# CHARLES UNIVERSITY

# FACULTY OF PHARMACY IN HRADEC KRÁLOVÉ

## Department of Biophysics and Physical Chemistry


# Mathematics and implementations of physiologically based pharmacokinetic modeling

Diploma Thesis


Yestay Rakhimov



September 2018 Supervisor: doc. Erik Jurjen Duintjer Tebbens, Ph.D.

,, I declare that this thesis is my original work and I have not received any unauthorized assistance in it completion. All sources of information are named in references and cited properly. This thesis has not been used for obtaining a different or the same degree."

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Hradec Králové

Yestay Rakhimov

I would like to thank my supervisor doc. Erik Jurjen Duintjer Tebbens, Ph.D. for his patient, careful and expert leadership. I thank him for the valuable advice and immense help.

# Contents

# Abstract

Charles University
Faculty of Pharmacy in Hradec Králové
Department of Biophysics and Physical Chemistry

Candidate: Yestay Rakhimov
Supervisor: doc. Erik Jurjen Duintjer Tebbens, Ph.D.
Title of diploma thesis: Mathematics and implementations of physiologically based pharmacokinetic modeling

The thesis addresses some basic aspects of pharmacokinetic modeling, which is used to describe pharmacokinetic processes. Understanding these processes is important for example to determine optimal concentrations of drugs dosing.

The thesis focuses on mathematical proofs of a number of pharmacokinetic equations, which are often not given in standard books. The derived equations are illustrated with numerical experiments for a particular drug in the software PharmCalcCl and MATLAB.

# Abstrakt

Univerzita Karlova
Farmaceutická fakulta v Hradci Králové
Katedra biofyziky a fyzikální chemie

Kandidát: Yestay Rakhimov
Školitel: doc. Erik Jurjen Duintjer Tebbens, Ph.D.
Název diplomové práce: Mathematics and implementations of physiologically based pharmacokinetic modeling

Práce se věnuje některým základním aspektům farmakokinetického modelování, které se používají k popisu farmakokinetických procesů. Pochopení těchto procesů je důležité například pro stanovení optimálních koncentrací dávkování léků.

Diplomová práce se zaměřuje na matematické důkazy řady farmakokinetických rovnic, které často nejsou uvedeny ve standardních knihách. Odvozené rovnice jsou ilustrovány numerickými experimenty pro určitý lék v softwaru PharmCalcCl a MATLAB.

# Introduction

Pharmacokinetics contributes to solving the problem of the effectiveness and safety of pharmacotherapy by investigating the dependence of therapeutic, toxic and side effects of drugs on their concentrations at the site of action or in the analyzed biological environment (most often in the blood) and the calculation of optimal modes of drug administration for creating and maintaining optimal concentrations of drugs [22].

Pharmacokinetic models are used to simplify the study of pharmacokinetics. The pharmacokinetic model describes the kinetics (change in time) of the distribution of drugs administered to the body [24]. The pharmacokinetic model allows, within the limits of certain assumptions, to find changes in the drug concentration in time with different methods of its administration into the body, to calculate the optimal ratio between the parameters of input and output of the drug, to provide the necessary therapeutic effect [20].

In this thesis we focus on most-frequently used one-compartmental and two-compartmental models. We give detailed mathematical proofs of pharmacokinetic equations, which are often not in the standard books. In the first chapter, basics of pharmacokinetics, we describe important pharmacokinetic processes, the main reaction types and we end the chapter with brief introduction in compartmental theory. In our second chapter we will consider one-compartmental intravenous injection in single and multiple doses, intravenous infusion and discuss about extravascular drug application. We perform numerical experiments in the software PharmCalcCl [5] for the drug gentamicin [23]. In the next

third chapter, we discuss about two-compartmental models and describe its typical parameters. We end our thesis with chapter, approximation of the AUC, describing some popularly used numerical methods, Trapezoidal and Simpson's rule, and also perform numerical experiments in the MATLAB sofware [18].

We end this introduction with the original and official scope of the thesis introduced in SIS (Studijní informační systém).

## The goals of the thesis

The goals of the thesis are:
- to give a thorough description of the mathematics behind modern PBPK (physiologically based pharmacokinetic) modeling,
- to give a description and evaluation of the implementation of PBPK currently available in the MATLAB software,
- to work on possible improvements or extensions of that software.

We would like to point out that, we used knowledges about more standard PBPK. We mainly focused on mathematical proofs of pharmacokinetic equations. In the MATLAB we performed numerical experiments, where we demonstrated how to calculate $AUC$ and difference between numerical methods. Because of license problems of the MATLAB software and lack of time, we could not work on possible improvements or extensions of this software.

# Chapter 1

# Basics of pharmacokinetics

In this chapter we briefly introduce some basic notions necessary in the following chapters. First we start describing pharmacokinetic processes: ADME (Absorption, Distribution, Metabolism, Excretion), then we introduce rates of reactions: zero-order and first-order and we end the chapter with a very brief descriptions of one-compartment, two-compartment and multicompartment models. The descriptions in this chapter are based on the book [13] and [4].

