

# Regulated Feedback Networks with Degradation

by

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Submitted in Partial Fulfillment of the Requirements

for the Degree of

Master of Science

in the

Mathematics

Program

YOUNGSTOWN STATE UNIVERSITY

August, 2015

# Regulated Feedback Networks with Degradation

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## ABSTRACT

Pharmacokinetic and pharmacodynamic (PK/PD)-models describe and predict the time course of drug effects resulting from a certain dosage administered to an organism. PK/PD models benefit all phases of preclinical and clinical drug development. Their wider application in clinical therapy is to determine the specific dosage for a patient. In this thesis, we review several PK/PD models and investigate the time-to-peak,  $T$ , of the models. We state and prove a theorem about the uniqueness of  $T$ . The theorem considers PK/PD modes which are linear and nonlinear in the response variable. We show that if the forcing function and the response function satisfy some conditions, then there exists only one peak in the response variable. We apply this theorem to several PK/PD models which have a unique  $T$  and show that the condition of the theorem were satisfied. The theorem is also used to investigate how  $T$  changes with respect to drug dosage  $D$  for the turnover models considered.

Thanks be to God. I also cannot express enough thanks to my supervisor, Dr. George Yates for his continued support and encouragement. I offer my sincere appreciation for the learning opportunities provided by my supervisor.

My completion of this thesis could not have been accomplished without the support of faculty members in the Mathematics and Statistics Department of Youngstown State University – thank you for your good knowledge impact, patience and positive attitude during lectures and after lectures. A big thanks to Dr. Pollack for his input, support and guidance in proving the main theorem of this thesis.

Mum, Dad and siblings, I really appreciate your continued effort of encouragement, care, and love.

To Paul and Rhonda Brewer, words cannot express my immense gratitude. I will say God bless you and all my beloved brethren at Austintown Church of Christ.

Finally, a warm thank you to my best friend Judith Ansa Osa-Larbi for her support and love.

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# Chapter 1

## Introduction

The health of living organisms changes frequently due to environmental, genetic, dietary and various other reasons. These changes trigger responses from the organism such as growth factors, concentration of hormones or any other biological responses. The administration of drugs to living organisms has become an important part in assisting living organisms to produce the necessary responses to the changes in its environment. There are two different reactions which occur between an organism and the concentration of drug which are defined in the next section.

The analysis throughout this paper focuses on administration of drugs into the blood stream of an organism, however, it is valid for any application governed by a first order ordinary differential equation with diminishing forcing and other mild restriction on the form of the feedback.

### 1.1 Motivation for PK/PD Models

The effective use of drugs has been advanced by better understanding of the relationship between the administered dose and the resulting biological responses or pharmacological effects ; Krzyzanski (2000). The ability to produce a required response of an administered drug is determined by its pharmacokinetic or pharmacodynamic



properties.

**Pharmacokinetics** describes the time course of the concentration of a drug in a body fluid, either in the plasma or blood, that results from a given dosage of a drug. This is basically, *how the body responds to a drug*.

**Pharmacodynamics** also describes the intensity of a drug effect in relation to its concentration in the fluid. In simple words, *what the drug does to the body*; Meibohm and Derendorf (1997).

So PK/PD models incorporate these two processes and tries to determine the effects resulting from a drug administration over some time period.

## 1.2 PK/PD Models

We discuss several theoretical PK/PD models by Meibohm and Derendorf (1997), Krzyzanski and Jusko (1998), Peletier et al. (2005) and Nguyen et al. (2009). These are called the *turnover models*, and are discussed in [chapter 2](#).

We also investigate other models by Theis et al. (2011) which use a simple reaction model  $A \rightarrow B$  that is regulated by a transient input that deactivates  $B$  over time by degradation. This simple reaction is modified and extended to include other back-reactions, and is discussed in [chapter 2](#).

### 1.2.1 PK/PD Models and Time to Peak

Some specific outcomes have been associated with the maximal amplitude of a response and the time (time-to-peak) for such a peak response, and there are many studies which investigate this phenomenon. For example, Theis et al. (2011), Nguyen et al. (2009) and Gabrielsson and Peletier (2014) have obtained some results in this respect.

In [chapter 2](#), we introduce and investigate several models by Theis giving some details

of their solutions. We also discuss the dimensionless version of the turnover models referenced in [Nguyen et al. \(2009\)](#) and find the general solution to the models.

In [chapter 3](#), we state and prove a theorem which shows the existence of only one maximum amplitude (time-to-peak) for a general PK/PD model under some required conditions.

Analysis on time-to-peak is discussed in [chapter 4](#) where the dependence of time-to-peak on the drug dosage is investigated using a general linear PK/PD model.

# Chapter 2

## Review of Selected Models

PK/PD models have been discussed by many researchers. The models discussed here are typical PK/PD models with some variations. We will explain and review 3 of the models stated by [Theis et al. \(2011\)](#) with results leading to our model which is discussed in the following chapters. We will also formalize some of the results discussed by [Khavari \(2011\)](#).

### 2.1 PK/PD Models by Theis

The six models discussed here are sometimes called reaction models, which will be referred as **RM-1** through **RM-6**. These models as proposed by [Theis et al. \(2011\)](#) are first order ordinary differential equations describing how the response of a system changes with time, when a drug has been administered into the system of an organism. We let  $R(t)$  be the time dependent variable representing the response of a system.

### 2.1.1 RM-1

RM-1 is the first order initial value problem,

$$\begin{aligned}\frac{dR(t)}{dt} &= af(t) - kR(t) \\ R(0) &= 0.\end{aligned}\tag{2.1.1}$$

In this model, rate of change of the response  $R(t)$  depends on a forcing  $f(t)$  and the parameter  $a$ , considered as the drug dosage, which is a constant in this model. So  $af(t)$  is the rate at which the concentration of drug varies with time in the system.

We will require that  $f(t)$  diminishes as time elapses. This requirement is also realistic since one will expect the concentration of a drug in a system to diminish with time.

The change in response at any time also depends on the response of the organism. This phenomenon is explained by the term  $kR(t)$  where the negative sign indicates a reduction in  $R(t)$  for positive rate constant  $k$ . The initial condition assumes there is no response until the drug is administered to the body.

We can find the general solution for this model by using an integrating factor

$$\mu(t) = e^{\int_{t_0}^t k d\tau} = e^{k(t-t_0)}.\tag{2.1.2}$$

The differential equation (2.1.1) becomes

$$\frac{d}{dt}(R(t)\mu(t)) = a\mu(t)f(t),\tag{2.1.3}$$

which can be integrated both sides from  $t_0$  to  $t$ , giving

$$R(t) = \frac{1}{\mu(t)} \left( R(t_0) + a \int_{t_0}^t f(\tau)\mu(\tau)d\tau \right).\tag{2.1.4}$$

This discusses two cases for the switching function,  $f(t)$ , a discrete and continuous

form. For the discrete case, This lets  $f(t) = \begin{cases} 1 & \text{for } t < 1 \\ 0 & \text{for } t \geq 1. \end{cases}$  For  $t < 1$  together with the initial condition  $t_0 = 0, R(0) = 0$  we have

$$R(t) = \frac{a}{k}(1 - e^{-kt}) \quad \text{for } 0 \leq t < 1. \quad (2.1.5)$$

From (2.1.5) we get  $R(1) = \frac{a}{k}(1 - e^{-k})$ . Since  $R$  is assumed to be continuous function for all  $t$ , it is defined at  $t = 1$ . For  $t \geq 1$ , we take  $t_0 = 1$  and  $\mu(t) = e^{kt-k}$ . Using the above solution, (2.1.4) gives that

$$R(t) = R(1)e^{k(1-t)} \quad (2.1.6)$$

and  $R(t) = \frac{a}{k}(e^{-k(t-1)} - e^{-kt}) \quad \text{for } t \geq 1. \quad (2.1.7)$

Thus  $R(t) = \begin{cases} \frac{a}{k}(1 - e^{-kt}) & \text{for } 0 \leq t < 1 \\ \frac{a}{k}(e^{-k(t-1)} - e^{-kt}) & \text{for } t \geq 1. \end{cases} \quad (2.1.8)$

Figure 2.1 shows a plot of the solution using  $a = 0.5$  and  $k = 3$ .

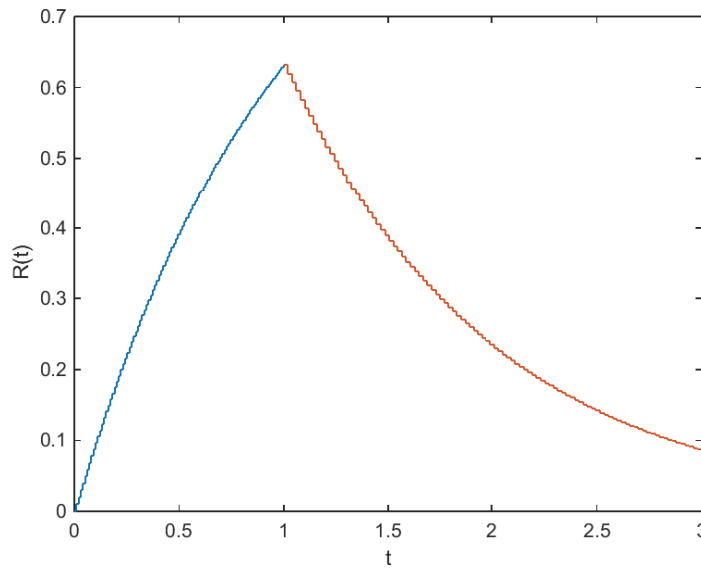


Figure 2.1: Discrete case of RM-1 for  $a = 1$  and  $k = 1$

For the continuous case, This let  $f(t) = \frac{1}{1+t}$ . Using the general equation in (2.1.4) we get that

$$R(t) = \frac{a}{e^{kt}} \left( \int_0^t \frac{e^{k\tau}}{1+\tau} d\tau \right). \quad (2.1.9)$$

Making a substitution for  $u = k(1 + \tau)$  we have

$$R(t) = ae^{-k(t+1)} \left( \int_k^{k(t+1)} \frac{e^u}{u} du \right). \quad (2.1.10)$$

The Exponential Integral is defined as  $Ei(x) = \int_{-\infty}^x \frac{e^y}{y} dy$  and hence the explicit solution can be written as

$$R(t) = ae^{-k(t+1)} [Ei(kt + k) - Ei(k)]. \quad (2.1.11)$$

Figure 2.2 shows a plot of the solution using  $a = 1$  and  $k = 1$ .

