e^{A(t)}}.$$

As

$$\lim_{t\to\infty}\frac{\int_0^t e^{A(s)}ds}{e^{A(t)}} = \lim_{t\to\infty}\frac{e^{A(t)}}{BH_-(c(t))e^{A(t)}} = \frac{1}{B},$$

we obtain

$$\lim_{t\to\infty} R(t) = 1.$$

For this problem as well we are interested in T_{max}, the time at which the response $R(t)$ reaches its maximum value, defined as before.

Lemma 3.4 ***(a)*** *If* ***H1*** *holds, then there exists a time* T_{max} *such that*

$$R'(T_{max}(D), D) = 0 \qquad \textit{and} \qquad R''(T_{max}(D), D) \leq 0.$$

(b) *If* ***H1*** *and* ***H2*** *hold, then* T_{max} *is unique.*

Proof. **(a)** We know that $R(0) = 1$ and $R(\infty) = 1$, while $R'(0) > 0$. This proves the existence of T_{max}. At $t = T_{max}$ the function $R(t)$ has a maximum, so that $R''(T_{max}) \leq 0$.

(b) We consider the isocline, the line along which $R'(t) = 0$:

$$\Gamma = \{t > 0 : R(t) = R^*(t)\},$$

where $R^*(t)$ is given by the equation

$$H_-(c(t))R^*(t) = 1$$

or

$$R^*(t) = \frac{1}{H_-(c(t))}.$$

We know that $\Gamma(0) > 1$ and $\Gamma(\infty) = 1$. Furthermore it follows from

$$\frac{d}{dt}h(c(t)) = h'(c(t))c'(t) < 0$$

that Γ is a monotone decreasing function.
Now let us consider the two regions Ω_- and Ω_+ where Ω_- is the region under Γ and Ω_+ is the region above Γ. As $R(0) = 1$ the orbit starts in Ω_- and increases until it reaches Γ, so it has to intersect. Then it continues in Ω_+, but by the vector field it cannot intersect Γ a second time. Therefore T_{max} is unique.

4 Linear Function

In this chapter we will consider the situation in which

$$h(c) = \alpha c, \qquad 0 < \alpha < 1$$

for

$$H_+(c) = 1 + h(c) \qquad \text{and} \qquad H_-(c) = 1 - h(c).$$

These functions will be implemented in equation (3.1) and (3.2) respectively.
We are especially interested in the behaviour of T_{max} for varying initial doses D.

4.1 Problem I: Stimulation

We consider the problem

$$R'(t) = B\{H_+(c(t)) - R(t)\}, \qquad R(0) = 1, \tag{4.1}$$

$$H_+(c) = 1 + \alpha c. \tag{4.2}$$

Lemma 4.1 *The solution of problem (4.1) is given by*

$$R(t) = \begin{cases} 1 + \frac{\alpha BD}{B-1}(e^{-t} - e^{-Bt}) & \textit{for } B \neq 1; \\ 1 + \alpha Dte^{-t} & \textit{for } B = 1. \end{cases} \tag{4.3}$$

Proof. We know from (3.3) that the general solution of this differential equation is given by

$$R(t) = e^{-Bt} + Be^{-Bt} \int_0^t e^{Bs} H_+(c(s))ds.$$

By substituting expression (4.2) for H_+ we obtain the desired solution.

In Chapter 3 we have already seen that T_{max} is unique. However we would like to know as well how it varies with the initial dose D. In Theorem 4.1 we will determine $T_{max}(D)$ explicitly.

Theorem 4.1 *Let $B > 0$ and $\alpha > 0$ be fixed. Then for all $D > 0$*

$$T_{max}(D) = \begin{cases} \frac{1}{B-1} \log B & \textit{for } B \neq 1; \\ 1 & \textit{for } B = 1. \end{cases} \tag{4.4}$$

Proof. We know from Lemma 4.1 that

$$R(t) = \begin{cases} 1 + \frac{\alpha BD}{B-1}(e^{-t} - e^{-Bt}) & \text{for } B \neq 1; \\ 1 + \alpha Dte^{-t} & \text{for } B = 1. \end{cases}$$

Figuur 5: Plot of the body response R versus the time t for different initial doses D and constants $\alpha = 0.3$ and $B = 2$ in case of *stimulation* and with a *linear* effect function $H(c)$. Notice that as D increases, the maximal body response increases as well, but it takes the same time to reach this peak.

By differentiating $R'(t)$ we obtain:

$$R'(t) = \begin{cases} \frac{\alpha BD}{B-1}\{Be^{-Bt} - e^{-t}\} & \text{for } B \neq 1; \\ \alpha De^{-t}(1-t) & \text{for } B = 1. \end{cases}$$

Now by $R'(T_{max}) = 0$ we find the desired solution for $T_{max}(D)$.

Notice that $T_{max}(D)$ does not depend on D.

4.2 Problem II: Elimination

We consider the problem

$$R'(t) = B\left\{1 - H_-(c(t))R(t)\right\}, \qquad R(0) = 1, \tag{4.5}$$

$$H_-(c) = 1 - \alpha c. \tag{4.6}$$

Lemma 4.2 *The solution of problem (4.4) is given by*

$$R(t) = e^{-A(t)}\{1 + B\int_0^t e^{A(s)}ds\}, \tag{4.7}$$

with

$$A(t) = B\left\{t + \alpha D(e^{-t} - 1)\right\}. \tag{4.8}$$

Figuur 6: Here we see the function $T_{max}(D)$ for $B = 2$ in case of *stimulation* for $H(c)$ a *linear* function. Notice that T_{max} obviously does not depend on the initial dose D.

Proof. We know from (3.4) and (3.5) that

$$R(t) = e^{-A(t)} \left\{ 1 + B \int_0^t e^{A(s)} ds \right\},$$

with

$$A(t) = \int_0^t BH_-(c(\tau))d\tau.$$

By substituting expression (4.6) for H_- we obtain the desired solution.

Our primary focus is on the behaviour of T_{max}, the time of maximal response, as the dose D varies. In Theorem 4.2 we will discuss the behaviour as D is very small: $D \to 0$; in Theorem 4.3 we will discuss the behaviour as D is very large: $D \to \infty$.

Theorem 4.2 *Let $B > 0$ and $\alpha \in (0, 1)$ be fixed. Then*
(a)

$$\lim_{D \to 0} T_{max}(D) = \begin{cases} \frac{1}{B-1} \log B & \text{for } B \neq 1; \\ 1 & \text{for } B = 1. \end{cases}$$

(b)

$$\lim_{D \to 0} \frac{dT_{max}}{dD} = \begin{cases} \alpha \left\{ -\frac{B+2}{B-2} e^{-T_0} + \frac{B}{B-2} \right\} & \text{for} \quad B \neq 1, \quad B \neq 2, \\ \alpha \left\{ \frac{3}{e} - 1 \right\} & \text{for} \quad B = 1, \\ \alpha \left\{ 3 - 2T_0 - 3e^{-T_0} \right\} = \alpha \left\{ \frac{3}{2} - 2 \log 2 \right\} & \text{for} \quad B = 2, \end{cases}$$

with $T_0 = \lim_{D \to 0} T_{max}(D)$, which means that

$$\lim_{D \to 0} \frac{dT_{max}}{dD} > 0 \qquad \text{for all} \qquad B > 0.$$

Figuur 7: Plot of the body response R versus the time t for different initial doses D and constants $B = 2$ and $\alpha = 0.3$ in case of *elimination* and $H(c)$ a *linear* function. Notice that as D increases, the maximal body response increases as well and it takes more time to reach this peak.