Pharmacokinetics deals with how the organism acts on the drug, its fate in the body, how the time course of the drug concentrations changes. Pharmacodynamics, on the other hand, deals with how the drug affects the body, what are the mechanisms of drug action [17].

There are 4 main types of pharmacokinetic processes [3] (see Figure 1.1):
1) Absorption - drug movement into the blood from the site of administration (e.g. from the digestive tract, muscle, subcutaneous tissue).
2) Distribution - distribution of the drug in the blood into the body and into the site of action, into tissues and organs (in the blood, a lipophilic drug can be bound to serum proteins).
3) Metabolism (biotransformation) of the drug - metabolic conversion of the drug to an

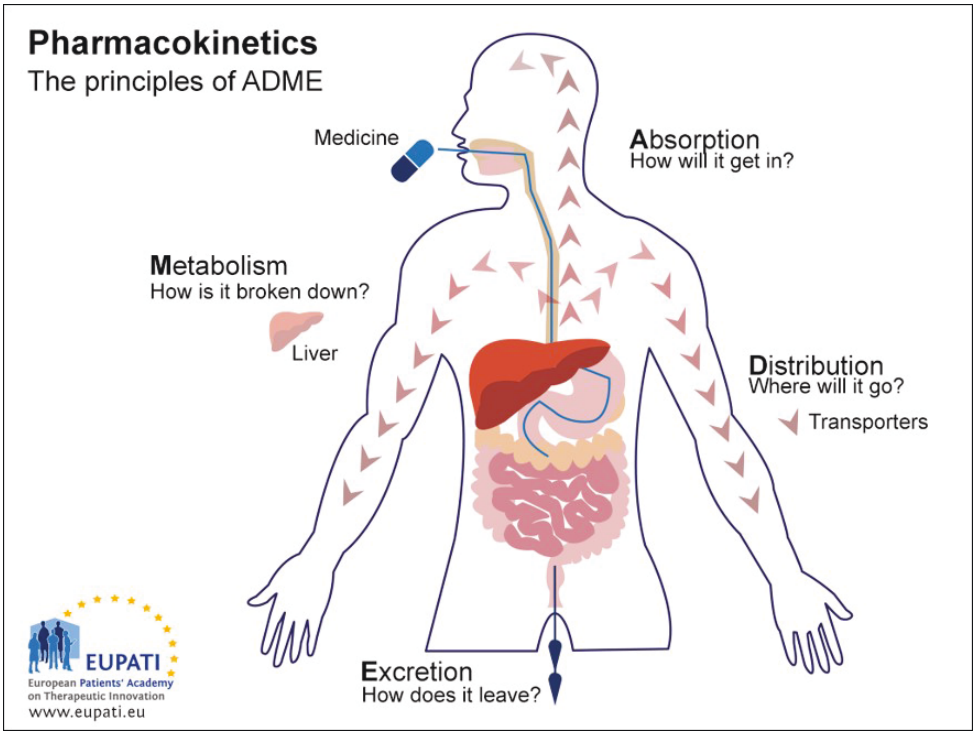



Figure 1.1: The key principles of Pharmacokinetics – the study of the effect the body has on a medicine – are represented in the acronym ADME (the picture is taken from [6]).

inactive substance that is more hydrophilic and easier to remove from the body (sometimes an inactive drug (pro-drug) can be activated to become an active drug).
4) Excretion - excretion of the substance or its metabolite from the body, most commonly by kidneys and bile.

These pharmacokinetic processes, often referred to as ADME, determine the drug concentration in the body when medicines are prescribed.

## 1.1 Reaction types

The relationship between the reaction velocity and the composition of the reaction mixture is expressed by general rate equation. For most reactions, the reaction rate depends only on the concentration of the starting components. There are several reaction types, like e.g. zero-order reaction, first-order and second-order reactions. In this chapter we will describe mainly first and zero-order reactions, because most drugs are subject to first-order and some drugs are subject to zero-order reactions.

If the following conditions are met: first, the reaction takes place in a closed system, second, there are no intermediate products, third, there are no other reactions in the system at the same time, then using a mass balance equation one can prove that

$$r = -\frac{dC(t)}{dt}, \tag{1.1}$$

where $r$ is the reaction rate (in units of concentration over time) and $C(t)$ is the instantaneous concentration of the substance [16].

### 1.1.1 Zero-order reaction

The rate constant of a zero order reaction is independent of the concentration of the reactants. These reactions are typical for systems where the reaction medium (catalyst, active surface) is saturated with a reactant. The mathematical relationship for the speed of these reactions is

$$r = k, \tag{1.2}$$

where $k$ is a reaction rate constant (in units of $[\frac{M}{s}]$).

Thus the reaction rate $r$ of a zero-order reaction equals the reaction rate coefficient $k$:

$$r = -\frac{dC(t)}{dt} = k. \tag{1.3}$$

If we integrate this differential equation, we obtain the following relationship:

$$C(t) = -kt + C_0, \tag{1.4}$$

where $C_0$ is the initial concentration.