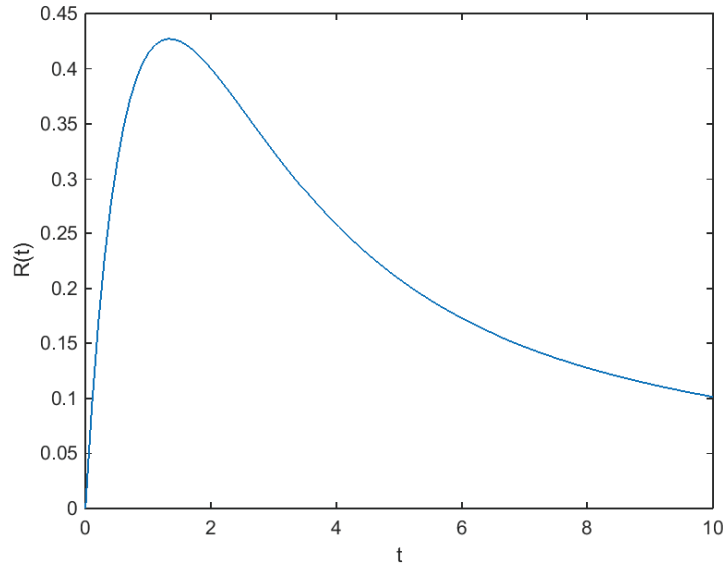


Figure 2.2: Continuous case of RM-1 for  $a = 1$  and  $k = 1$

Both solutions of RM-1, (2.1.8) and (2.1.11), explains that the response variable

diminishes as time becomes large. This result corresponds to the realistic situation when the concentration of a drug diminishes.

### 2.1.2 RM-2

This model is a system of 2 first order linear differential equations, given by

$$\frac{dA(t)}{dt} = -A(t)f(t) \quad (2.1.12)$$

$$\frac{dR(t)}{dt} = A(t)f(t) - kR(t) \quad (2.1.13)$$

with initial condition  $A(0) = 0 \quad (2.1.14)$

$$R(0) = 0 \quad (2.1.15)$$

In this model, the drug function is denoted  $A(t)$  and  $R(t)$  is the drug response variable. The drug concentration,  $A(t)f(t)$ , allows the dosage to change with respect to time. Using the continuous function  $f(t) = \frac{1}{1+t}$  we can solve for  $A(t)$  and substitute it into the equation for  $R(t)$ . Solving for  $A(t)$  we have that,

$$\int_0^t \frac{dA(\tau)}{A(\tau)} = - \int_0^t \frac{1}{1+\tau} d\tau. \quad (2.1.16)$$

By substituting  $u = (1 + \tau)$  and integrating, we then have

$$\ln \frac{A(t)}{A(0)} = -\ln(1+t) + \ln(1) \quad (2.1.17)$$

and

$$A(t) = \frac{a}{1+t}. \quad (2.1.18)$$

Substituting this result into the differential equation for  $R(t)$  we have the first order differential equation

$$\frac{dR(t)}{dt} = \frac{a}{(1+t)^2} - kR(t) \quad (2.1.19)$$

This equation is of the form (2.1.1) with same integrating factor as (2.1.2). Using the derived solution in (2.1.4) we have that

$$R(t) = ae^{-kt} \int_0^t \frac{e^{ks}}{(1+s)^2} ds. \quad (2.1.20)$$

By the method of integration by parts we let  $u = e^{ks}$  and  $dv = \frac{1}{(1+s)^2} ds$  and have

$$R(t) = ae^{-kt} \left[ \frac{-e^{kt}}{(1+t)^2} + 1 + k \int_0^t \frac{e^{ks}}{1+s} ds \right]. \quad (2.1.21)$$

Using the substitution  $\tau = k(1+s)$  and the definition of the exponential integral, we get

$$R(t) = a \left[ e^{-kt} - \frac{1}{1+t} + \frac{k}{e^{k(1+t)}} [Ei(k(1+t)) - Ei(k)] \right]. \quad (2.1.22)$$

Figure 2.3 shows a plot of the solution using  $a = 1$  and  $k = 1$ .

The result of this model also suggests that as time goes to infinity, the response diminishes. This is a result one will expect in a real situation since after a drug has been used by an organism, the response of the organism to the drug has to diminish over time.

### 2.1.3 RM-3

The RM-3 model suggests a case where the drug function  $A(t)$  is regulated depending on the response  $R(t)$ . In this case, the changes in drug dosage (increase or decrease in



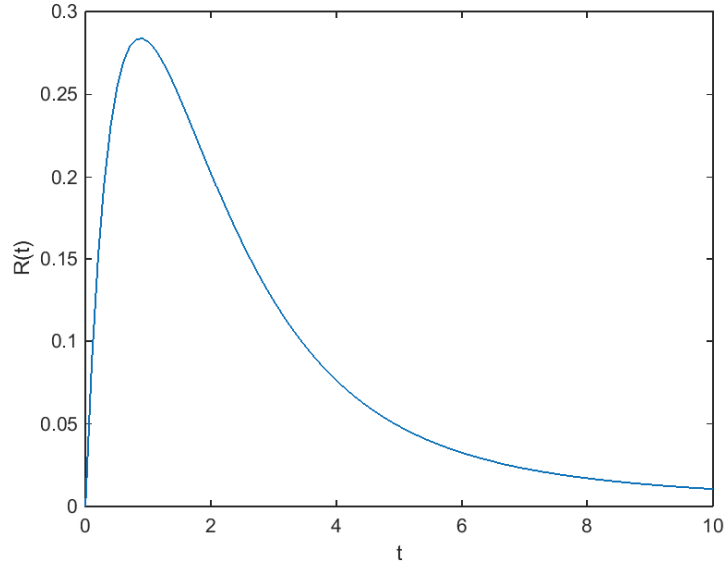


Figure 2.3: Solution for RM-2 using  $a = 1$  and  $k = 1$

dosage) depends on how the body's response is, at a point in time. In other words, a drug dosage is increased or decreased if the body's response is effective or not. Model RM-3 is described as follows;

$$\frac{dA(t)}{dt} = kR(t) - A(t)f(t) \quad (2.1.23)$$

$$\frac{dR(t)}{dt} = A(t)f(t) - kR(t), \quad (2.1.24)$$

with the initial conditions  $A(t) = a \quad (2.1.25)$

$$R(0) = 0. \quad (2.1.26)$$

For this system, note that

$$\frac{dA(t)}{dt} + \frac{dR(t)}{dt} = 0, \quad (2.1.27)$$

which implies that  $A(t) + R(t) = Q \quad (2.1.28)$

where  $Q$  is a constant. Using the initial conditions we have,  $Q = a$  and thus

$$A(t) = a - R(t). \quad (2.1.29)$$

Substituting this result into (2.1.24) we have

$$\frac{dR(t)}{dt} = af(t) - (f(t) + k)R(t). \quad (2.1.30)$$

Using  $f(t) = \frac{1}{1+t}$  we can solve this linear equation by finding the integrating factor

$$\mu = e^{\int_0^t (\frac{1}{1+t} + k) dt} = (1+t)e^{kt} \quad (2.1.31)$$

and

$$R(t) = \frac{a(1 - e^{-kt})}{k(1+t)}. \quad (2.1.32)$$

Substituting this result in (2.1.29) we have

$$A(t) = a + \frac{a(e^{-kt} - 1)}{k(1+t)}. \quad (2.1.33)$$

Figure 2.4 shows a plot of the solution using  $a = 1$  and  $k = 1$ .

The solution of RM-3 also diminishes as time goes to infinity. In addition to the above models, the following three models are also given by Theis et al. (2011) but we give no closed form solution.

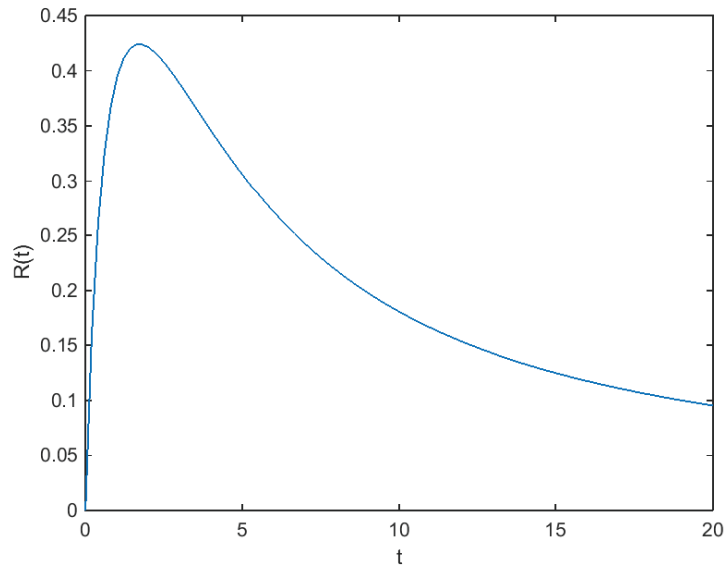


Figure 2.4: Solution of RM-3 using  $a = 1$  and  $k = 1$

#### 2.1.4 RM-4, RM-5 and RM-6

RM-4 considers the case where the rate of proportion for  $R(t)$  can be regulated from two different parameters  $k$  and  $q$ . It is a linear system given by;

$$\begin{aligned}\frac{dA(t)}{dt} &= kR(t) - A(t)f(t) \\ \frac{dR(t)}{dt} &= A(t)f(t) - (k + q)R(t)\end{aligned}$$

RM-5 modifies the rate of proportion of the response variable by using the current response  $R(t)$  with  $q$ . RM-5 is a nonlinear model given by

$$\begin{aligned}\frac{dA(t)}{dt} &= kR(t) - A(t)f(t) \\ \frac{dR(t)}{dt} &= A(t)f(t) - (k + q \cdot R(t))R(t)\end{aligned}$$

RM-6 is a variation of RM-5 given by

$$\begin{aligned}\frac{dA(t)}{dt} &= kR(t) - A(t)f(t) \\ \frac{dR(t)}{dt} &= A(t)f(t) - (k \cdot R(t) + q)R(t).\end{aligned}$$

In the next section, we review, four PK/PD models which have received considerable analysis by others.

## 2.2 Turnover Models

The turnover models (TM) and are divided into two groups; **inhibiting models** (TM-1, TM-2) and **stimulating models** (TM-3, TM-4). Original Models are given by Krzyzanski and Jusko (1998) and Sharma and Jusko (1996). However, we use the non-dimensionalized versions found in Nguyen et al. (2009).