Proof. We expand the solution $R(t)$ into a power series of $\varepsilon = \alpha D$:

$$R(t) = 1 + \varepsilon r_1 + \varepsilon^2 r_2 + \mathcal{O}(\varepsilon^3).$$

The differential equation then becomes

$$\begin{aligned}\varepsilon r_1'(t) + \varepsilon^2 r_2'(t) + \cdots &= B\{1 - (1 - \varepsilon e^{-t})\}\{1 + \varepsilon r_1(t) + \varepsilon^2 r_2(t) + \cdots\} \\ &= B\{\varepsilon(e^{-t} - r_1(t)) + \varepsilon^2(e^{-t} r_1(t) - r_2(t)) + \cdots\}\end{aligned}$$

Collecting coefficients of equal powers of ε and equating them to zero, we find that r_1 satisfies

$$r_1' = -Br_1 + Be^{-t}, \qquad r_1(0) = 0$$

and that r_2 satisfies

$$r_2' = -Br_2 + Be^{-t} r_1, \qquad r_2(0) = 0.$$

Solving these equations we find

$$r_1(t) = \begin{cases} \frac{B}{B-1}\{e^{-t} - e^{-Bt}\} & \text{for } B \neq 1 \\ te^{-t} & \text{for } B = 1. \end{cases} \tag{4.9}$$

and

$$r_2(t) = \begin{cases} \frac{B^2}{(B-1)(B-2)} e^{-2t} + \frac{B^2}{B-1} e^{-(B+1)t} - \frac{B^2}{B-2} e^{-Bt} & \text{for } B \neq 1, \qquad B \neq 2, \\ e^{-t} - (t+1)e^{-2t} & \text{for } B = 1, \\ 4(t-1)e^{-2t} + 4e^{-3t} & \text{for } B = 2. \end{cases} \tag{4.10}$$

We also expand $T_{max} = T_\varepsilon$ in a power series of ε:

$$T_\varepsilon = T_0 + \varepsilon T_1 + \cdots.$$

Then, since $R'(T_{max}) = 0$

$$r_1'(T_0 + \varepsilon T_1) + \varepsilon r_2'(T_0) + \cdots = 0.$$

Collecting equal powers of ε and equating them to zero, gives us for the zeroth order term:

$$r_1'(T_0) = 0$$

and for the first order term:

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

This gives us for T_0:

$$\frac{B}{B-1}\{Be^{-BT_0} - e^{-T_0}\} = 0$$

and hence

$$T_0(B) = \begin{cases} \frac{1}{B-1}\log(B) & \text{for } B \neq 1, \\ 1 & \text{for } B = 1. \end{cases}$$

For T_1 it follows that

$$T_1(B) = \begin{cases} -\frac{B+2}{B-2}e^{-T_0} + \frac{B}{B-2} & \text{for } B \neq 1, \qquad B \neq 2, \\ \frac{3}{e} - 1 & \text{for } B = 1, \\ 3 - 2T_0 - 3e^{-T_0} = \frac{3}{2} - 2\log 2 & \text{for } B = 2. \end{cases}$$

It follows from Figure 8 that $T_1(B) \geq 0$ for all $B > 0$.

Lemma 4.3 *The function $T_0(B)$ is continuous on $(0, \infty)$.*

Proof. The only possible discontinuity is $B = 1$. Now let us consider

$$\lim_{B \to 1} \frac{1}{B-1}\log B.$$

As this results in a so-called $\frac{0}{0}$-limit we use l'Hôpital's rule:

$$\lim_{B \to 1} \frac{1}{B-1}\log B = \lim_{B \to 1} \frac{1}{B} = 1.$$

This means that $T_0(B)$ is a continuous function.

Lemma 4.4 *The function $T_1(B)$ is continuous on $(0, \infty)$.*

Figuur 8: From this plot it follows that $T_1(B) > 0$ for all values of $B > 0$.

Proof. As $T_0(B)$ is continuous by Lemma 4.3, the only possible discontinuity is $B = 2$. Therefore we examine

$$\lim_{B\to 2} T_1(B) = \lim_{B\to 2} \frac{-(B+2)e^{-T_0} + B}{B-2}.$$

As both the numerator and the denominator go to zero for $B \to 2$, we are allowed to use l'Hôptal's rule. This gives us

$$\lim_{B\to 2} T_1(B) = \frac{3}{2} - 2\log 2.$$

Lemma 4.5 *Let $\alpha \in (0,1)$ and $B > 0$ be fixed. Then*

$$T_{max}(D) > \log \alpha D.$$

Proof. Consider the isocline

$$R^*(t) = \frac{1}{1 - \alpha D e^{-t}}.$$

We notice that for $t = \log \alpha D$ it has a singularity. Furthermore

$$R^*(t) \begin{cases} < & 0 \quad \text{for} \quad t < \log \alpha D, \\ > & 1 \quad \text{for} \quad t > \log \alpha D. \end{cases}$$

As we know that the solution $R(t) > 1$ for all $t > 0$, this means that $R(t, D)$ crosses the isocline $R^*(t, D)$ at a point for which $t = T_{max}(D) > \log \alpha D$.

Figuur 9: Plot of $T_{max}(D)$ in case of *elimination* for $H(c)$ a *linear* function.

Theorem 4.3 *Let $B > 0$ and $\alpha \in (0,1)$ be fixed. Then*

$$\lim_{D\to\infty} \frac{T_{max}(D)}{\log D} = 1.$$

Proof. From Lemma 4.5 we know that

$$T_{max}(D) > \log \alpha D,$$

and hence

$$\liminf_{D\to\infty} \frac{T_{max}(D)}{\log D} > \liminf_{D\to\infty} \frac{\log \alpha}{\log D} + 1 \geq 1.$$

Hence, we only need to prove that

$$\limsup_{D\to\infty} \frac{T_{max}(D)}{\log D} \leq 1.$$

Suppose that

$$\limsup_{D\to\infty} \frac{T_{max}(D)}{\log D} = k > 1. \tag{4.11}$$

Then, as $\liminf_{D\to\infty} \frac{T_{max}(D)}{\log D} \leq 1$, for $k' \in (1,k)$ there exists a sequence $\{D_i\}$, such that $D_i \to \infty$ as $i \to \infty$:

$$T_{max}(D_i) = k' \log D_i, \qquad i = 1, 2, \cdots$$

In the rest of the proof $D \to \infty$ will mean convergence along this sequence and we will drop the prime of k'. For $0 < t < \frac{1}{2}\log \alpha D$

$$H_-(c(t)) = 1 - \alpha D e^{-t} < 1 - \alpha D e^{-\frac{1}{2}\log \alpha D} = 1 - \sqrt{\alpha D}.$$