The reaction proceeds at a constant rate and it is independent of the concentration of substance present in the body. Here is a list of some drugs following zero-order kinetics: phenytoin, phenylbutazone, warfarin, heparin, ethanol, theophylline, tolbutamide, aspirin and other salicylates.

### 1.1.2 First-order reaction

These reactions depend on the concentration of one reactant. The rate equation has the form:

$$r = k \cdot C(t), \tag{1.5}$$

where $r$ is reaction rate (in units of concentration over time), $k$ is the reaction rate coefficient (in units of reversed time), and $C(t)$ is the instantaneous concentration of the substance.

The reaction rate $r$ of a first-order reaction equals the reaction rate coefficient $k$ times concentration $C(t)$:

$$r = -\frac{dC(t)}{dt} = k \cdot C(t). \tag{1.6}$$

By integrating this differential equation we get:

$$C(t) = C_0 \cdot e^{-kt}, \tag{1.7}$$

where $C(t)$ is the instantaneous concentration of the substance, $C_0$ is the initial concentration. In pharmacokinetics $k$ is denoted as $k_e$ - elimination rate constant.

It is assumed that the majority of processes of ADME follow first-order reactions and most drugs used in clinical practice at therapeutic dosages will show first-order rate

processes, i.e. the rate of elimination will be first-order. Drugs following first-order reaction have the property that as the amount of drug administered increases, the body is able to react by eliminating the drug at an increased level and accumulation will not occur. However, if we continue to increase the amount of drug administered then all drugs will change from showing a first-order process to a zero-order process, for example in an overdose situation.

## 1.2 Pharmacokinetic models

A compartment is an abstract region of our body, where we assume substances concentrations are homogeneously distributed. It is the building stone of a simplified model of reality serving to illustrate the ADME processes [1]. The compartments may be small or large, but they are usually abstract units. Typical examples of compartments include plasma (also blood), intracellular and extracellular fluid, adipose tissue, organs, cells ect. They are separated by membranes. The whole system describes a set of compartments between which substances are exchanged.

### 1.2.1 One-compartment model

This type of model is the simplest. The entire body is considered as one compartment (see Figure 1.2). It is assumed that the substance is dispersed quickly and evenly after application. For this reason, it is impossible to accurately illustrate the distribution of the substance in the body. This type of model has a meaning when describing and predicting drug movement, for example, when repeatedly administered [**?**].

It is important to note that this does not imply that the drug concentration in plasma is equal to the drug concentration in the tissues. However, changes in the plasma concentration quantitatively reflect changes in the tissues. A typical relationship between concentration versus time profile is shown in the Figure 1.4 for a drug with first-order

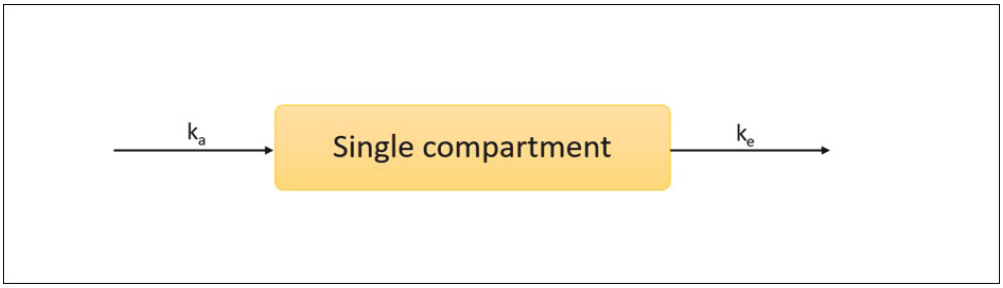



Figure 1.2: One-compartment model. $k_a$ $[h^{-1}]$ is absorption rate constant, $k_e$ $[h^{-1}]$ is elimination rate constant (drawn in PowerPoint).

reactions.

### 1.2.2 Two-compartment model

Most substances can not be instantly dispersed throughout the body. To simulate this, a two-compartment system is used. The first one is central and the other is peripheral (see Figure 1.3). We assume that the substance is exchanged between compartments in order to maintain balance. Although these compartments often have no physiological or anatomical meaning, it is assumed that the central compartment includes tissues that are highly perfused such as heart, lungs, kidneys, liver and brain. The peripheral compartment includes less well-perfused tissues such as muscle, fat and skin.

In a two-compartment model the drug is administered into the central compartment, but the drug does not achieve instantaneous homogenous distribution between the two compartments. The drug distributes between the central and peripheral compartment. A typical drug concentration versus time profile is shown in the Figure 1.5. The form of the curve, after taking a sufficient number of blood samples, is used to determine whether we have 1 or 2 compartments.