### 2.2.1 Inhibiting and Stimulating Models

All the turnover models have this general equation.

$$\frac{dr(t)}{dt} = F(t) - H(t)r(t) \tag{2.2.1}$$

and 
$$r(0) = 1 \tag{2.2.2}$$

Similar to the reactions models,  $r(t)$  is the response variable,  $F(t)$  is the gain term and  $H(t)r(t)$  is the loss term. We define the function  $\phi(t, D)$  which is used frequently as;

$$\phi(t, D) = \frac{De^{-t}}{1 + De^{-t}} = \frac{D}{D + e^t} \tag{2.2.3}$$

where  $D$  is a parameter indicating the magnitude of the initial drug dosage. So  $\phi(t, D)$  models the concentration of drug dosage. The first and second model describes inhibition and has the following definition for  $F$  and  $H$ ;

$$\text{TM-1} \quad F(t) = k(1 - \alpha\phi(t, D)), \quad H(t) = k$$

$$\text{TM-2} \quad F(t) = k, \quad H(t) = k(1 - \alpha\phi(t, D))$$

The third and fourth models describe stimulation;

$$\text{TM-3} \quad F(t) = k(1 + \alpha\phi(t, D)), \quad H(t) = k$$

$$\text{TM-4} \quad F(t) = k, \quad H(t) = k(1 + \alpha\phi(t, D))$$

Now, note that if  $D = 0$ , the gain term (indicated by arrow in left part of [Figure 2.5](#)) is  $k$  and the loss term (right part of [Figure 2.5](#)) is  $kR$ .

So when some dosage of drug is administered initially, TM-1 uses the concentration  $\phi(t, D)$  to reduce the proportion of gain or input  $k$  ([Figure 2.5](#)) which in turn affects how  $R$  changes. TM-2 also uses  $\phi(t, D)$  to reduce the proportion of loss (output) which also affects how  $R$  changes. Hence TM-1 and TM-2 are called Inhibiting Models.

In a similar approach, TM-3 and TM-4 increase the proportion of the gain and loss respectively. Hence TM-3 and TM-4 are called Stimulating Models.

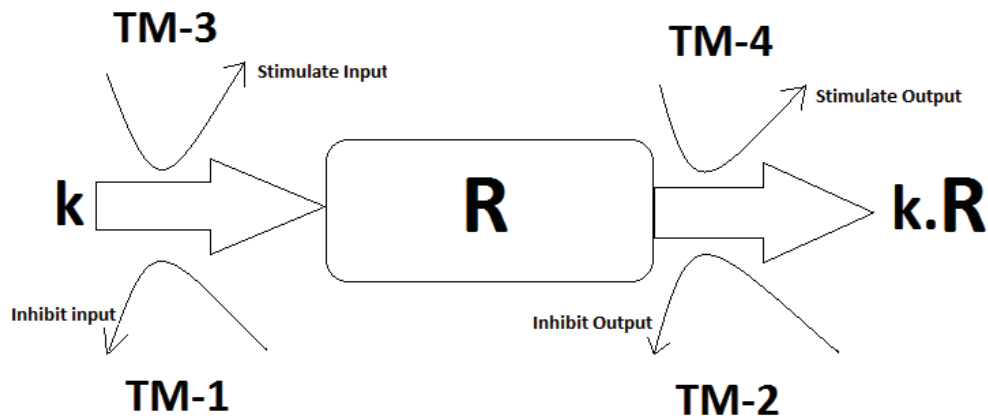


Figure 2.5: Illustration of the four turnover models

In all cases,  $k$  is a positive constant and  $\alpha$  is a constant in the range,  $(0, 1]$ .

We must make a substitution to shift the initial response value to 0. This substitution is not only convenient for analysis but requires modification of the loss and gain terms.

Its significance will be discussed later in [chapter 3](#) after proving **The Peak Theorem**.

In **TM-1**, we make the substitution  $r(t) = 1 - \alpha R(t)$ . So for  $t = 0$ ,

$$r(0) = 1 - \alpha R(0)$$

which implies that for  $t = 0$ ,  $R(0) = 0$ .

Now,  $\frac{dr(t)}{dt} = -\alpha \frac{dR(t)}{dt}$ , so using the above substitution,

$$-\alpha \frac{dR(t)}{dt} = F(t) - H(t)(1 - \alpha R(t))$$

which implies that

$$\frac{dR(t)}{dt} = \frac{1}{\alpha} [H(t) - F(t)] - H(t)R(t).$$

Substituting the values of  $F$  and  $H$  for RM-1 above, we have

$$\frac{dR(t)}{dt} = \frac{1}{\alpha} [k - k(1 - \alpha\phi)] - kR(t)$$

which then gives us

$$\frac{dR(t)}{dt} = k\phi(t, D) - kR(t)$$

For TM-1, the IVP we will later discuss is

$$\frac{dR(t)}{dt} = f(t) - h(t)R(t)$$

$$R(0) = 0 \tag{2.2.4}$$

where  $f(t) = k\phi(t, D)$  and  $h(t) = k$ .

For **TM-2**, we make the substitution  $r(t) = 1 + \alpha R(t)$ . So  $R(0) = 0$  and  $\frac{dr(t)}{dt} = \alpha \frac{dR(t)}{dt}$ .

Making the appropriate substitution, we get

$$\alpha \frac{dR(t)}{dt} = F(t) - H(t)(1 + \alpha R(t))$$

which implies that  $\frac{dR(t)}{dt} = \frac{1}{\alpha}[F(t) - H(t)] - H(t)R(t).$

and  $\frac{dR(t)}{dt} = \frac{1}{\alpha}[k - k(1 - \alpha\phi(t, D))] - k(1 - \alpha\phi(t, D))R(t)$

which then gives us  $\frac{dR(t)}{dt} = k\phi(t, D) - k(1 - \alpha\phi(t, D))R(t)$

Hence the IVP for TM-2 is

$$\frac{dR(t)}{dt} = f(t) - h(t)R(t)$$

with  $R(0) = 0$  (2.2.5)

where  $f(t) = k\phi(t, D)$  and  $h(t) = k(1 - \alpha\phi(t, D)).$

In **TM-3**, we will let  $R(t) = 1 + r(t)$  and have  $R(0) = 0$  and  $\frac{dr(t)}{dt} = \frac{dR(t)}{dt}$ . With the appropriate substitution we have

$$\alpha \frac{dR(t)}{dt} = F(t) - H(t)(1 + R(t))$$

which implies that  $\frac{dR(t)}{dt} = \frac{1}{\alpha}[k(1 + \alpha\phi(t, D)) - k] - kR(t)$

which then gives us  $\frac{dR(t)}{dt} = k\phi(t, D) - kR(t)$

Hence the IVP for **TM-3** is

$$\frac{dR(t)}{dt} = f(t) - h(t)R(t)$$

with  $R(0) = 0$  (2.2.6)

where  $f(t) = k\phi(t, D)$  and  $h(t) = k.$

Likewise, making a substitution for  $r(t) = 1 - R(t)$ , the IVP for **TM-4** becomes

$$\frac{dR(t)}{dt} = f(t) - h(t)R(t)$$

with  $R(0) = 0$  (2.2.7)

where  $f(t) = k\phi(t, D)$  and  $h(t) = k(1 + \alpha\phi(t, D))$ . Note that TM-1 and TM-3 are equivalent in the transformed variables.

## 2.2.2 General Solution of the Turnover Models

The general solution for the turnover models is

$$R(t) = e^{-\int_0^t h(\tau) d\tau} \left[ \int_0^t \left( f(\tau) e^{\int_0^\tau h(s) ds} \right) d\tau \right]$$

We will attempt to find the explicit solution of each of the 4 models by writing them in an integral form.

- **General Solution for TM-1 and TM-3**

TM-1 and TM-3 have the same equation under the new substitution hence same general solution.

$$R(t) = e^{-\int_0^t k d\tau} \left[ \int_0^t \left( k\phi(\tau, D) e^{\int_0^\tau k ds} \right) d\tau \right]$$

which then gives us  $R(t) = ke^{-kt} \int_0^t \phi(\tau, D) e^{k\tau} d\tau$

**Figure 2.6** shows a plot of the solution using  $\alpha = 0.5$ ,  $k = 1$  and  $D = 1$ .

- **General Solution for TM-2**



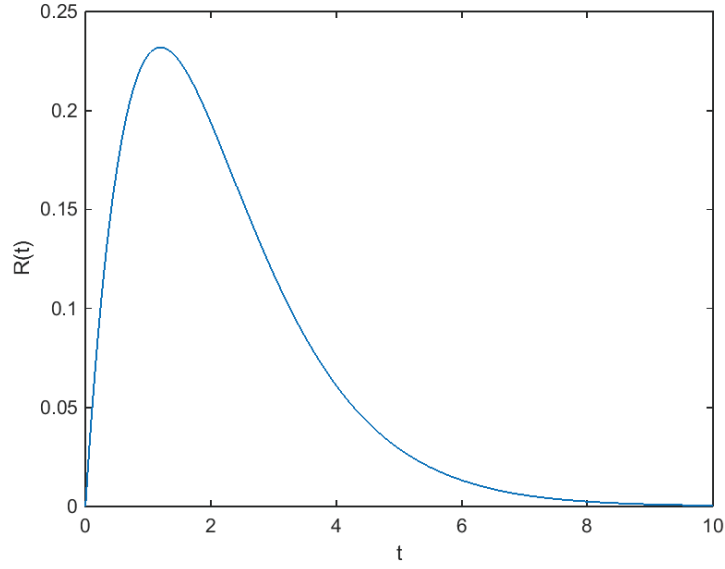


Figure 2.6: Solution of TM-1 and TM-3 using  $\alpha = 0.5$ ,  $k = 1$ ,  $D = 1$

In a similar way, the general solution of (2.2.5) is given as

$$R(t) = e^{-\int_0^t k(1-\alpha\phi(\tau,D))d\tau} \left[ \int_0^t k\phi(\tau, D) e^{\int_0^\tau k(1-\alpha\phi(s,D))ds} d\tau \right]$$

and

$$R(t) = k e^{-kt + \alpha k \int_0^t \phi(\tau, D) d\tau} \left[ \int_0^t \phi(\tau, D) e^{k\tau - \alpha k \int_0^\tau \phi(s, D) ds} d\tau \right] \quad (2.2.8)$$

Figure 2.7 shows a plot of the solution using  $\alpha = 0.5$ ,  $k = 1$  and  $D = 1$ .

- **General solution for TM-4**

By change of sign, the general solution of TM-4 follows from TM-2.

$$R(t) = k e^{-kt - \alpha k \int_0^t \phi(\tau, D) d\tau} \left[ \int_0^t \phi(\tau, D) e^{k\tau + \alpha k \int_0^\tau \phi(s, D) ds} d\tau \right] \quad (2.2.9)$$

Figure 2.8 shows a plot of the solution using  $\alpha = 0.5$ ,  $k = 1$  and  $D = 1$ .

Finding an explicit solution to PK/PD models is difficult and in most cases impossible to find in closed-form.