Letting $D \to \infty$ we obtain

$$\lim_{D\to\infty} H_-(c(T_{max}(D))) = 1.$$

We thus obtain

$$R'(t) = B\{1 - H_-(c(t))R(t)\} > B\{1 - (1 - \sqrt{\alpha D})R(t)\} \qquad \text{for} \;\; 0 < t < \frac{1}{2}\log \alpha D.$$

Define $\tilde{R}(t)$ as the solution of the differential equation

$$\tilde{R}'(t) = B\{1 + (\sqrt{\alpha D} - 1)\tilde{R}(t)\}, \qquad \tilde{R}(0) = 1.$$

From basic ODE theory we know that $R(t) > \tilde{R}(t)$ for all $0 < t < \frac{1}{2}\log \alpha D$. Solving the differential equation for $\tilde{R}(t)$, we obtain

$$\tilde{R}(t) = \left\{1 + \frac{1}{\sqrt{\alpha D} - 1}\right\} e^{B(\sqrt{\alpha D}-1)t} - \frac{1}{\sqrt{\alpha D} - 1}.$$

Then

$$R(T_{max}) = R(k \log D) > R(\frac{1}{2}\log D) > R(\frac{1}{2}\log \alpha D) > \tilde{R}(\frac{1}{2}\log \alpha D).$$

Letting $D \to \infty$ we notice that

$$\tilde{R}(\frac{1}{2}\log \alpha D) = \left\{1 + \frac{1}{\sqrt{\alpha D} - 1}\right\} e^{B(\sqrt{\alpha D}-1)\log \alpha D} - \frac{1}{\sqrt{\alpha D} - 1} \to \infty.$$

This means that

$$R(T_{max}(D), D) \to \infty \qquad \text{for} \;\; D \to \infty.$$

It then follows that

$$R'(T_{max}(D), D) = B[1 - H_-(c(T_{max}))R(T_{max})] \to -\infty \qquad \text{for} \;\; D \to \infty,$$

so that

$$\lim_{D\to\infty} R'(T_{max}(D), D) < 0.$$

This contradicts the fact that $R'(T_{max}) = 0$. Hence, (4.11) cannot hold, so that

$$\limsup_{D\to\infty} \frac{T_{max}(D)}{\log D} \leq 1.$$

Remark If we consider the behaviour of $R(t, D)$ for very large values of D, we notice that the time T_{max} for the system to reach the maximal body response increases with D, as well as the value of the peak $R(T_{max})$ in body response. It turns out that there is no limit for the value of this peak. This we can explain by considering the effect function $H(c) = 1 + \alpha c$, with $c = De^{-t}$. For very large values of D, the effect function becomes very large as well:

$$H(c(t, D)) \to \infty \qquad \text{as} \qquad D \to \infty.$$

Therefore the value of the peak $R(T_{max})$ is not limited.

5 Logistic Function

In this chapter we will consider the situation in which

$$h(c) = \alpha \frac{c}{1+c}, \qquad 0 < \alpha < 1$$

for

$$H_+(c) = 1 + h(c) \qquad \text{and} \qquad H_-(c) = 1 - h(c).$$

These functions will be implemented in equation (3.1) and (3.2) respectively.

5.1 Problem I: Stimulation

We consider the problem

$$R'(t) = B\{H_+(c(t)) - R(t)\}, \qquad R(0) = 1, \tag{5.1}$$

$$H_+(c) = 1 + \alpha \frac{c}{1+c}. \tag{5.2}$$

Lemma 5.1 *The solution of problem (5.1) is given by*

$$R(t) = 1 + \alpha B D e^{-Bt} \int_0^t \frac{e^{(B-1)s}}{1 + De^{-s}} ds. \tag{5.3}$$

Proof. We know from (3.3) that

$$R(t) = e^{-Bt} + Be^{-Bt} \int_0^t e^{Bs} H_+(c(s)) ds.$$

By substituting expression (5.2) for $H_+(c(t))$ we obtain the desired solution.

As in Chapter 4, the primary focus is on the behaviour of T_{max}, the time of maximal response, as the dose D varies. In Theorem 5.1 we will discuss the behaviour as D is very small: $D \to 0$; in Theorem 5.2 we will discuss the behaviour as D is very large: $D \to \infty$. For both cases we will use analytic methods. Numerical methods will be used for values of D in between. In Figure 13 we have plotted the function $T_{max}(D)$ for various values of B and we did not notice any relevant change for different values of B.

Theorem 5.1 *Let $B > 0$ and $\alpha > 0$ be fixed. Then*
(a)

$$\lim_{D \to 0} T_{max}(D) = \begin{cases} \frac{1}{B-1} \log B & \textit{for} \quad B \neq 1; \\ 1 & \textit{for} \quad B = 1. \end{cases}$$

Figuur 10: Plot of the body response R versus time t for different initial doses D and constants $\alpha = 0.9$ and $B = 2$ in case of *stimulation* for $H(c)$ a *logistic* function. Notice that for increasing values of D it takes more time until the maximal response is achieved and the peak in the response increases.

(b)

$$\lim_{D\to 0} \frac{dT_{max}}{dD} = \begin{cases} \frac{1}{B-2}\{2e^{-T_0} - 1\} & \textit{for} \quad B \neq 2; \\ \log 2 - \frac{1}{2} & \textit{for} \quad B = 2, \end{cases}$$

with $T_0 = \lim_{D\to 0} T_{max}(D)$*, what means that*

$$\lim_{D\to 0} \frac{dT_{max}}{dD} \geq 0 \qquad \textit{for all} \qquad B > 0.$$

Proof. We expand the solution $R(t, D)$ into a power series of D:

$$R(t, D) = 1 + Dr_1(t) + D^2 r_2(t) + \cdots$$

The differential equation then becomes:

$$Dr_1'(t) + D^2 r_2'(t) + \cdots = B\left\{\alpha \frac{De^{-t}}{1 + De^{-t}} - Dr_1(t) - D^2 r_2(t) + \cdots\right\}.$$

Collecting coefficients of equal powers of D and equating them to zero we find that r_1 satisfies

$$r_1'(t) + Br_1(t) = \alpha Be^{-t}, \qquad r_1(0) = 0$$

and that r_2 satisfies

$$r_2'(t) + Br_2(t) = \alpha Be^{-2t}, \qquad r_2(0) = 0.$$

Solving these equations we find

$$r_1(t) = \begin{cases} \frac{\alpha B}{B-1}\{e^{-t} - e^{-Bt}\} & \text{for} \quad B \neq 1; \\ \alpha t e^{-t} & \text{for} \quad B = 1 \end{cases} \tag{5.4}$$

and

$$r_2(t) = \begin{cases} \frac{\alpha B}{B-2}\{e^{-2t} - e^{-Bt}\} & \text{for} \quad B \neq 2; \\ 2\alpha t e^{-2t} & \text{for} \quad B = 2. \end{cases} \tag{5.5}$$