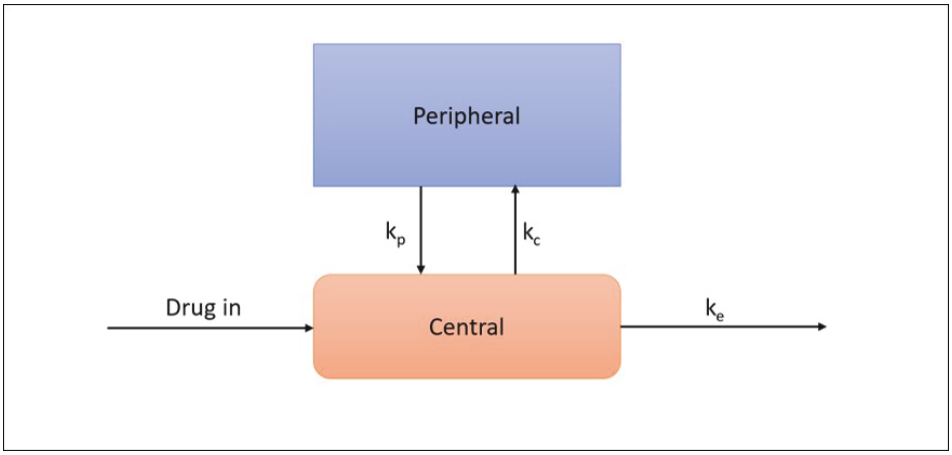



Figure 1.3: Two-compartment model. $k_p$, $k_c$ and $k_e$ are first-order rate constants: $k_p$ is rate of transfer from peripheral to central compartment, $k_c$ is rate of transfer from central to peripheral compartment, $k_e$ is rate of elimination from central compartment.

### 1.2.3 Multicompartment model

With a growing number of compartments, the system becomes more complex. An example of a multi-compartment system is a three-compartment system, which consists of a central compartment and two peripherals. The central one in general is better perfused with blood than the other two. Graphs of plasma concentration versus time profile of a drug are shown in Figure 1.6.

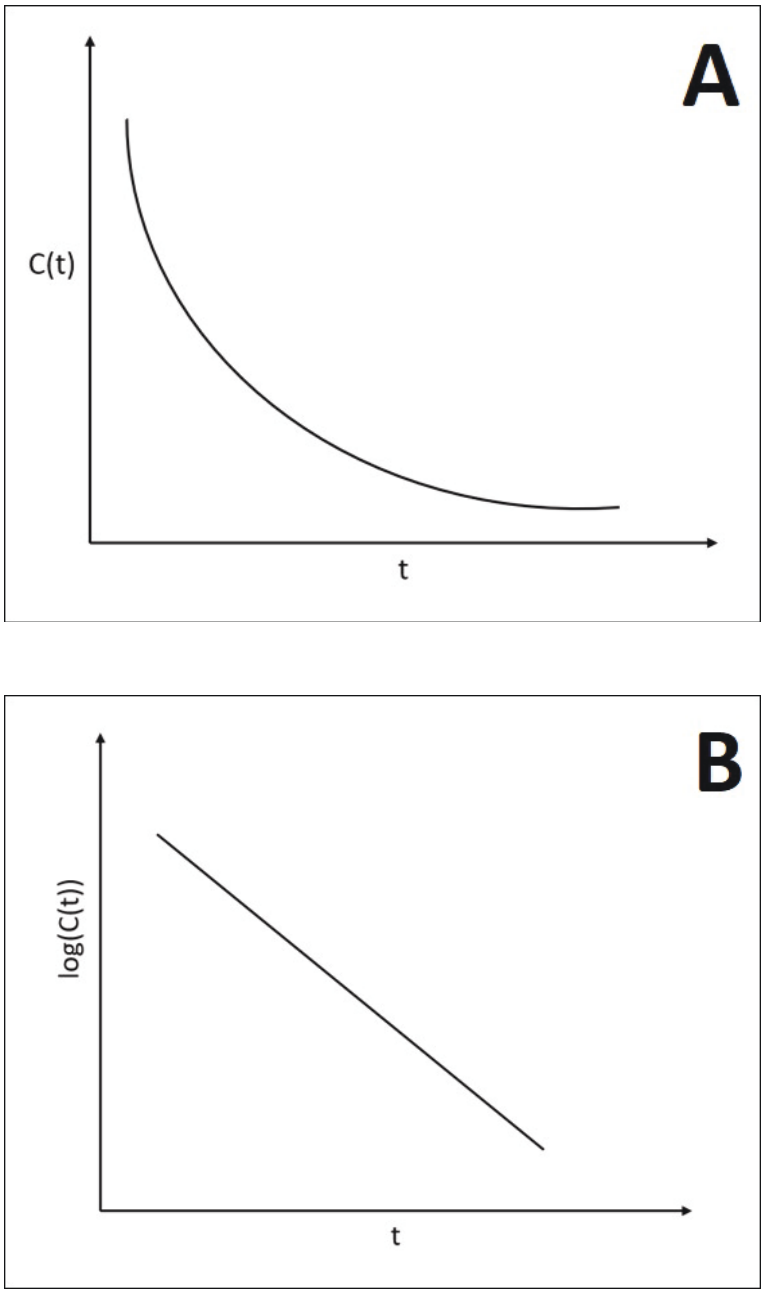



Figure 1.4: One-compartment model: A) plasma concentration $C(t)$ versus time $t$ profile of a drug; B) $log(C(t))$ vs time $t$ shows a linear relation (drawn in PowerPoint).