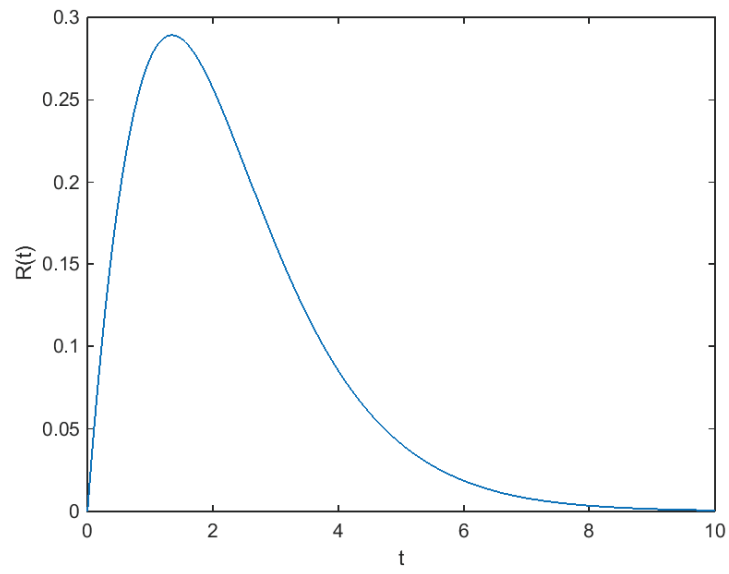


Figure 2.7: Solution of TM-2 using  $\alpha = 0.5$ ,  $k = 1$ ,  $D = 1$

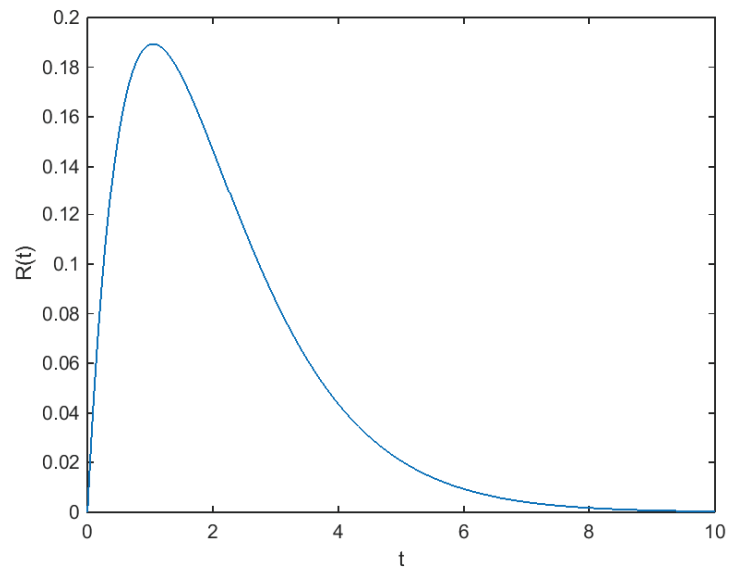


Figure 2.8: Solution of TM-4 using  $\alpha = 0.5$ ,  $k = 1$ ,  $D = 1$

Nonetheless, there are other ways to find the properties of  $R$  without finding its explicit solution. In [chapter 3](#), we will show the dynamics of the response  $R(t)$  as time changes. We will also show the existence of a time  $T$  where maximum response occurs.

# Chapter 3

## The Time to Peak

The response variable  $R$  is maximum or minimum when  $\frac{dR(t)}{dt} = 0$ . The time  $t = T$  at which this maximum or minimum occurs is of interest since it is the time when a drug concentration is at its highest or lowest value.

We will determine if there is more than one value of  $T$  where  $R$  takes on an extreme value in any PK/PD model. We will also explore the dependence of  $T$  on drug dosage  $D$ .

For all the models discussed,  $T$  is implicitly defined so it is difficult to analyze. In this chapter, we state and prove the **Peak Theorem** which gives a general result on the time to peak,  $T$ .

### 3.1 The Peak Theorem (Theorem P)

This insight and understanding of the Peak Theorem is due to Dr. David Pollack of Youngstown State University. Theorem P was first stated and proved by Pollack and [Khavari \(2011\)](#). In this section, we provide details and a concise proof of the theorem.

The focus of this analysis is to provide results on  $T$  which is explicitly defined for all the models discussed in [chapter 2](#) and for any other model which satisfy the hypothesis

of theorem P.

Consider the following IVP

$$\frac{dr(t)}{dt} = c(t)[g(t) - p(r)] \quad (3.1.1)$$

$$r(0) = 0 \quad (3.1.2)$$

where  $c(t)$  is a differentiable function with  $0 < b_1 < c(t) < b_2$  and  $g(t)$  is a positive, differentiable and diminishing function. That is,  $g(t) > 0$ ,  $g'(t) < 0$  and  $\lim_{t \rightarrow \infty} g(t) = 0$ . The function  $p(r)$  is continuously differentiable in  $r$  and is strictly increasing with  $p(0) = 0$  and  $\lim_{r \rightarrow \infty} p(r) > g(0)$ .

**3.1.1 Theorem P (Peak Theorem).** *Let  $R(t)$  be a solution of the above IVP then*

1.  $R(t)$  is **defined** for  $t \geq 0$  on  $[0, \infty)$ .
2.  $R(t)$  is **bounded**; i.e.  $\exists M$  such that  $0 \leq R(t) < M$  where  $0 < M < \infty$ .
3.  $R(t)$  has a **unique maximum**; i.e.  $\exists$  a time  $T_1 > 0$  such that  $R(t)$  is strictly increasing on  $[0, T_1]$  and strictly decreasing on  $[T_1, \infty)$
4. Response **diminishes to zero** i.e.  $\lim_{t \rightarrow \infty} R(t) = 0$ .

To prove this theorem, we first review the proof of the *Intermediate Value Theorem* with a slight notification.

**3.1.2 Theorem (Intermediate Value Theorem-Modified-[IVTM]).** *Let  $f : [a, b] \rightarrow \mathbb{R}$  be a continuous function such that  $f(a) > 0$  and  $f(b) \leq 0$ . Then  $\exists \kappa \in (a, b]$  such that  $f(\kappa) = 0$  and  $f(x) > 0$  for  $a \leq x < \kappa$ .*

*Proof.* Define  $N = \{x \in [a, b] \mid f(x) \leq 0\}$  and let  $\kappa = \inf(N)$ . We want to show that  $f(\kappa) = 0$ .

Suppose that  $f(\kappa) > 0$ , then  $\kappa \notin N$  since  $f(x) \leq 0$  for all  $x \in N$ . This is a contradiction. Hence  $f(\kappa) \leq 0$ .

Now suppose that  $f(\kappa) < 0$ . By continuity let  $\epsilon > 0$  then  $\exists \delta > 0$  such that  $|f(x) - f(\kappa)| < \epsilon$  whenever  $|x - \kappa| < \delta$ . Let  $f(\kappa) = -\epsilon$  then

$$-\epsilon < f(x) - f(\kappa) < \epsilon$$

and 
$$2f(\kappa) < f(x) < 0 \quad \forall x \in (\kappa - \delta, \kappa + \delta).$$

This is a contradiction to the assumption that  $\kappa = \inf(N)$  since  $f(x) < 0$  for  $x \in (\kappa - \delta, \kappa)$ . Hence  $f(\kappa) \geq 0$ .

This shows that  $f(\kappa) = 0$  since  $f(\kappa) \leq 0$  and  $f(\kappa) \geq 0$ . □

**3.1.3 Lemma.** Given that  $f(\kappa) = 0$  and  $f(x) > 0$  for all  $a \leq x < \kappa$ , then  $f'(\kappa) \leq 0$ .

*Proof.* By definition

$$\begin{aligned} f'(\kappa) &= \lim_{x \rightarrow \kappa^-} \frac{f(x) - f(\kappa)}{x - \kappa} \\ &= \lim_{x \rightarrow \kappa^-} -\frac{f(x)}{\kappa - x} \end{aligned}$$

and since  $-\frac{f(x)}{\kappa - x} < 0$ , 
$$f'(\kappa) \leq 0. \tag{3.1.3}$$

Thus, the proof. □

Next, we prove *theorem P*. The proof will be done in sections using IVTM and Lemma **3.1.3**.

Let  $R(t)$  be a solution of the IVP for theorem P.

**I** From the IVP,  $c(t)$ ,  $g(t)$  and  $p(r)$  are continuous and  $p(r)$  is continuously differentiable. By the existence and uniqueness theorem of initial value problems [Teschl \(2012\)](#), the solution,  $R(t)$ , exists and is unique. Hence,  $R(t)$  is defined.

**II** We now show that  $R'(0) > 0$  and  $R(t) > 0 \forall t \in (0, \infty)$ .

*Proof.* If  $R(t)$  is a solution of the IVP (3.1.1), then

$$\begin{aligned}\frac{dR(0)}{dt} &= c(0)[g(0) - p(R(0))] \\ &= c(0)[g(0) - p(0)] \\ &= c(0)g(0) \\ &> 0 \quad \text{since } c(0) > 0, \text{ and } g(0) > 0.\end{aligned}$$

Having showed that  $R'(0) > 0$ , we now prove that  $R(t) > 0 \forall t > 0$ . Note that  $R'(t)$  is continuous since from the IVP  $c(t)$ ,  $g(t)$  and  $p(R(t))$  are continuous. So by definition,  $\forall \epsilon > 0, \exists \delta > 0$ , we have  $|R'(t) - R'(0)| < \epsilon$  whenever  $0 < t < \delta$ . Let  $\epsilon = R'(0)$  since  $R'(0) > 0$ , then

$$\begin{aligned}|R'(t) - R'(0)| &< R'(0) \\ 0 < R'(t) &< 2R'(0) \quad \forall t \in (0, \delta).\end{aligned}$$

Using the fact that  $R(t)$  is continuous and differentiable in the interval  $0 < t < \delta$ , by the *Mean Value Theorem*

$$\frac{R(t) - R(0)}{t - 0} = R'(\tau), \text{ for some } 0 < \tau < \delta.$$

This gives,  $R(t) = tR'(\tau) > 0$

Now, using the fact that  $R(t) > 0 \forall t \in (0, \delta)$  we now prove that  $R(t) > 0$  for all  $t \in [0, \infty)$ .

Suppose  $R(t) \not> 0$  for all  $t \in [0, \infty)$  then  $R(t) \leq 0$  for some  $t \in [0, \infty)$ . Let  $a \in (0, \delta)$  and  $\delta < b < \infty$  with  $R(b) \leq 0$ . By the IVTM and lemma 3.1.3  $\exists \kappa \in [a, b]$  such that  $R(\kappa) = 0$ ,  $R'(\kappa) \leq 0$  and  $R(t) > 0$  for  $a < t < \kappa$ .

Calculating  $R'(\kappa)$ ,

$$\begin{aligned} R'(\kappa) &= c(\kappa)[g(\kappa) - p(R(\kappa))] \\ &= c(\kappa)g(\kappa) > 0 \end{aligned}$$

which is a contradiction to IVTM and the lemma that  $R'(\kappa) \leq 0$ . Hence assumption is false and so  $R(t) > 0$  for all  $t \in (0, \infty)$ .  $\square$

**III** We show that  $R(t)$  is bounded above, i.e. there exists an  $M > 0$ , such that  $R(t) < M$  for all  $t \in [0, \infty)$ . We define  $M > 0$  such that  $p(M) = g(0)$ .