We also expand $T_{max}(D) = T_D$ in a series of powers of D:

$$T_D = T_0 + DT_1 + \cdots.$$

Then, since $R'(T_{max}) = 0$,

$$r_1'(T_0 + DT_1) + Dr_2'(T_0) + \cdots = 0.$$

Collecting equal powers of D and equating them to zero, gives us for the zeroth order term:

$$r_1'(T_0) = 0$$

and for the first order term:

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

The first equality gives us

$$\begin{cases} \frac{\alpha B}{B-1}\{Be^{-BT_0} - e^{-T_0}\} = 0 & \text{for} \quad B \neq 1, \\ \alpha e^{-T_0}(1 - T_0) = 0 & \text{for} \quad B = 1. \end{cases}$$

Hence we obtain

$$T_0(B) = \begin{cases} \frac{1}{B-1}\log(B) & \text{for} \quad B \neq 1; \\ 1 & \text{for} \quad B = 1. \end{cases}$$

The $\mathcal{O}(D)$ term yields

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

so it follows that

$$T_1(B) = \begin{cases} \frac{1}{B-2}\{2e^{-T_0} - 1\} & \text{for} \quad B \neq 2; \\ \log 2 - \frac{1}{2} & \text{for} \quad B = 2. \end{cases}$$

In Figure 11 we show that $T_1(B) > 0$ for all $B > 0$.

Figuur 11: Plot of $T_1(B)$ in case of *stimulation* for $H(c)$ a *logistic* function. It follows that $T_1(B) \geq 0$ for all values of $B > 0$.

Lemma 5.2 *The function $T_1(B)$ is continuous on $(0, \infty)$.*

As we have seen in the Lemma 4.3 the function $T_0(B)$ is continuous. This means that the only possible discontinuity of $T_1(B)$ can occur at $B = 2$. Now let us consider

$$\lim_{B \to 2} \frac{1}{B-2}\{2e^{-T_0} - 1\}.$$

We notice that this forms a so-called $\frac{0}{0}$-limit, so we are allowed to use l'Hôpital's rule:

$$\lim_{B \to 2} \frac{2e^{\frac{\log(B)}{1-B}} - 1}{B-2} = \lim_{B \to 2} 2\left\{\frac{1}{B(1-B)} + \frac{\log(B)}{(1-B)^2}\right\} e^{\frac{\log(B)}{1-B}} = \log 2 - \frac{1}{2}.$$

Remark If we compare these results with the linear case we have seen in Chapter 4, we notice that the function $T_0(B)$ is the same in both cases, but the function $T_1(B)$ is not.

This completes the analysis of the behaviour of T_{max} for small doses D.

We will now continue by discussing the limiting behaviour of the solution $R(t, D)$ for large values of D and we will try and find the asymptotics of T_{max} for large D as well.

Lemma 5.3 *We have*

$$R(t, D) \to 1 + \alpha(1 - e^{-Bt}) \qquad \textit{as} \qquad D \to \infty$$

uniformly on bounded intervals $[0, t_0]$.

Proof. We know from Lemma 5.1 that

$$R(t) = 1 + \alpha B D e^{-Bt} \int_0^t \frac{De^{(B-1)s}}{1 + De^{-s}} ds.$$

Taking the limit for $D \to \infty$ we obtain

$$\lim_{D\to\infty} R(t) = 1 + \alpha B e^{-Bt} \lim_{D\to\infty} \int_0^t \frac{De^{(B-1)s}}{1+De^{-s}} ds = 1 + \alpha B e^{-Bt} \lim_{D\to\infty} \int_0^t \frac{e^{(B-1)s}}{e^{-s}+\frac{1}{D}} ds.$$

Because of uniform convergence we can interchange the limit and the integration sign, what gives us

$$\begin{aligned} 1 + \alpha B e^{-Bt} \int_0^t \lim_{D\to\infty} \frac{e^{(B-1)s}}{e^{-s}+\frac{1}{D}} ds &= 1 + \alpha B e^{-Bt} \int_0^t e^{Bs} ds \\ &= 1 + \alpha(1 - e^{-Bt}). \end{aligned}$$

Corollary 5.1 *We have*

$$T_{max}(D) \to \infty \qquad as \qquad D \to \infty \tag{5.6}$$

for all $B > 0$, $\alpha \in (0,1)$.

Proof. We have

$$R'(t) = B\left\{1 + \frac{\alpha De^{-t}}{1+De^{-t}} - R(t)\right\} = B\left\{1 + \alpha \frac{e^{-t}}{e^{-t}+\frac{1}{D}} - R(t)\right\}.$$

Letting $D \to \infty$ this becomes

$$B\{1 + \alpha - 1 - \alpha + \alpha e^{-Bt}\} = B\alpha e^{-Bt} > 0 \qquad \text{for all} \qquad 0 < t < t_0,\ t_0 < \infty.$$

This implies that

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

Notice that in the integral in the expression for $R(t)$ we find the term De^{-s}. In search of new variables to facilitate our calculations we consider this term more closely:

$$De^{-s} = e^{-s}e^{\log D} = e^{\log D - s}.$$

Therefore it would not be a strange idea to write

$$t = \log D + \tau$$

and

$$T_{max}(D) = \log(D) + \tau_{max}(D).$$

Lemma 5.4 *Write $R(t,D) = R^*(\tau, D)$. Then*

$$R^*(\tau, D) \to \phi(\tau) \qquad as \qquad D \to \infty$$

uniformly on bounded intervals $[-M, M]$, with

$$\phi(\tau) = 1 + \alpha B e^{-B\tau} \int_{-\infty}^{\tau} \frac{e^{(B-1)\sigma}}{1+e^{-\sigma}} d\sigma$$

a strictly decreasing function such that

$$\phi(-\infty) = 1 + \alpha \qquad and \qquad \phi(+\infty) = 1.$$

Proof. Let us start with substituting $t = \log(D) + \tau$. We then obtain

$$c = De^{-t} = e^{-t+\log(D)} = e^{-\tau},$$
$$H(c(\tau)) = 1 + \alpha \frac{e^{-\tau}}{1+e^{-\tau}}.$$

As

$$R(t,D) = e^{-Bt} + Be^{-Bt} \int_0^t e^{Bs} H_+(c(s)) ds,$$

$R^*(\tau, D)$ becomes

$$\begin{aligned} R^*(\tau, D) &= D^{-B} e^{-B\tau} + BD^{-B} e^{-B\tau} \int_{-\log(D)}^{\tau} D^B e^{B\sigma} \left\{ 1 + \alpha \frac{e^{-\sigma}}{1+e^{-\sigma}} \right\} d\sigma \\ &= D^{-B} e^{-B\tau} + 1 + \alpha B e^{-B\tau} \int_{-\log(D)}^{\tau} \frac{e^{(B-1)\sigma}}{1+e^{-\sigma}} d\sigma. \end{aligned}$$

Then

$$\lim_{D\to\infty} R^*(\tau, D) = \phi(\tau).$$

Letting $\tau \to -\infty$ we obtain

$$\phi(-\infty) = \lim_{\tau\to-\infty} 1 + \alpha B e^{-B\tau} \int_{-\infty}^{\tau} e^{B\sigma} d\sigma = 1 + \alpha.$$

Letting $\tau \to \infty$ we obtain

$$\phi(\infty) = \lim_{\tau\to\infty} 1 + \alpha B e^{-B\tau} \int_{-\infty}^{\tau} e^{(B-1)\sigma} d\sigma = 1.$$

Corollary 5.2 *We have*

$$\tau_{max}(D) \to -\infty \qquad as \qquad D \to \infty. \tag{5.7}$$

Figuur 12: Behaviour of $R(t)$ for increasing values of D in case of *stimulation* for $H(c)$ a *logistic* function.