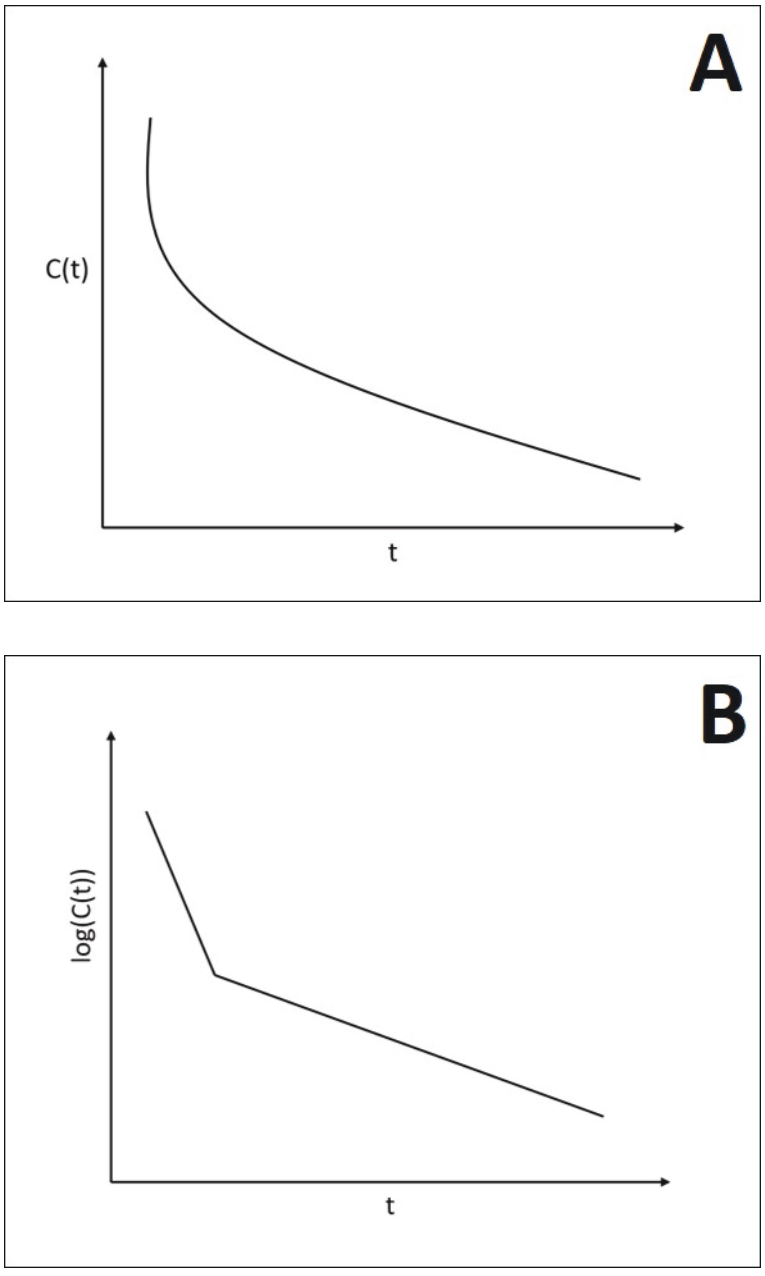



Figure 1.5: Two-compartment model: A) plasma concentration $C(t)$ versus time $t$ profile of a drug shows a curve; B) $log(C(t))$ vs time $t$ plot shows a biphasic response. The figure is for central compartment (drawn in PowerPoint).