*Proof.* Let  $\Phi(t) = M - R(t)$  then  $\Phi(0) = M > 0$ . To show that  $R(t) < M$   $\forall t \in [0, \infty)$  we must show that  $\Phi(t) > 0, \forall t \in [0, \infty)$ .

Assuming the contrary, then  $R(t) \geq M$  which implies  $\Phi(b) \leq 0$  for some  $b \in (0, \infty)$ .

Now, by the IVTM, let  $a = 0$  which means  $\Phi(a) > 0$  and  $0 < b < \infty$ , then  $\exists \kappa \in (a, b]$  such that  $\Phi(\kappa) = 0, \Phi(t) > 0$  for  $0 < t < \kappa$  and  $\Phi'(\kappa) \leq 0$ .

Notice that  $\Phi'(t) = -R'(t)$  and for  $\Phi(\kappa) = 0$  we have  $R(\kappa) = M$ . So the IVP (3.1.1) at  $t = \kappa$  gives

$$\begin{aligned} \Phi'(\kappa) &= -\{c(\kappa)[g(\kappa) - p(R(\kappa))]\} \\ &= -c(\kappa)[g(\kappa) - p(M)]. \end{aligned}$$

From our definition  $p(M) = g(0)$  which implies that

$$\Phi'(\kappa) = c(\kappa)(g(0) - g(\kappa)).$$

Since  $g(0) - g(\kappa) > 0$  and  $c(\kappa) > 0$ , we have  $\Phi'(\kappa) > 0$ . This is a contradiction,



so  $R(t) < M$  for all  $t \in [0, \infty)$ . □

Since  $0 < R(t) < M$  for all  $t$  in the domain of definition of  $R$ , it implies that the solution exists on  $[0, \infty)$ . The next two proofs show that  $R(t)$  increases initially to reach a maximum and then decreases to zero afterwards. Define the regions

$$A_1 = \{(t, r) | g(t) - p(r) > 0\}$$

$$A_2 = \{(t, r) | g(t) - p(r) = 0\}$$

and

$$A_3 = \{(t, r) | g(t) - p(r) < 0\}.$$

Note that, these are the only regions where the solution  $R(t)$  exists or is defined.

**IV** We show that  $R(t)$  is strictly increasing in the region  $A_1$  and leaves this region at some time.

*Proof.* Given that  $g(t) - p(r) > 0$  is in  $A_1$  and  $c(t) > 0$ , the solution  $R(t)$  is always increasing in  $A_1$  since  $R'(t) > 0$  in that region.

Now assume that the solution stays in  $A_1$  for all times, that is  $g(t) > p(R(t))$  for all times. Choose  $t_0 > 0$  so that  $R(t_0) > 0$  then since  $R(t)$  is increasing whenever  $t > t_0$ ,  $R(t) > R(t_0)$  in  $A_1$ .

Also,  $p(r)$  is strictly increasing and so  $p(R(t)) > p(R(t_0))$ . Hence, by our assumption  $g(t) > p(R(t)) > p(R(t_0))$  for all times  $t > t_0$ .

This is a contradiction since  $\lim_{t \rightarrow \infty} g(t) = 0$ . □

From **I**, **II** and **III**, we have shown that the solution  $R(t)$  is increasing in  $A_1$  and bounded above by some number  $M$ .

Since  $R(t)$  cannot stay in  $A_1$  at all times, there exists a time  $T$  where it leaves  $A_1$ ; meaning when  $g(t) - p(R(t)) \leq 0$ . But  $g(t) - p(R(t)) = 0$  is when  $R'(t) = 0$

and so region  $A_2$  corresponds to the time  $T$  when the response  $R(t)$  is at its maximum.

In the next proof we show that there is only one such  $T$  and whenever  $t > T$ , the solution is decreasing i.e.  $R'(t) < 0$  and stays in the region  $A_3$ , never returning to  $A_1$  or  $A_2$ .

**V** Let  $T > 0$  be the first time  $R(t)$  is in  $A_2$ . We show that for all  $t > T$ ,  $R(t) \in A_3$ . In other words, if  $T$  is the first time  $R(t)$  is in  $A_2$  then for  $t > T$ ,  $R'(t) < 0$ .

*Proof.* Assume the contrary. Then  $\exists t > T$  such that  $R'(t) \geq 0$ .

Let  $t_1$  be the first time after  $T$  when  $R'(t) = 0$ . So  $R'(T) = R'(t_1) = 0$  where  $T < t_1 < \infty$ , and  $R'(t) < 0$  for  $T < t < t_1$ . By differentiability of  $R'(t)$ ,

$$\begin{aligned} R''(t_1) &= \lim_{t \rightarrow t_1^-} \frac{R'(t) - R'(t_1)}{t - t_1} \\ &= \lim_{t \rightarrow t_1^-} \frac{R'(t)}{t - t_1} \\ &\geq 0 \quad \text{for } R'(t) < 0 \text{ and } t - t_1 < 0. \end{aligned} \tag{3.1.4}$$

However, taking the derivative of  $r'(t)$  in (3.1.1) at  $t_1$ ,  $R''(t_1)$ , we have

$$\begin{aligned} R''(t_1) &= c'(t_1)[g(t_1) - p(R(t_1))] + c(t_1)[g'(t_1) - p'(R(t_1))R'(t_1)] \\ &= c'(t_1)[g(t_1) - p(R(t_1))] + c(t_1)[g'(t_1) - p'(R(t_1)) \cdot 0] \\ &= c'(t_1)[g(t_1) - p(R(t_1))] + c(t_1)g'(t_1). \end{aligned}$$

At  $t_1$ ,  $R'(t_1) = 0$  which implies that  $c(t_1)[g(t_1) - p(R(t_1))] = 0$ . Since  $c(t) > 0$ ,  $g(t_1) - p(R(t_1)) = 0$ . This gives us

$$\begin{aligned} R''(t_1) &= c(t_1)g'(t_1) \\ &< 0 \quad \text{since } c(t_1) > 0 \text{ and } g'(t_1) < 0. \end{aligned}$$

This is a contradiction to the previous result (3.1.4) that  $R''(t) \geq 0$ .  $\square$

This result implies that there is only one  $T$  where  $R(t)$  is maximum. When  $R(t)$  increases to maximum, it stays in the region  $A_3$  afterwards where  $R(t)$  is strictly decreasing and never returns to  $A_1$  or  $A_2$ . The next proof shows that  $\lim_{t \rightarrow \infty} R(t) = 0$ .

**VI** Claim:  $\lim_{t \rightarrow \infty} R(t) = 0$

*Proof.* Suppose not, then  $\lim_{t \rightarrow \infty} R(t) = \alpha$  where  $\alpha > 0$ . Note that  $R(t)$  is always positive so  $\alpha$  cannot go below zero.

Since  $R(t)$  is decreasing,  $R(t) \geq \alpha$  whenever  $t > T$ . By hypothesis,  $p(R(t))$  is a strictly increasing function, thus

$$p(R(t)) \geq p(\alpha)$$

or

$$-p(R(t)) \leq -p(\alpha)$$

which implies that

$$g(t) - p(R(t)) \leq g(t) - p(\alpha)$$

and

$$c(t)[g(t) - p(R(t))] \leq c(t)[g(t) - p(\alpha)]$$

and so

$$R'(t) \leq c(t)[g(t) - p(\alpha)]$$

Now, since  $g(t) \rightarrow 0$  as  $t \rightarrow \infty$ , there exist a time  $t_1 > T$ , where  $g(t) < \frac{1}{2}p(\alpha)$

for all  $t > t_1$ . This then implies that

$$R'(t) < c(t) \left[ \frac{1}{2}p(\alpha) - p(\alpha) \right]$$

$$R'(t) < -\frac{1}{2}c(t)p(\alpha).$$

From the hypothesis,  $c(t)$  is bounded below by  $b_1$ , hence

$$R'(t) < -\frac{1}{2}b_1p(\alpha).$$

For any  $t > t_1$ , by the mean value theorem, there exists  $\tau \in (t_1, t)$  such that

$$R'(\tau) = \frac{R(t) - R(t_1)}{t - t_1}.$$

Since  $\tau$  is a time after  $t_1$

$$\frac{R(t) - R(t_1)}{t - t_1} < -\frac{1}{2}b_1p(\alpha)$$

$$R(t) < R(t_1) - \frac{1}{2}b_1p(\alpha)(t - t_1).$$

Note that  $R(t_1)$  is finite but as  $t$  gets large  $t - t_1 \rightarrow \infty$ . So there is some  $t$  after  $T$  where  $R(t) < 0$ .

This is a contradiction to our earlier result that  $R(t) \geq 0$ .

Hence,  $\lim_{t \rightarrow \infty} R(t) = 0$ . □

This concludes the proof of theorem P.

## 3.2 Application of the Peak Theorem

In this section, we apply theorem P to the PK/PD models discussed in [chapter 2](#), to understand more about their time to peak.

### 3.2.1 Peak Theorem and Theis Models

We rewrite each of the models to obtain the form of the model used by the theorem.

1. For **RM-1** in (2.1.1) we have the form

$$\frac{dR(t)}{dt} = k \left[ \frac{a}{k} f(t) - R(t) \right]$$

In the notation used in theorem P,

$$c(t) = k,$$

$$g(t) = \frac{a}{k} f(t)$$

and

$$p(R(t)) = R(t).$$

For the discrete case of RM-1,  $g(t) = 0$  for  $t < 1$  and  $g(t) = \frac{a}{k}$  for  $t \geq 1$ , which doesn't satisfy the properties of  $g(t)$  in theorem P, hence, the theorem cannot be applied.

Nonetheless, it has a single peak at  $T = 1$ . Notice that for  $t < 1$ ,  $R(t)$  is increasing (2.1.7) and its maximum at  $t = 1$  and for  $t \geq 1$ ,  $R(t)$  is decreasing and its also maximum at  $t = 1$ .

The continuous case of RM-1 has

$$c(t) = k,$$

$$g(t) = \frac{a}{k(1+t)}$$

and

$$p(R(t)) = R(t).$$

Note that  $c(t) = k$  which is a constant so it is continuous and bounded. More

so,  $g(t)$  is a positive function and diminishing since

$$g'(t) = -\frac{a}{b(1+t)^2} < 0$$

and

$$\lim_{t \rightarrow \infty} g(t) = 0.$$

For  $p(R(t))$ , note that  $p(0) = R(0) = 0$  and since  $R(t)$  is linear, it's a strictly increasing continuous function and there exist a time  $t$  where  $R(t) \geq g(0)$ .

Hence, by application, the solution of the continuous case of RM-1 by Theis has only one peak.