Remark From (5.7) we readily see that

$$\varepsilon e^{T_{max}} = e^{T_{max} - \log(D)} = e^{\tau_{max}} \to 0 \qquad \text{as} \qquad D \to \infty.$$

Remark In Figure 10 we already noticed that for increasing values of D the time T_{max} for the body response $R(t, D)$ to reach its peak increases as well. In Figure 12 we have plotted the graph of $R(t, D)$ for very large values of D. We can see that T_{max} increases with D and that the value of the body response at the peak $R(T_{max}(D), D)$ increases as well, but not unlimited. This can be explained by considering the effect function $H(c) = 1 + \alpha \frac{c}{1+c}$ with $c = De^{-t}$. For vary large values of D the effect function is limited:

$$\lim_{D \to \infty} H(c(t, D)) = \lim_{D \to \infty} 1 + \alpha \frac{De^{-t}}{1 + De^{-t}} = 1 + \alpha.$$

Hence, the value of the maximal response $R(T_{max}(D), D)$ is limited as well. We see that for D very large the function $R(t, D)$ forms a wave. The function $\phi(\tau)$ from Lemma 5.4 describes this wave.

Lemma 5.5 *Let $B > 0$ and $\alpha > 0$ be fixed. Then for all $D > 0$*

$$\lim_{D \to \infty} \frac{T_{max}(D)}{\log D} = \frac{1}{B + 1}.$$

Proof. We know that for the peaktime $T_{max}(D)$

$$R(T_{max}) = H(c(T_{max})).$$

This means that

$$1 + \alpha B D e^{-BT_{max}} \int_0^{T_{max}} \frac{e^{(B-1)s}}{1 + De^{-s}} ds = 1 + \alpha \frac{De^{-T_{max}}}{1 + De^{-T_{max}}},$$

or

$$e^{-BT_{max}} \int_0^{T_{max}} \frac{e^{(B-1)s}}{1+De^{-s}} ds = \frac{1}{B} \frac{e^{-T_{max}}}{1+De^{-T_{max}}}.$$

Using the subsitution $x = \varepsilon e^s$, $y = \varepsilon e^{T_{max}}$ with $\varepsilon = \frac{1}{D}$ we obtain

$$y^{-B} \int_\varepsilon^y \frac{x^{B-1}}{1+x} dx = \frac{1}{B} \frac{1}{1+y},$$

or

$$\int_\varepsilon^y \frac{x^{B-1}}{1+x} dx = \frac{1}{B} \frac{y^B}{1+y}.$$

Recall that

$$\frac{1}{1+z} = 1 - z + z^2 - z^3 + \cdots \qquad \text{for} \qquad |z| < 1.$$

Our equality then becomes

$$\frac{1}{B}\{y^B - \varepsilon^B\} - \frac{1}{B+1}\{y^{B+1} - \varepsilon^{B+1}\} + \cdots = \frac{1}{B}\{y^B - y^{B+1} + \cdots\},$$

or

$$y^{B+1} = (B+1)\varepsilon^B + \cdots$$

what means that

$$y(\varepsilon) \sim (B+1)^{\frac{1}{B+1}} \varepsilon^{\frac{B}{B+1}} \qquad \text{as} \qquad \varepsilon \to 0.$$

Now returning to our initial variables it follows that

$$T_{max}(D) = \frac{1}{B+1} \log(D) \qquad \text{for} \quad D \to \infty.$$

Remark The velocity of the wave we saw in Figure 12 is equal to $\frac{1}{B+1}$.

5.2 Problem II: Elimination

We consider the problem

$$R'(t) = B\left\{1 - H_-(c(t))R(t)\right\}, \qquad R(0) = 1, \tag{5.8}$$

$$H_-(c) = 1 - \alpha \frac{c}{1+c} \qquad 0 < \alpha < 1. \tag{5.9}$$

Figuur 13: Plot of $T_{max}(D)$ in case of *stimulation* for $H(c)$ a *logistic* function, $\alpha = 0.3$, $B = 2$. Notice that it is quite clear that $\frac{dT_{max}}{dD} > 0$ for all values of $D > 0$.

Lemma 5.6 *The solution of Problem (5.6) is given by*

$$R(t) = e^{-A(t)} \left\{ 1 + B \int_0^t e^{A(s)} ds \right\}, \tag{5.10}$$

with

$$A(t) = Bt - \alpha B \int_0^t \frac{De^{-s}}{1 + De^{-s}} ds. \tag{5.11}$$

Proof. We know from (3.4) and (3.5) that

$$R(t) = e^{-A(t)} \left\{ 1 + B \int_0^t e^{A(s)} ds \right\},$$

with

$$A(t) = \int_0^t BH_-(c(\tau)) d\tau.$$

By substituting the expression (5.9) for $H_-(c)$ into (5.8) we obtain the desired solution.

Again our primary focus is on the behaviour of T_{max}, the time of maximal response, as the dose D varies. We will start by discussing the behaviour of T_{max} as D is very small in Theorem 5.3: $D \to 0$; in Theorem 5.4 we will then discuss the behaviour as D is very large: $D \to \infty$. For both cases we will use analtic methods for the asymptotic behaviour and numeric methods for finite values of D. The plots included in this paper are all for one value of B, but we have seen in our research that for varying values of B there are no significant changes in the graph of $T_{max}(D)$.

Figuur 14: Body response $R(t)$ for different initial doses D in case of *elimination* for $H(c)$ a *logistic* function. Notice that for increasing values of D the peak in the body response increases as well, and it takes more time for the system to reach this peak.