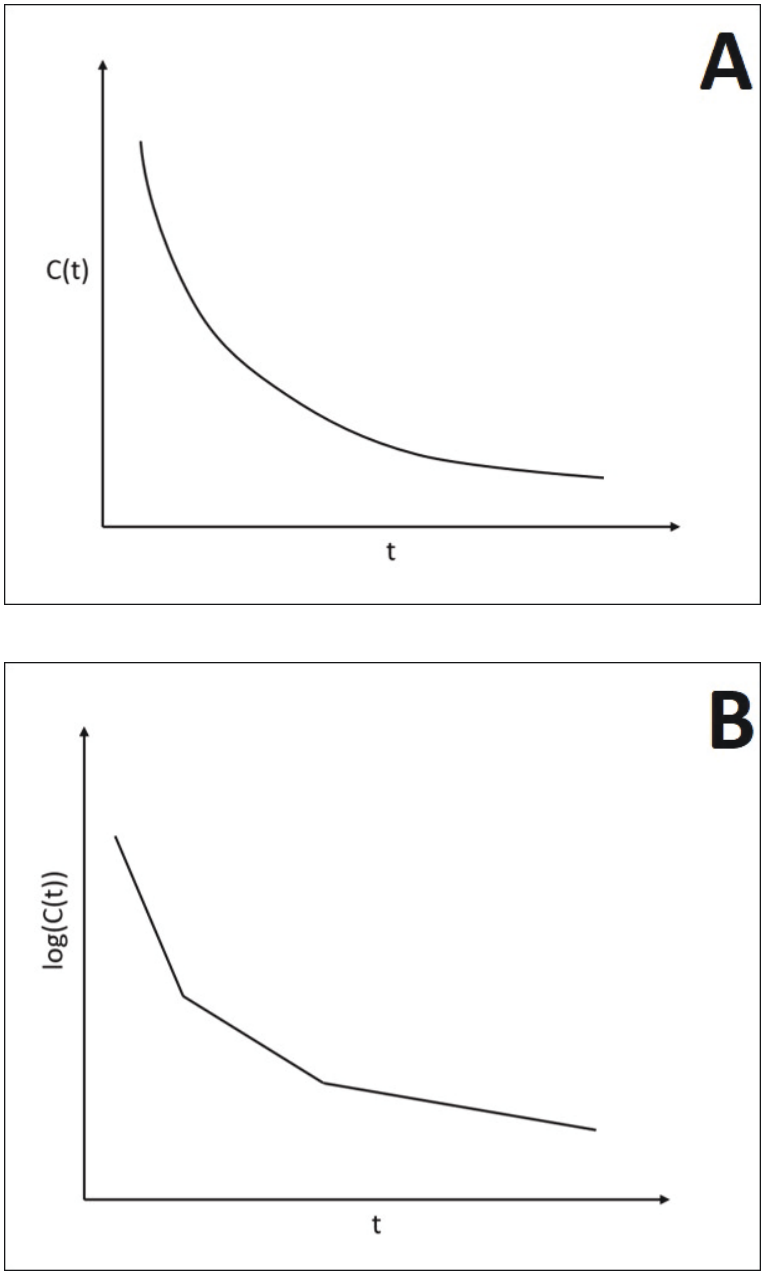



Figure 1.6: Three-compartment model: A) plasma concentration $C(t)$ versus time $t$ profile of a drug shows more than one exponential; B) time profile of a drug showing $log(C(t))$ vs time $t$ (drawn in PowerPoint).

# Chapter 2

# One-compartmental models

In this chapter we describe the pharmacokinetics for one-compartmental models. We will consider one-compartmental intravenous injection, infusion, single and multiple doses, also extravascular drug application. We give mathematical proofs of pharmacokinetic equations and perform numerical experiments in the software PharmCalcCl. The description in this chapter is based on the books [13] and [4].

## 2.1 Intravenous injection, single doses

In a one-compartment model, for drugs with first-order elimination, the change in concentration over time can be expressed according to (1.7) as

$$C(t) = C_0 \cdot e^{-k_e t}, \tag{2.1}$$

where:

$C(t)$ $[\frac{mg}{l}]$ = the plasma drug concentration at time $t$ $[h]$,
$C_0$ $[\frac{mg}{l}]$ = the initial plasma drug concentration at time $t = 0$,
$k_e$ $[h^{-1}]$ = the elimination rate constant,
$e$ = Euler's number (approximately 2.718).

If the injected dose is $D$ $[mg]$, then we can express the initial plasma drug concentration by the following equation

$$C_0 = \frac{D}{V_d}, \tag{2.2}$$

where $V_d$ $[l]$ is the volume of distribution, which is defined as that volume of plasma in which the total amount of drug in the whole body would be required to be dissolved in order to reflect the drug concentration attained in plasma.

**Lemma 2.1.1** *The relation between the elimination half-life $t_{\frac{1}{2}}$ and the elimination rate constant $k_e$ is given by the equation:*

$$t_{\frac{1}{2}} = \frac{\ln 2}{k_e} \approx \frac{0,693}{k_e}. \tag{2.3}$$

Proof: Because $C(t) = C_0 \cdot e^{-k_e t}$, see (2.1), we have

$$C_0 \cdot e^{-k_e t_{\frac{1}{2}}} = \frac{C_0}{2} \Leftrightarrow$$

$$e^{-k_e t_{\frac{1}{2}}} = \frac{C_0}{2C_0} = \frac{1}{2} \Leftrightarrow$$

$$-k_e t_{\frac{1}{2}} = \ln \frac{1}{2} = \ln 2^{-1} \Leftrightarrow$$

$$t_{\frac{1}{2}} = \frac{\ln 2^{-1}}{-k_e} = \frac{-\ln 2^{-1}}{k_e} = \frac{\ln 2}{k_e} \approx \frac{0,693}{k_e}. \quad \square$$

It follows that for the elimination rate constant we have

$$k_e = \frac{\ln 2}{t_{\frac{1}{2}}}, \tag{2.4}$$

thus $k_e$ in (2.1) can be determined from measurement of $t_{\frac{1}{2}}$.

To determine $V_d$ in (2.2) from measurements, one often uses the area under the curve. In the field of pharmacokinetics, the *area under the curve* $A_C$ $[\frac{mg \cdot h}{l}]$, also sometimes abbreviated as $AUC$, denotes the area under the curve (mathematically computed as a definite integral) in a plot of concentration of drug in blood plasma against time.