2. From (2.1.19), RM-2 can be written as

$$\frac{dR(t)}{dt} = k \left[ \frac{a}{k(1+t)^2} - R(t) \right]$$

For this model,  $c(t)$  and  $p(R(t))$  are same as RM-1 so the hypothesis of the theorem is satisfied. Next, we have

$$g(t) = \frac{a}{k(1+t)^2}.$$

It's easy to see that  $g(t) > 0$  and  $\lim_{t \rightarrow \infty} g(t) = 0$ . Now,

$$g'(t) = -\frac{2a}{k(1+t)^3} < 0$$

and so  $g(t)$  is diminishing. As from RM-1,  $R(t)$  is linear there is a time where  $R(t) \geq g(0) = \frac{a}{k}$ . Therefore, the second model by Theis also has a unique time to peak.

3. The equation for RM-3, (2.1.30), can be written as

$$\frac{dR(t)}{dt} = (f(t) + k) \left[ \frac{af(t)}{f(t) + k} - R(t) \right].$$

For  $f(t) = \frac{1}{1+t}$ , we see that

$$c(t) = \frac{1}{1+t} + k$$

and for  $0 < t < \infty$ ,  $c(t)$  is bounded below by  $k$  when  $t = \infty$  and above by  $k + 1$  when  $t = 0$ ; i.e.

$$k < c(t) < k + 1$$

with  $k > 0$  which satisfies the properties of  $c(t)$  in theorem P.

Now,

$$g(t) = \frac{af(t)}{f(t) + k} = \frac{a}{1 + k(1+t)}.$$

We see that  $g(t) > 0$  for  $a > 0$  and  $\lim_{t \rightarrow \infty} g(t) = 0$ . We also have

$$g'(t) = -\frac{ak}{(kt + k + 1)^2} < 0.$$

In conclusion, RM-3 also satisfies the hypothesis of theorem P, hence the solution has a unique maximum and diminishes to zero.

### 3.3 Peak Theorem and Turnover Models

In this section we apply the Peak Theorem to the turnover models also discussed in [chapter 2](#).

1. The inhibiting model TM-1 stated in (2.2.4) can be rewritten as

$$\frac{dR(t)}{dt} = k[\phi(t, D) - R(t)]$$

with parameter  $D > 0$  and  $k > 0$ . Here,

$$c(t) = k$$

which is bounded and

$$p(R(t)) = R(t)$$

which is same in Theis' models discussed in the previous section. For TM-1,

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

defined in (2.2.3) and

$$g(0) = \frac{D}{1 + D}.$$

For the limit,  $\lim_{t \rightarrow \infty} g(t) = \lim_{t \rightarrow \infty} \frac{D}{e^t + D} = 0$ . We also have that

$$g'(t) = -\frac{De^t}{(D + e^t)^2} < 0 \quad \text{for all } t.$$

Hence, TM-1 satisfies the hypothesis of theorem P and so has one unique peak.

2. The second turnover model TM-2 (2.2.5) can be written as

$$\frac{dR(t)}{dt} = (1 - \alpha\phi(t, D)) \left[ \frac{\phi(t, D)}{1 - \alpha\phi(t, D)} - R(t) \right].$$



In this case

$$c(t) = k(1 - \alpha\phi(t, D))$$

and

$$g(t) = \frac{\phi(t, D)}{1 - \alpha\phi(t, D)}.$$

Since

$$c'(t) = \frac{De^t}{(D + e^t)^2} > 0,$$

$c(t)$  is strictly increasing so as  $t \rightarrow \infty$ ,  $c(t)$  is bounded above by  $k$ , i.e.  $\lim_{t \rightarrow \infty} c(t) = k(1 - \alpha \cdot 0) = k$ . For  $t = 0$ ,  $c(0) = k(1 - \alpha \frac{D}{1+D})$  and so it's bounded below by  $k(1 - \frac{\alpha D}{1+D})$ .

Note that  $0 < \alpha < 1$  and  $0 < \frac{D}{1+D} < 1$  and so  $1 - \frac{\alpha D}{1+D} < 1$ . Thus, we've shown that  $c(t)$  is bounded i.e.

$$0 < k \left( 1 - \frac{\alpha D}{1 + D} \right) < c(t) < k.$$

For

$$g(t) = \frac{\phi(t, D)}{1 - \alpha\phi(t, D)} = \frac{D}{e^t + (1 - \alpha)D},$$

and since  $0 < \alpha < 1$ ,  $g(t) > 0$  for all  $t \geq 0$ .

Note that  $g(0) = \frac{D}{1+(1-\alpha)D} > 0$ . Also, since  $e^t \rightarrow \infty$  as  $t \rightarrow \infty$ ,  $g(t) \rightarrow 0$  as  $t \rightarrow \infty$ . We also differentiate  $g(t)$  and we get

$$g'(t) = -\frac{De^t}{(D(1 - \alpha) + e^t)^2} < 0.$$

Thus  $g(t)$  satisfies required conditions of theorem P. We see that  $p(R(t)) = R(t)$  is linear so there exists a  $t$  where  $R(t) \geq g(0)$ , since  $g(0) < \infty$ . Hence, theorem P can be applied to TM-2.

3. Since TM-3 is equivalent to TM-1, theorem P also applies to TM-3.

4. The last turnover model, TM-4, (2.2.7) can also be written as

$$\frac{dR(t)}{dt} = k(1 + \alpha\phi(t, D)) \left( \frac{\phi(t, D)}{1 + \alpha\phi(t, D)} - R(t) \right).$$

In this case 
$$c(t) = k(1 + \alpha\phi(t, D))$$

which is bounded below by  $k$  when  $t = \infty$  and bounded above by  $k + \frac{\alpha k D}{1 + D}$ .

Hence, properties of  $c(t)$  are satisfied for theorem P.

Also,

$$g(t) = \frac{\phi(t, D)}{1 + \alpha\phi(t, D)} = \frac{D}{e^t + \alpha D + D} > 0$$

for  $t \in [0, \infty)$ . We also have that  $g(0) = \frac{D}{1 + D + \alpha D}$  which is positive and bounded.

Differentiating  $g(t)$ , we get

$$g'(t) = -\frac{De^t}{(e^t + \alpha D + D)^2} < 0.$$

In conclusion, theorem P can be applied.

The solution of these models are always positive, each has one peak and the solution goes to zero as time goes to infinity.

In the next chapter, we investigate how the time to peak  $T$ , depends on the drug dosage  $D$ .

# Chapter 4

## Dependence of $T$ on $D$

In this chapter we consider a more general equation than discussed in [chapter 2](#) and [chapter 3](#). All solutions that satisfy the conditions of the Peak Theorem, have only one  $T$ . In this chapter we investigate the dependence of  $T$  on the drug dosage  $D$ . We determine integral conditions for which  $T$  increases as  $D$  increases or vice-versa.

We consider the linear initial value problem

$$\frac{dR(t, D)}{dt} = f(t, D) - h(t, D)R(t, D) \quad (4.0.1)$$

$$R(0, D) = 0 \quad (4.0.2)$$

where  $h(t, D)$  and  $f(t, D)$  are positive quantities. This equation includes all the linear PK/PD models discussed in previous chapters.

We write the solution of this first order linear differential equation in an integral form.

Using the integrating factor

$$\mu(t, D) = e^{\int_0^t h(\tau, D) d\tau}, \quad (4.0.3)$$

we find that

$$\frac{dR(t, D)}{dt} \mu(t, D) - h(t, D)R(t, D)\mu(t, D) = \mu(t, D)f(t, D) \quad (4.0.4)$$

$$\frac{d}{dt} (R(t, D)\mu(t, D)) = \mu(t, D)f(t, D). \quad (4.0.5)$$

Now, integrating both sides,

$$R(\tau, D)\mu(\tau, D)\Big|_0^t = \int_0^t \mu(\tau, D)f(\tau, D)d\tau \quad (4.0.6)$$

$$R(t, D)\mu(t, D) = R(0, D) + \int_0^t \mu(\tau, D)f(\tau, D)d\tau \quad (4.0.7)$$

$$R(t, D) = \frac{1}{\mu(t, D)} \left( \int_0^t \mu(\tau, D)f(\tau, D)d\tau \right) \quad (4.0.8)$$

## 4.1 The General Model and the Peak Theorem

Rewriting (4.0.1) in the form of theorem P,

$$\frac{dR(t, D)}{dt} = h(t, D) \left[ \frac{f(t, D)}{h(t, D)} - R(t, D) \right]. \quad (4.1.1)$$

To satisfy the condition of theorem P, we take

$$c(t) = h(t, D)$$

and require  $h(t, D)$  to be bounded i.e.  $0 < b_1 < h(t, D) < b_2$  where  $b_1, b_2 \in (0, \infty)$

We take

$$g(t) = \frac{f(t, D)}{h(t, D)}.$$

We require  $\frac{f(t, D)}{h(t, D)} > 0$  at all times and  $\frac{f(0, D)}{h(0, D)} < \infty$  since  $g(0)$  is bounded above. By so doing, we get that  $R(t) > \frac{f(0, D)}{h(0, D)}$  at some  $R$ .

Theorem P requires that  $g'(t) < 0$ , which requires  $\left(\frac{f(t,D)}{h(t,D)}\right)' < 0$ . Since

$$\frac{d}{dt} \left( \frac{f(t,D)}{h(t,D)} \right) = \frac{h(t,D)f'(t,D) - f(t,D)h'(t,D)}{h^2(t,D)} \quad (4.1.2)$$

we require  $h(t,D)f'(t,D) - f(t,D)h'(t,D) < 0$ . (4.1.3)

If both  $f(t,D)$  and  $h(t,D)$  are positive, we have the condition that

$$\frac{f'(t,D)}{f(t,D)} - \frac{h'(t,D)}{h(t,D)} < 0. \quad (4.1.4)$$

## 4.2 Time to Peak $T$ and its Derivative $T_D$

If the maximum response  $R_{max}$ , occurs at  $t = T$  then  $\frac{dR}{dt} = 0$  and from (4.0.1) we get

$$-h(T,D)R(T,D) + f(T,D) = 0. \quad (4.2.1)$$

It is worth noting that  $T$  is a function of the dosage  $D$ , that is  $T = T(D)$ . From (4.2.1),  $f$ ,  $h$  and  $R$  are given functions hence they're known quantities and  $T$  is defined implicitly by this equation.

Our goal is to determine how  $T$  changes as  $D$  changes. We take partial derivatives of (4.2.1) to obtain a relationship for  $T_D$

$$\begin{aligned} -R(T,D)(h_T(T,D)T_D + h_D(T,D)) - h(T,D)(R_T(T,D)T_D + R_D(T,D)) \\ + f_T(T,D)T_D + f_D(T,D) = 0 \end{aligned} \quad (4.2.2)$$

where the subscripts  $T$  and  $D$  represent partial derivatives.