Theorem 5.2 *Let $B > 0$ and $\alpha > 0$ be fixed. Then*
(a)

$$\lim_{D\to 0} T_{max}(D) = \begin{cases} \frac{1}{B-1}\log B & \textit{for} \quad B \neq 1, \\ 1 & \textit{for} \quad B = 1. \end{cases}$$

(b)

$$\lim_{D\to 0} \frac{dT_{max}}{dD} = \begin{cases} \alpha\{\frac{B-1}{B-2} - \frac{B}{B-2}e^{-T_0}\} & \textit{for} \quad B \neq 1, \quad B \neq 2, \\ \frac{\alpha}{e} & \textit{for} \quad B = 1, \\ \alpha(1-\log 2)) & \textit{for} \quad B = 2, \end{cases}$$

with $T_0 = \lim_{D\to\infty} T_{max}(D)$, what means that

$$\lim_{D\to 0} \frac{dT_{max}}{dD} > 0 \qquad \textit{for all} \qquad B > 0.$$

Proof. We start by using the power series of e^x to expand H_-:

$$H(c(t)) = 1 - \alpha D e^{-t} + \alpha D^2 e^{-2t} + \cdots$$

Next we expand $R(t, D)$ into a power series of D:

$$R(t, D) = 1 + Dr_1(t) + D^2 r_2(t) + \cdots$$

Substituting this into the differential equation gives us

$$Dr_1'(t) + D^2 r_2'(t) + \cdots = B\{1 - (1 - \alpha D e^{-t} + \alpha D^2 e^{-2t} + \cdots)[1 + Dr_1(t) + D^2 r_2(t) + \cdots]\}.$$

Collecting coefficients of equal powers of D and equating them to zero we find that r_1 satisfies

$$r_1' + Br_1 = \alpha B e^{-t}, \qquad r_1(0) = 0$$

and r_2 satisfies

$$r_2' + Br_2 = \alpha B e^{-t} r_1 - \alpha B e^{-2t}, \qquad r_2(0) = 0.$$

Solving these equations we find

$$r_1(t) = \begin{cases} \frac{\alpha B}{B-1}\{e^{-t} - e^{-Bt}\} & \text{for} \quad B \neq 1, \\ \alpha t e^{-t} & \text{for} \quad B = 1. \end{cases} \tag{5.12}$$

and

$$r_2(t) = \begin{cases} \frac{\alpha^2 B}{(B-1)(B-2)} e^{-2t} - \frac{\alpha^2 B(B-1)}{B-2} e^{-Bt} + \frac{\alpha^2 B^2}{B-1} e^{-(B+1)t} & \text{for} \quad B \neq 1, \quad B \neq 2, \\ -\alpha^2 t e^{-2t} & \text{for} \quad B = 1, \\ 2\alpha^2 t e^{-2t} + 4\alpha^2 e^{-3t} - 4\alpha^2 e^{-2t} & \text{for} \quad B = 2. \end{cases} \tag{5.13}$$

We also expand $T_{max}(D) = T_D$ in a series of powers of D. Then, since $R'(T_{max}) = 0$,

$$D r_1(T_D) + D^2 r_2'(T_D) + \cdots = 0,$$

or

$$r_1'(T_0) = 0, \qquad \text{and} \qquad r_1'(T_0 + DT_1) + D r_2'(T_0) = 0.$$

The first equality gives us

$$\frac{\alpha}{B-1}\{B e^{-BT_0} - e^{-T_0}\} = 0 \qquad \text{for} \qquad B \neq 1$$

and

$$\alpha e^{-T_0}(1 - T_0) = 0 \qquad \text{for} \qquad B = 1.$$

This yields

$$T_0(B) = \begin{cases} \frac{1}{B-1}\log(B) & \text{for} \quad B \neq 1, \\ 1 & \text{for} \quad B = 1. \end{cases}$$

For the second equality we have

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

so we obtain

$$T_1(B) = \begin{cases} \alpha\left\{\frac{B-1}{B-2} - \frac{B}{B-2} e^{-T_0}\right\} & \text{for} \quad B \neq 1, \quad B \neq 2, \\ \frac{\alpha}{e} & \text{for} \quad B = 1, \\ \alpha(1 - \log 2)) & \text{for} \quad B = 2. \end{cases}$$

From figure 15 we see that $T_1 \geq 0$ for all $B > 0$ for all values of B.

Figuur 15: Plot of $T_1(B)$ in case of *elimination* for $H(c)$ a *logistic* function. We can see clearly that for all values of $B > 0$ we have $T_1(B) \geq 0$. Furthermore $\lim_{B\to\infty} T_1(B) = \alpha \lim_{B\to\infty} \left\{ \frac{B-1}{B-2} - \frac{B}{B-2} e^{-T_0(B)} \right\} = \alpha(1 - e^0) = 0$.

Lemma 5.7 *The function $T_1(B)$ is continuous on $(0, \infty)$.*

Proof. As T_0 is a continuous function, it follows that the only possible discontinuity is at $B = 2$. Now let us consider

$$\lim_{B\to 2} \left\{ \frac{B-1}{B-2} - \frac{B}{B-2} e^{-T_0} \right\}.$$

Notice that this is a so-called $\frac{0}{0}$-limit, so we are allowed to use l'Hôpital's rule:

$$\begin{aligned} \lim_{B\to 2} \left\{ \frac{B-1}{B-2} - \frac{B}{B-2} e^{-T_0} \right\} &= \lim_{B\to 2} \left\{ 1 - e^{\frac{\log(B)}{1-B}} \left\{ 1 + B \left\{ \frac{\log(B)}{(1-B)^2} + \frac{1}{B(1-B)} \right\} \right\} \right\} \\ &= 1 - \log 2. \end{aligned}$$

Hence

$$\lim_{B\to 2} T_1(B) = \alpha(1 - \log 2).$$

Remark Again the function $T_0(B)$ is the same as in sections 4.2 and 5.1, but $T_1(B)$ is not.

Lemma 5.8 *We have*

$$R(t) \to \frac{1}{1-\alpha} \left\{ 1 - \alpha e^{-(1-\alpha)Bt} \right\} \qquad \textit{as} \qquad D \to \infty$$

uniformly on bounded intervals $[0, t_0]$.

Proof. We know from (3.4) and (3.5) that

$$R(t) = e^{-A(t)}\{1 + B\int_0^t e^{A(s)}ds\},$$

with

$$A(t) = Bt - \alpha B\int_0^t \frac{De^{-s}}{1+De^{-s}}ds.$$

Taking the limit for $D \to \infty$ we obtain

$$\lim_{D\to\infty} A(t) = (1-\alpha)Bt$$

and

$$\begin{aligned}\lim_{D\to\infty} R(t) &= e^{-(1-\alpha)Bt}\left\{1 + B\lim_{D\to\infty}\int_0^t e^{(1-\alpha)Bs}ds\right\}\\ &= e^{-(1-\alpha)Bt}\left\{1 + \frac{1}{1-\alpha}(e^{(1-\alpha)Bt} - 1)\right\}.\end{aligned}$$

This gives us the desired result.

Corollary 5.3 *We have*

$$T_{max}(D) \to \infty \qquad as \qquad D \to \infty \tag{5.14}$$

for all $B > 0$, $\alpha \in (0,1)$.

Proof. We have

$$R'(t) = B\left\{1 - \left\{1 - \alpha\frac{De^{-t}}{1+De^{-t}}\right\}R(t)\right\} = B\left\{1 - \left\{1 - \alpha\frac{e^{-t}}{e^{-t}+\frac{1}{D}}\right\}R(t)\right\}.$$

Letting $D \to \infty$ this becomes

$$B\left\{1 - (1-\alpha)\frac{1}{1-\alpha}(1 - \alpha e^{-(1-\alpha)Bt})\right\} = \alpha B e^{-(1-\alpha)Bt} > 0.$$

This yields that

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

As in section 5.1 we write $t = \log D + \tau$ and $T_{max}(D) = \log(D) + \tau_{max}(D)$.