Typically, the area is computed starting at the time the drug is administered and ending when the concentration of plasma is negligible. The $A_C$ represents the total drug exposure over time. This is useful when trying to determine whether two different formulations of the same dose (for example a capsule and a tablet) release the same dose of drug to the body. Another use is in the therapeutic drug monitoring of drugs with a narrow therapeutic index. For example, gentamicin is an antibiotic that can be nephrotoxic (kidney damaging) and ototoxic (hearing damaging); measurement of gentamicin through concentrations in a patient's plasma and calculation of the $A_C$ is used to guide the dosage of this drug. According to the following lemma, the $A_C$ is also useful to determine the $V_d$.

**Lemma 2.1.2** *In the single-compartment model, the $A_C$ parameter satisfies:*

$$A_C = \frac{C_0}{k_e} = \frac{D}{k_e V_d}. \tag{2.5}$$

Proof:

$$\begin{aligned} A_C = \int_0^\infty C_0 e^{-k_e t} dt &= C_0 \int_0^\infty e^{-k_e t} dt = \left[ C_0 \cdot \frac{e^{-k_e t}}{-k_e} \right]_0^\infty \\ &= C_0 \left( \frac{e^{-\infty}}{-k_e} - \frac{e^0}{-k_e} \right) = C_0 \left( 0 - \frac{1}{-k_e} \right) = \frac{C_0}{k_e}. \quad \square \end{aligned}$$

Thus assuming linear pharmacodynamics with elimination rate constant $k_e$, we have shown that $A_C$ is proportional to the dosage $D$. To compute $V_d$ we can use

$$V_d = \frac{D}{k_e \cdot A_C}.$$

In this context, *clearance* $Cl$ $[\frac{l}{h}]$ is defined as the volume of plasma from which the drug is completely removed per unit time and satisfies:

$$Cl = k_e \cdot V_d. \tag{2.6}$$

Therefore, $A_C$ can be expressed as

$$A_C = \frac{C_0}{k_e} = \frac{D}{k_e V_d} = \frac{D}{Cl}, \tag{2.7}$$

and clearance is given by

$$Cl = \frac{D}{A_C}. \tag{2.8}$$

We end the section with an example for illustration of the change in concentration over time (see (2.1)). We used data from a summary of product characteristics (SPC) of gentamicin (antibiotic drug) given in [23]. Each 2 $ml$ ampoule of solution for injection contains 80 $mg$ gentamicin (as gentamicin sulfate). We have from [23] that the apparent volume of distribution is about 0.25 $l/kg$ for gentamicin. Standardly, for a 70 $kg$ person, we will get $V_d = 0,25 \cdot 70 = 17,5\, l$. We therefore calculated $C_0$ for gentamicin as (see (2.2)):

$$C_0 = \frac{D}{V_d} = \frac{80}{17.5} = 4.57\, mg/l.$$

The elimination half-life was given in [23] as 2.5 $h$. From that we calculated $k_e$ (see 2.4):

$$k_e = \frac{\ln 2}{t_{\frac{1}{2}}} \approx \frac{0.693}{2.5} = 0.277\, h^{-1}.$$

To calculate the change in concentration over time $C(t)$ (see (2.1)), we used the software Excel (see Figure 2.1).

## 2.2 Intravenous injection, multiple doses

In practice most drugs are administered over a period of time in several doses. When we administer a drug at regular dosing intervals, it starts to accumulate in the distribution area (e.g. most common blood plasma) and the drug concentration will rise until a steady-state, which occurs when the administered drug amount (in a given time period) is equal to the eliminated drug amount in that same period. The concentration function is then a periodic function moving between $C_{max}$ and $C_{min}$. The peak $C_{max}$ and trough $C_{min}$ plasma concentrations of the drug are similar during all the periods at steady-state conditions (see Figure 2.2).