Dropping all the  $(T, D)$  for convenience, we have that

$$-R \cdot h_T \cdot T_D - R \cdot h_D - h \cdot R_T \cdot T_D - h \cdot R_D + f_T \cdot T_D + f_D = 0 \quad (4.2.3)$$

$$T_D(f_T - R \cdot h_T - h \cdot R_T) = (R \cdot h_D + h \cdot R_D - f_D). \quad (4.2.4)$$

Now, (4.0.8) gives us a general solution for  $R(t, D)$ . We take partial derivative of  $R$  with respect to  $D$

$$R_D = -\frac{\mu_D}{\mu^2} \left( \int_0^T (\mu \cdot f) d\tau \right) + \frac{1}{\mu} \left( \int_0^T (\mu \cdot f_D + f \cdot \mu_D) d\tau \right) \quad (4.2.5)$$

which then gives

$$R_D = -\frac{\mu_D}{\mu} R + \frac{1}{\mu} \left( \int_0^T (\mu \cdot f_D + f \cdot \mu_D) d\tau \right). \quad (4.2.6)$$

From (4.0.3),  $\mu_D = \mu \int_0^t h_D d\tau$ , substituting this result into equation (4.2.6),

$$R_D = -R \int_0^T h_D d\tau + \frac{1}{\mu} \int_0^T \left( \mu \cdot f_D + \mu \cdot f \int_0^\tau h_D ds \right) d\tau \quad (4.2.7)$$

$$= -R \int_0^T h_D d\tau + \frac{1}{\mu} \int_0^T \mu \left( f_D + f \int_0^\tau h_D ds \right) d\tau. \quad (4.2.8)$$

Substituting  $R_D$  in (4.2.8) into (4.2.4) we get

$$T_D(f_T - R \cdot h_T - h \cdot R_T) = R \cdot h_D - f_D - h \left[ R \int_0^T h_D d\tau - \frac{1}{\mu} \int_0^T \mu \left( f_D + f \int_0^\tau h_D ds \right) d\tau \right] \quad (4.2.9)$$

Now

$$R_T = \frac{\partial R(T, D)}{\partial T} = \frac{\partial}{\partial T} \left[ \frac{1}{\mu(T, D)} \left( \int_0^T \mu(\tau, D) f(\tau, D) d\tau \right) \right].$$

So

$$R_T = \frac{1}{\mu(T, D)} \left( \int_0^T \mu(\tau, D) f(\tau, D) d\tau \right)' + \left( \frac{1}{\mu(T, D)} \right)' \left( \int_0^T \mu(\tau, D) f(\tau, D) d\tau \right)$$

where the ' denotes partial differentiation with respect to T. So we have

$$\left( \int_0^T \mu(\tau, D) f(\tau, D) d\tau \right)' = \mu(T, D) f(T, D).$$

Also,

$$\left( \frac{1}{\mu(T, D)} \right)' = -h(T, D)R(T, D) + f(T, D). \quad (4.2.10)$$

Substituting (4.2.10) into (4.2.9), we have

$$\begin{aligned} & T_D(f_T - R \cdot h_T - h \cdot (-h \cdot R + f)) \\ &= R \cdot h_D - f_D - h \left[ R \int_0^T h_D d\tau - \frac{1}{\mu} \int_0^T \mu \left( f_D + f \int_0^\tau h_D ds \right) d\tau \right] \end{aligned} \quad (4.2.11)$$

The  $R$  in (4.2.11) is the solution when the reaction is at a maximum, hence, from (4.2.1)

$$R(T, D) = \frac{f(T, D)}{h(T, D)}.$$

Making this substitution in (4.2.11) gives us

$$T_D \left( f_T - f \cdot \frac{h_T}{h} \right) = f \cdot \frac{h_D}{h} - f_D - f \int_0^T h_D d\tau + \frac{h}{\mu} \int_0^T \mu \left( f_D + f \int_0^\tau h_D ds \right) d\tau. \quad (4.2.12)$$

From this we investigate if  $T$  is increasing or decreasing with respect to  $D$  by com-

paring the signs of the two expressions **LHE** - Left-Hand Expression,

$$f \left( \frac{f_T}{f} - \frac{h_T}{h} \right) \quad (4.2.13)$$

and **RHE** - Right-Hand Expression

$$f \left( \frac{h_D}{h} - \frac{f_D}{f} \right) - f \int_0^T h_D d\tau + \frac{h}{\mu} \int_0^T \mu \left( f_D + f \int_0^\tau h_D ds \right) d\tau. \quad (4.2.14)$$

We do so by using the properties of the functions involved i.e.  $f, h$  at  $T$ , which help make useful conclusions about the time to peak  $T$ .

### 4.3 Investigating the Sign of $T_D$

Since  $f > 0$  and from (4.1.4)  $\frac{f_T}{f} - \frac{h_T}{h} < 0$ ,

$$f \left( \frac{f_T}{f} - \frac{h_T}{h} \right) < 0$$

and the sign of LHE is always negative.

To investigate the sign of the RHE, we will use the turnover models to help compare the terms in the RHE.



### 4.3.1 RHE for Turnover TM-1 and TM-3

Recall that

$$f(t, D) = k \frac{D}{e^t + D}$$

and

$$h = k.$$

Since

$$h_D = 0 = \int_0^T h_D d\tau,$$

we have

$$\text{RHE} = -f_D + \frac{k}{\mu} \int_0^T \mu f_D \tau. \quad (4.3.1)$$

Since,

$$f_D = \frac{ke^T}{(e^T + D)^2} \quad (4.3.2)$$

and

$$\mu = e^{\int_0^T h d\tau} = e^{kT} \quad (4.3.3)$$

we have

$$\text{RHE} = \frac{-ke^T}{(e^T + D)^2} + \frac{k}{e^{kT}} \int_0^T k \frac{e^{\tau(k+1)}}{(e^\tau + D)^2} d\tau. \quad (4.3.4)$$

Multiplying by  $\frac{e^{kT}}{k}$  we get

$$\frac{e^{kT}}{k} \text{RHE} = -\frac{e^{T(k+1)}}{(e^T + D)^2} + k \int_0^T \frac{e^{\tau(k+1)}}{(e^\tau + D)^2} d\tau. \quad (4.3.5)$$

$$\frac{e^{kT}}{k} \text{RHE} = -\frac{e^{Tk}}{e^T + D} \cdot \frac{e^T}{e^T + D} + k \int_0^T \frac{e^{\tau(k+1)}}{(e^\tau + D)^2} d\tau. \quad (4.3.6)$$

From (4.2.1),

$$f(T, D) = h(T, D)R(T, D)$$

and from (4.0.8)

$$R(T, D) = \frac{1}{\mu(T, D)} \left( \int_0^T \mu(\tau, D) f(\tau, D) d\tau \right).$$

Substituting  $R(T, D)$  into  $f(T, D)$ , we have

$$f(T, D) = \frac{h(T, D)}{\mu(T, D)} \left( \int_0^T \mu(\tau, D) f(\tau, D) d\tau \right). \quad (4.3.7)$$

This implies that 
$$\frac{D}{e^T + D} = \frac{k}{e^{kT}} \int_0^T \frac{De^{k\tau}}{e^\tau + D} d\tau \quad (4.3.8)$$

$$\frac{De^{kT}}{e^T + D} = \int_0^T \frac{kDe^{k\tau}}{e^\tau + D} d\tau. \quad (4.3.9)$$

Now, substituting (4.3.9) into (4.3.6), we have

$$\frac{e^{kT}}{k} \text{RHE} = \frac{e^T}{D(e^T + D)} \cdot - \int_0^T \frac{kDe^{k\tau}}{e^\tau + D} d\tau + k \int_0^T \frac{e^{\tau(k+1)}}{(e^\tau + D)^2} d\tau. \quad (4.3.10)$$

$$= \int_0^T \left[ \frac{ke^{\tau(k+1)}}{(e^\tau + D)^2} - \frac{ke^T e^{k\tau}}{(e^T + D)(e^\tau + D)} \right] d\tau \quad (4.3.11)$$

$$= k \int_0^T \frac{e^{k\tau}}{(e^\tau + D)} \left[ \frac{e^\tau}{e^\tau + D} - \frac{e^T}{e^T + D} \right] d\tau. \quad (4.3.12)$$

Note that  $\frac{e^\tau}{e^\tau + D}$  is an increasing function, i.e.

$$\frac{d}{d\tau} \left( \frac{e^\tau}{e^\tau + D} \right) = \frac{De^\tau}{(e^\tau + D)^2} > 0 \quad (4.3.13)$$

This shows that  $\frac{e^{kT}}{k} \text{RHE} < 0$  and  $\text{RHE} < 0$ . So the sign of  $T_D$  is positive ( $T_D > 0$ )

hence, the time to peak is increases as dosage  $D$  increases.

### 4.3.2 RHE for TM-2

Before considering this case we make some general modification by substituting (4.3.7) into the first term of RHE (4.3.4). So we have,

$$\begin{aligned} f \left( \frac{h_D}{h} - \frac{f_D}{f} \right) &= \frac{h}{\mu} \left( \frac{h_D}{h} - \frac{f_D}{f} \right) \int_0^T \mu f d\tau \\ &= \frac{h(T, D)}{\mu(T, D)} \int_0^T \left[ \mu(\tau, D) f(\tau, D) \left( \frac{h_D(T, D)}{h(T, D)} - \frac{f_D(T, D)}{f(T, D)} \right) \right] d\tau. \end{aligned} \quad (4.3.14)$$

For the second term in RHE (4.3.4) we have,

$$\begin{aligned} -f \int_0^T h_D d\tau &= - \left( \frac{h}{\mu} \int_0^T \mu f d\tau \right) \cdot \int_0^T h_D d\tau \\ &= \frac{h(T, D)}{\mu(T, D)} \int_0^T \left[ \mu(\tau, D) f(\tau, D) \left( - \int_0^T h_D(s, D) ds \right) \right] d\tau \end{aligned} \quad (4.3.15)$$

Substituting (4.3.14) and (4.3.15) into RHE (4.3.4), we have

$$\begin{aligned} RHE &= \frac{h(T, D)}{\mu(T, D)} \int_0^T \left[ \mu(\tau, D) f(\tau, D) \left( \frac{h_D(T, D)}{h(T, D)} - \frac{f_D(T, D)}{f(T, D)} \right) \right. \\ &\quad \left. + \mu(\tau, D) f(\tau, D) \left( - \int_0^T h_D(\tau, D) d\tau \right) \right. \\ &\quad \left. + \mu(\tau, D) f_D(\tau, D) + \mu(\tau, D) f(\tau, D) \int_0^\tau h_D(s, D) ds \right] d\tau \end{aligned} \quad (4.3.16)$$

which then becomes

$$\begin{aligned} RHE &= \frac{h(T, D)}{\mu(T, D)} \int_0^T \mu(\tau, D) f(\tau, D) \left[ \left( \frac{h_D(T, D)}{h(T, D)} - \frac{f_D(T, D)}{f(T, D)} \right) \right. \\ &\quad \left. + \frac{f_D(\tau, D)}{f(\tau, D)} + \int_0^\tau h_D(s, D) ds - \int_0^T h_D(s, D) ds \right] d\tau. \end{aligned}$$

and simplifies to

$$\begin{aligned} \text{RHE} = \frac{h(T, D)}{\mu(T, D)} \int_0^T \mu(\tau, D) f(\tau, D) \left[ \left( \frac{f_D(\tau, D)}{f(\tau, D)} - \frac{f_D(T, D)}{f(T, D)} \right) \right. \\ \left. + \frac{h_D(T, D)}{h(T, D)} - \int_\tau^T h_D(s, D) ds \right] d\tau. \end{aligned} \quad (4.3.17)$$

For TM-2,

$$f = k \frac{D}{e^t + D} \text{ and } h = k \left( 1 - \alpha \frac{D}{e^t + D} \right).$$

Then,

$$\frac{f_D(\tau, D)}{f(\tau, D)} - \frac{f_D(T, D)}{f(T, D)} = \frac{1}{D} \left( \frac{e^\tau}{e^\tau + D} - \frac{e^T}{e^T + D} \right) \quad (4.3.18)$$

and

$$\frac{h_D(T, D)}{h(T, D)} = - \frac{\alpha e^T}{(e^T + D)(e^T + D(1 - \alpha))}.$$

Also,

$$\begin{aligned} \int_\tau^T h_D(s, D) ds &= \int_\tau^T - \frac{\alpha k e^s}{(e^s + D)^2} ds \\ &= -\alpha k \int_{e^\tau + D}^{e^T + D} \frac{du}{u^2} \\ &= \alpha k \left( \frac{1}{e^T + D} - \frac{1}{e^\tau + D} \right) \end{aligned}$$

Note that the sign of  $\frac{h_D(T, D)}{h(T, D)}$  is negative.