Lemma 5.9 *Write $R(t) = R^*(\tau)$. Then*

$$R^*(\tau) \to \phi(\tau) \qquad as \qquad D \to \infty$$

uniformly on bounded intervals $[-M, M]$, with

$$\phi(\tau) = \frac{Be^{-B\tau}}{(1+e^{-\tau})^{\alpha B}} \int_{-\infty}^{\tau} e^{B\sigma}(1+e^{-\sigma})^{\alpha B} d\sigma$$

a strictly decreasing function so that

$$\phi(-\infty) = \frac{1}{1-\alpha} \qquad and \qquad \phi(+\infty) = 1$$

.

Proof. Let us start with substituting $t = \log(D) + \tau$. We then obtain

$$c(t) = De^{-t} = e^{-t+\log(D)} = e^{-\tau},$$

$$H = 1 - \alpha \frac{e^{-\tau}}{1+e^{-\tau}}$$

and

$$A(t) = B\int_0^t ds + \alpha B \int_0^t h(c(s))ds = Bt - \alpha B \int_{-\log(D)}^{\tau} \frac{e^{-\sigma}}{1+e^{-\sigma}} d\sigma$$
$$= B(\tau + \log(D)) + \alpha B \log(1+e^{-\tau}) - \alpha B \log(1+D).$$

This gives us

$$R^*(\tau, D) = D^{-B} e^{-B\tau} \left\{ \frac{1+D}{1+e^{-\tau}} \right\}^{\alpha B} \left\{ 1 + B \int_{-\log D}^{\tau} D^B e^{B\sigma} \left\{ \frac{1+e^{-\sigma}}{1+D} \right\}^{\alpha B} d\sigma \right\}.$$

Then

$$\lim_{D\to\infty} R^*(\tau, D) = \phi(\tau).$$

Letting $\tau \to -\infty$ we obtain

$$\phi(-\infty) = \lim_{\tau\to-\infty} Be^{-(1-\alpha)B\tau} \int_{-\infty}^{\tau} e^{(1-\alpha)B\sigma} d\sigma = \frac{1}{1-\alpha}.$$

Letting $\tau \to \infty$ we obtain

$$\phi(\infty) = \lim_{\tau\to\infty} Be^{-B\tau} \int_{-\infty}^{\tau} e^{B\sigma} d\sigma = Be^{-B\tau}\{\frac{1}{B}e^{B\tau}\} = 1.$$

Remark In Figure 16 we plotted some graphs of $R(t, D)$ for large values of D and we notice that they form a wave. The function $\phi(\tau)$ describes this wave. For increasing values of D the values of the peak $R(T_{max}(D), D)$ increase as well, just like the time T_{max} at

Figuur 16: Plot of the body response $R(t)$ for large values of D in case of *elimination* for $H(c)$ a *logistic* function.

which it is achieved. However, for $D \to \infty$ the value of the peak seems to be limited. This is caused by the effect function $H(c)$ which is limited itself:

$$\lim_{D\to\infty} H(c(t,D)) = \lim_{D\to\infty} 1 - \alpha \frac{De^{-t}}{1+De^{-t}} = 1-\alpha.$$

This explains the asymptotic behaviour of $R(T_{max}(D), D)$ for $D \to \infty$.

Corollary 5.4 *We have*

$$\tau_{max}(D) \to -\infty \qquad as \qquad D \to \infty. \tag{5.15}$$

Remark From (5.15) we ready see that

$$\varepsilon e^{T_{max}} = e^{T_{max} - \log D} = e^{\tau_{max}} \to 0 \qquad \text{as} \qquad D \to \infty.$$

Lemma 5.10 *Let $B > 0$ and $\alpha \in (0,1)$ be fixed. Then*

$$\lim_{D\to\infty} \frac{T_{max}(D)}{\log D} = \gamma$$

with

$$\gamma = \frac{1}{1+B(1-\alpha)}.$$

Proof. From (3.4) and (3.5) we know that

$$R(t,D) = e^{-A(t)} \left\{ 1 + B \int_0^t e^{A(s)} ds \right\},$$

with

$$A(t) = Bt - \alpha B \int_0^t \frac{De^{-s}}{1 + De^{-s}} ds.$$

Writing $D = \frac{1}{\varepsilon}$ we obtain

$$A(t) = Bt - \alpha B \int_0^t \frac{ds}{1 + \varepsilon e^s}.$$

Let us then introduce the substitution $y = \varepsilon e^t$, $x = \varepsilon e^s$. This gives us

$$A(t) = Bt - \alpha B \int_\varepsilon^y \frac{dx}{x(1+x)} = Bt + \alpha B \left\{ \log\Big(\frac{1+y}{y}\Big) - \log\Big(\frac{1+\varepsilon}{\varepsilon}\Big) \right\}.$$

Hence,

$$\begin{aligned} e^{A(t)} &= \varepsilon^{-B} y^B \Big(\frac{1+y}{y}^{\alpha B}\Big)\Big(\frac{1+\varepsilon}{\varepsilon}\Big)^{-\alpha B} \\ &= y^{B(1-\alpha)}(1+y)^{\alpha B}\varepsilon^{-B(1-\alpha)}(1+\varepsilon)^{-\alpha B}. \end{aligned}$$

Furthermore, at $t = T_{max}$ we have

$$R(T_{max}) = \frac{1}{H(c(T_{max}))}.$$

As

$$H(c(t)) = 1 - \alpha \frac{De^{-t}}{1 + De^{-t}} = 1 - \alpha \frac{1}{1+y} = \frac{1 - \alpha + y}{1+y},$$

this means

$$R(T_{max}) = \frac{1+y}{1-\alpha+y},$$

for $y = y(T_{max})$, or

$$e^{A(t)} R(T_{max}) = e^{A(t)} \frac{1+y}{1-\alpha+y}.$$

Using the expression for $e^{A(t)}$ we found earlier, this equality becomes

$$1 + F_0(y)\varepsilon^{-B(1-\alpha)}(1+\varepsilon)^{-\alpha B} = G(y)\varepsilon^{-B(1-\alpha)}(1+\varepsilon)^{-\alpha B},$$

with

$$G(y) = \frac{y^{B(1-\alpha)}(1+y)^{\alpha B+1}}{1-\alpha+y}$$

and

$$F_0(y) = B \int_\varepsilon^y x^{B(1-\alpha)-1}(1+x)^{\alpha B} dx.$$

This gives us

$$F(y) = F_0(y) + \psi(\varepsilon) = G(y), \tag{5.16}$$

with

$$\psi(\varepsilon) = \varepsilon^{B(1-\alpha)}(1+\varepsilon)^{\alpha B}.$$

Using Newton's Binomial Theorem we can write $G(y)$ as

$$G(y) = y^{B(1-\alpha)}(1 + (\alpha B + 1)y + \cdots)\frac{1}{(1-\alpha)\Big(1 + \frac{y}{1-\alpha}\Big)}.$$