The remaining terms are,

$$\begin{aligned} \frac{f_D(\tau, D)}{f(\tau, D)} - \frac{f_D(T, D)}{f(T, D)} - \int_\tau^T h_D(s, D) ds &= \frac{\frac{1}{D}[e^\tau(e^T + D) - e^T(e^\tau + D)] - \alpha k(e^\tau - e^T)}{(e^T + D)(e^\tau + D)} \\ &= \frac{(e^\tau - e^T)(1 - \alpha k)}{(e^T + D)(e^\tau + D)}. \end{aligned}$$

For  $1 - \alpha k > 0$  or  $k < \frac{1}{\alpha}$ ,  $\text{RHE} < 0$  and hence  $T_D$  is positive. In conclusion,  $T$  increases as  $D$  increases whenever  $k < \frac{1}{\alpha}$ .

### 4.3.3 RHE for TM-4

For TM-4,

$$f = k \frac{D}{e^t + D} \text{ and } h = k \left( 1 + \alpha \frac{D}{e^t + D} \right).$$

Since  $f$  is same as that for TM-1 to TM-3, from 4.3.17 and 4.3.18 we have

$$\frac{f_D(\tau, D)}{f(\tau, D)} - \frac{f_D(T, D)}{f(T, D)} = \frac{e^\tau - e^T}{(e^\tau + D)(e^T + D)} < 0$$

Also, 
$$\frac{h_D(T, D)}{h(T, D)} = \frac{\alpha e^T}{(e^T + D)(e^T + D(1 + \alpha))} > 0$$

and 
$$\begin{aligned} \int_\tau^T h_D(s, D) ds &= \int_\tau^T \frac{\alpha k e^s}{(e^s + D)^2} ds \\ &= \alpha k \left( \frac{1}{e^\tau + D} - \frac{1}{e^T + D} \right) \\ &= \frac{\alpha k (e^T - e^\tau)}{(e^\tau + D)(e^T + D)} \\ &> 0 \end{aligned}$$

Now 
$$\begin{aligned} \frac{f_D(\tau, D)}{f(\tau, D)} - \frac{f_D(T, D)}{f(T, D)} + \frac{h_D(T, D)}{h(T, D)} - \int_\tau^T h_D(s, D) ds \\ = \frac{1}{e^T + D} \left[ \frac{e^\tau - e^T}{e^\tau + D} + \frac{\alpha e^T}{e^T + D(1 + \alpha)} - \frac{\alpha k (e^T - e^\tau)}{e^\tau + D} \right] \end{aligned}$$

$$= \frac{(-1 - \alpha k)(e^T - e^\tau)(e^T + D(1 + \alpha)) + \alpha e^T (e^\tau + D)}{(e^T + D)(e^\tau + D)(e^T + D(1 - \alpha))}$$

(4.3.19)

So if  $-1 - \alpha k > 0$  or  $1 + \alpha k < 0$ , then RHE is positive, which will imply that  $T$  is decreasing as  $D$  increases. However, this assertion for  $T$  is false since  $1 + \alpha k$  is strictly positive.

# Chapter 5

## Discussion, Conclusion and Future Work

We begun by reviewing some of the models by Theis et al. (2011), Nguyen et al. (2009), Sharma and Jusko (1996), Dayneka et al. (1993) and others; giving some details of the models. We explained the models by giving the biological reasons for the terms involved. The reaction models, RM-1 to RM-6, from Theis et al. (2011), started with a simple PK/PD (first order linear differential equation) and increased the complexity by including additional parameters and constraints to describe observed dynamics in biological responses and data. We showed that there are several common features of the turnover models, TM-1 to TM-4 which produce responses by indirect mechanisms. The reaction models and turnover models helped our analysis and discussions in this paper.

In [chapter 3](#), we proved Peak Theorem (theorem P), which addresses the question of whether a maximum response occurs after a drug is administered. The theorem considers a general non-linear differential equation, of the form  $\frac{dr(t)}{dt} = c(t)[g(t) - p(r)]$ . We proved that if  $c(t)$  is a positive, continuous and bounded function,  $g(t)$  is a pos-

itive, continuous and diminishing function, and  $p(r)$  is strictly increasing continuous function where  $p(r) > g(0)$  at some  $t$ , then the solution  $r$  is defined, bounded, has a unique maximum at time  $T$  and diminishes to zero as  $t \rightarrow \infty$ . We applied theorem P to RM-1 to RM-3, and TM-1 to TM-4 and showed that each model satisfied the conditions of theorem P and thus has a single time to peak.

The existence of a single time to peak (theorem P) led the analysis of [chapter 4](#) where we investigated how the time to peak depends on drug dosage. We used a general linear differential equation [\(4.0.1\)](#) together with its general integral solution to derive an expression for  $T_D$  (changes in  $T$  with respect to changes in the drug dosage  $D$ ) [\(4.2.12\)](#). We found two expressions, LHE and RHE depending only on  $f$  and  $h$ , which show that  $T$  increases with  $D$  when LHE and RHE have the same signs and vice-versa.

This result led us to find some information on how  $T$  varies with  $D$  for the turnover models. First, we used the analysis in [chapter 4](#) to show that the sign of LHE is negative under the conditions of the Peak theorem. For TM-1 and TM-3, we showed that  $T$  increases when  $D$  increases. For TM-2, we showed that for  $k < \frac{1}{\alpha}$ ,  $T$  increases as  $D$  increases. However, [Nguyen et al. \(2009\)](#) showed that for  $k > \frac{1}{\alpha}$  and  $\alpha < \frac{1}{2}$ ,  $T$  increases with  $D$ . There still remain the range  $k > \frac{1}{\alpha}$  where  $\alpha > \frac{1}{2}$  to be investigated.

For future work, we can investigate TM-4 further by using a numerical approach to determine how  $T$  changes with  $D$ . This would benefit from clinical trial data to estimate values of  $\alpha$ ,  $k$  and  $D$ . We can also investigate and obtain conditions for the terms in RHE which will guarantee that  $T$  increases or decreases as  $D$  changes. We can also analyze the general nonlinear model [\(3.1.1\)](#) to investigate how  $T$  changes with  $D$  using a similar approach for the linear version in [chapter 4](#).

As mentioned earlier, the analysis in this paper focuses on administration of drugs into the system of an organism, however, it is valid for any application governed by a first order ordinary differential equation with diminishing forcing and other mild restriction on the form of the feedback.

In conclusion, this thesis has many applications for many regulated feedback networks.



# Appendix - Matlab Codes

## RM-1 Discrete Version

-----

```
a = 1;
k = 1;
t1 = linspace(0,1)';
t2 = linspace(1,3)';
X = [t1,t2];
Y = [a/k*(1-exp(-k*t1)),a/k*(exp(-k*(t2-1))-exp(-k*t2))];
figure
stairs(X,Y)
xlabel('t') % x-axis label
ylabel('R(t)') % y-axis label
```

## RM-1 Continuous Version

-----

```
a = 1;
k = 1;
t = linspace(0,1)';
Y = (a*exp(-k*(t+1))).*(-expint(-k*t-k)+expint(-k));
```

RM-2

----

```
a = 1;
k = 1;
t = linspace(0,1);
Y = a*(exp(-k*t)-(1./(1+t))+k*exp(-k*(1+t)).*(-expint(-k*t-k)+expint(-k)));
```

RM-3

----

```
a = 1;
k = 1;
t = linspace(0,20);
Y = a*(1-exp(-k*t))./(k*(1+t));
```

TM-1 and TM-3

-----

```
d = 1;
k = 1;
Pe = @(tau,d,k) d*exp(-tau)./(1+d*exp(-tau)).*exp(k*tau);
Y = zeros(1001,1);
i=1;
for t=0:0.01:10
    Y(i) = k*exp(-k*t)*integral(@(tau) Pe(tau,d,k),0,t);
    i=i+1;
end

t = linspace(0,10,1001);
```

```

figure
plot(t,Y)
xlabel('t')
ylabel('R(t)')

```

TM-2

----

```

d = 1;
k = 1;
a = 0.5;
P = @(tau,d) d*exp(-tau)./(1+d*exp(-tau));
Q = @(s,d) d*exp(-s)./(1+d*exp(-s));
Y = zeros(1001,1);
i=1;
for t=0:0.01:10
    Y(i) = k*exp(-k*t+a*k.*integral(@(tau)P(tau,d),0,t))
        .*integral(@(tau) P(tau,d).*exp(k*tau-a*k
        .*integral(@(s)Q(s,d),0,0.01)),0,t);
    i=i+1;
end

t = linspace(0,10,1001);
figure
plot(t,Y)
xlabel('t')
ylabel('R(t)')

```

TM-4

-----

```
d = 1;
k = 1;
a = 0.5;
P = @(tau,d) d*exp(-tau)./(1+d*exp(-tau));
Q = @(s,d) d*exp(-s)./(1+d*exp(-s));
Y = zeros(1001,1);
i=1;
for t=0:0.01:10
    Y(i) = k*exp(-k*t-a*k.*integral(@(tau)P(tau,d),0,t))
        .*integral(@(tau) P(tau,d).*exp(k*tau+a*k
        .*integral(@(s)Q(s,d),0,0.01)),0,t);
    i=i+1;
end

t = linspace(0,10,1001);
figure
plot(t,Y)
xlabel('t')
ylabel('R(t)')
```

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