Recall that

$$\frac{1}{1+z} = 1 - z + z^2 - z^3 + \cdots \qquad \text{for} \qquad |z| < 1.$$

$G(y)$ then becomes

$$\begin{aligned} G(y) &= \frac{1}{1-\alpha} y^{B(1-\alpha)}(1 + (\alpha B + 1)y + \cdots)\left\{1 - \frac{y}{1-\alpha} + \cdots\right\} \\ &= \frac{1}{1-\alpha} y^{B(1-\alpha)}\left\{1 + \Big(\alpha B - \frac{\alpha}{1-\alpha}\Big)y + \cdots\right\}. \end{aligned}$$

Analogously we can rewrite $F_0(y)$:

$$\begin{aligned} F_0(y) &= B\int_\varepsilon^y x^{B(1-\alpha)-1}(1+x)^{\alpha B}dx = B\int_\varepsilon^y x^{B(1-\alpha)-1}(1 + \alpha B x + \cdots)dx \\ &= \frac{1}{1-\alpha}\{y^{B(1-\alpha)} - \varepsilon^{B(1-\alpha)}\} + \frac{\alpha B^2}{B(1-\alpha)+1}\{y^{B(1-\alpha)+1} - \varepsilon^{B(1-\alpha)+1}\}. \end{aligned}$$

Hence, (5.16) becomes

$$\frac{\alpha}{1-\alpha}\left\{B - \frac{1}{1-\alpha}\right\} y^{B(1-\alpha)+1} = \frac{\alpha B^2}{B(1-\alpha)+1} y^{B(1-\alpha)+1} - \frac{\alpha}{1-\alpha}\varepsilon^{B(1-\alpha)} + h.o.t.,$$

where $h.o.t.$ means terms of $\mathcal{O}(y^{B(1-\alpha)+2})$ and $\mathcal{O}(\varepsilon^{B(1-\alpha)+1})$. Then

$$\left\{\frac{\alpha B - \alpha^2 B - \alpha}{(1-\alpha)^2} - \frac{\alpha B^2}{B(1-\alpha)+1}\right\} y^{B(1-\alpha)+1} = -\frac{\alpha}{1-\alpha}\varepsilon^{B(1-\alpha)} + h.o.t.$$

or

$$y^{B(1-\alpha)+1} = \{B(1-\alpha)^2 + 1 - \alpha\}\varepsilon^{B(1-\alpha)} + h.o.t. \approx K\varepsilon^{B(1-\alpha)}.$$

This means that

$$\varepsilon e^{T_{max}} = y \sim K^{\frac{1}{B(1-\alpha)+1}}\varepsilon^{\frac{B(1-\alpha)}{B(1-\alpha)+1}},$$

Figuur 17: Plot of $T_{max}(D)$ for $\alpha = 0.3$, $B = 2$ in case of *elimination* for $H(c)$ a *logistic* function. It becomes quite clear from this picture that $\frac{dT_{max}}{dD} > 0$ for all values of $D > 0$.

such that

$$e^{T_{max}} \sim C\varepsilon^{-\gamma},$$

for

$$C = \{B(1-\alpha)^2 + 1 - \alpha\}^{\frac{1}{B(1-\alpha)+1}}$$

and

$$\gamma = \frac{B(1-\alpha)}{B(1-\alpha)+1} - 1 = \frac{1}{B(1-\alpha)+1}.$$

Then

$$T_{max} \sim -\gamma \log \varepsilon = \gamma \log D.$$

Remark The constant γ is the velocity of the wave in Figure 16.

6 Conclusion

In this paper we have considered the so-called Turnover model, in our case defined by the problems

$$\frac{dR}{dt} = k_{in}H(c) - k_{out}R, \qquad R(0) = R_0$$

and

$$\frac{dR}{dt} = k_{in} - k_{out}H(c)R, \qquad R(0) = R_0,$$

where the effect function $H(c)$ thus either works as a stimulus or influences the elimination. In the previous chapters we have studied two possible functions $H(c)$, the first one simple and linear, the second one based on the *Hill-function*. In case of stimulation we took $H(c) = 1+h(c)$ and in case of elimination $H(c) = 1-h(c)$. We have seen that indeed there is a unique solution $R(t)$ for all four models we have thus considered. It seems that $R(t) > 1$ for all $t > 0$ and $\lim_{t\to\infty} R(t) = 1$, which means that the body response on the drug administered at time $t = 0$ only completely dies out after an infinit amount of time. Furthermore we proved that in all four cases there is exactly one time T_{max} at which the body response is maximal. The time at which this peak occurs depends on the initial dose D in the blood at time $t = 0$. In Chapters 4 and 5 we have studied the behaviour of this peak with changing initial dose D, with special interest for very large and very small dose. The results however were not really surprising. We found that in three of the four cases the maximal body response occurs right after the administration of the drugs if the initial dose D becomes very small. Analogously the maximal body response occurs only after a great amount of time for a very large initial dose D. In other words we see that

$$\lim_{D\to 0} T_{max}(D) = 0$$

and

$$\lim_{D\to\infty} \frac{T_{max}(D)}{\log(D)} = K$$

for $K > 0$ some constant.
Only in case of stimulation, when the function $H(c)$ is linear, the time T_{max} at which the body response is maximal turns out to be independent of the initial dose D. This situation is discussed in the first section of Chapter 4 of this paper. However, in the other three cases the situation thus is quite similar. This means there is no great difference between a stimulating and a eliminating function $H(c)$, a quite surprising result. Furthermore both a simple linear version of $H(c)$ as a more refined one corresponding to the Hill-function give the same general results. However, the results we found concerning the time T_{max} at which the maximal body response $R(T_{max})$ occurs in relation with the amount of drugs D in the blood at time $t = 0$ suggests it would be interesting to consider the behaviour of this *peak* with varying initial dose D. We would like to know whether it takes ever more time for the peak to take place if the initial dose is being increased, or if there exists a certain boundary value for D for which the time needed to reach the peak does not increase

anymore or perhaps even decreases. Therefore we needed to consider the derivative of the function $T_{max}(D)$ which describes the time T_{max} at which the peak occurs depending on the initial dose D. Unfortunately, it was impossible to compute this derivative explicitly, therefore we decided to study its behaviour, again for very large and very small values of D. Clearly, if $\frac{dT_{max}}{dD} < 0$ for small D and $\frac{dT_{max}}{dD} > 0$ for large D or the other way round, this would have implied that there is a minimum, or a maximum, of the time it takes to reach the peak in the body response. Our analysis however did not result in such a conclusion. We found that in all three cases in which T_{max} depends on the initial dose D that for very small initial dose the time at which the peak occurs increases for increasing dose, while for very small initial dose the time at which the peak occurs does not change for increasing initial dose. In other words

$$\lim_{D \to 0} \frac{dT_{max}}{dD} \geq 0,$$

and

$$\lim_{D \to \infty} \frac{dT_{max}}{dD} = 0.$$

Unfortunately it is not possible to conclude anything about the possible existence of a maximum or minimum of T_{max} from these data. However it seems plausibel to suggest that there is no such extremum of the time at which the peak occurs, so that it indeed takes ever more time for the body response to reach its maximum if the initial dose D is increased. Numerically we can indeed show that this is the case.

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