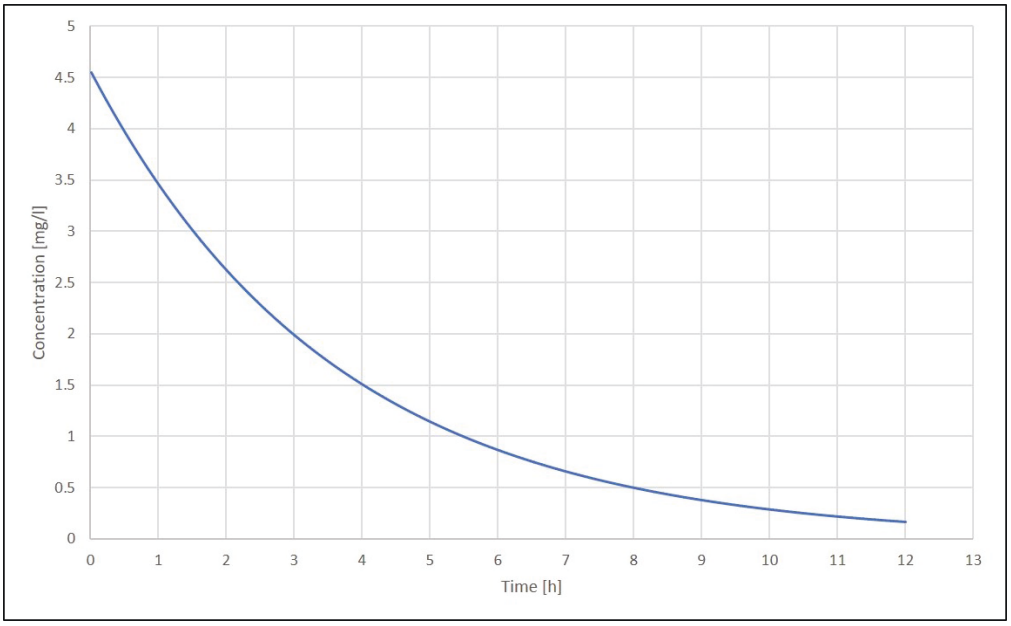



Figure 2.1: Plasma concentration versus time profile of gentamicin using a one-compartment model (according to values given in [23]).

The concentration at time $t$ after the first dose is:

$$C_1 = C_0 \cdot e^{-k_e t}.$$

After the dosing interval $\tau$, the concentration at time $t$ after the second dose originating from the first dose is:

$$C_2 = C_0 \cdot e^{-k_e(\tau+t)}.$$

The contribution from the second dose at time $t$ after the second dose is exactly $C_1 = C_0 \cdot e^{-k_e t}$, as for the first dose. Using the principle of superposition, the total concentration $C(t)$ at time $t$ after the second dose is:

$$\begin{aligned} C(t) &= C_1 + C_2 \\ &= C_0 \cdot e^{-k_e t} + C_0 \cdot e^{-k_e(\tau+t)} \\ &= C_0 \cdot (1 + e^{-k_e \tau}) \cdot e^{-k_e t} \end{aligned}$$

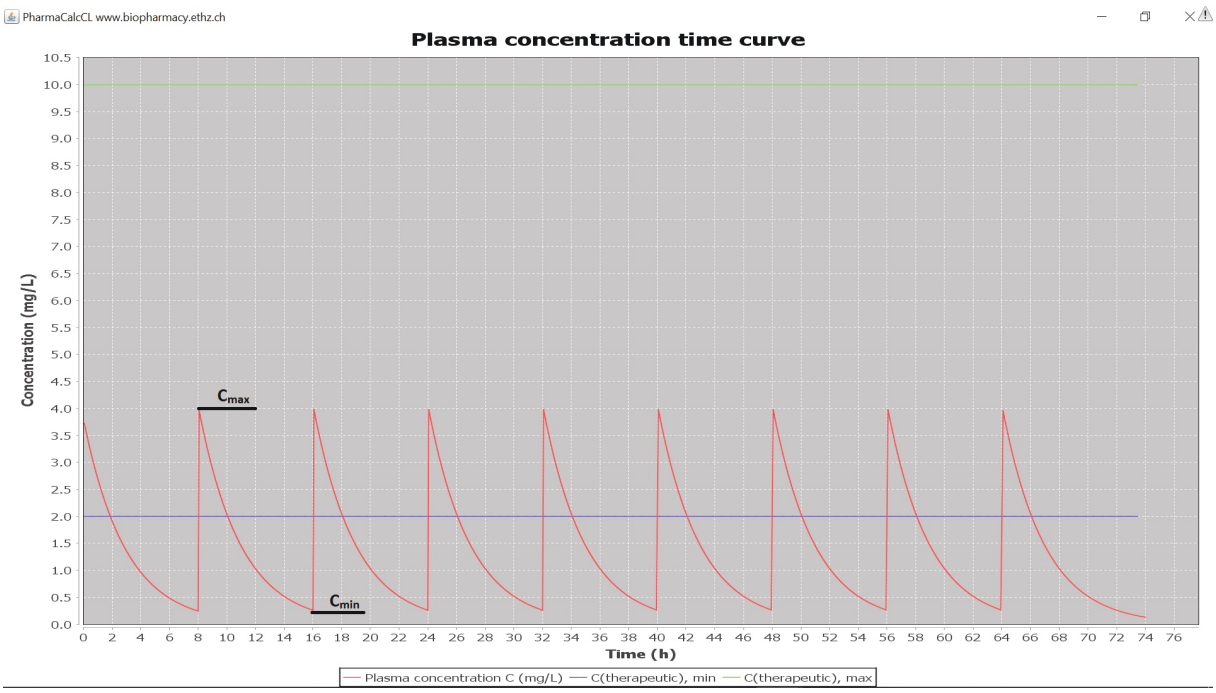



Figure 2.2: Plasma concentration versus time profile of IV doses of 80 $mg$ gentamicin (dosing interval $\tau$ is each 8 $h$) at steady state computed in the software PharmaCalcCL (see [5]).

$$
\begin{aligned}
&= C_0 \cdot \frac{(1+e^{-k_e\tau})(1-e^{-k_e\tau})}{1-e^{-k_e\tau}} \cdot e^{-k_e t} \\
&= C_0 \cdot \frac{1-e^{-2k_e\tau}}{1-e^{-k_e\tau}} \cdot e^{-k_e t}.
\end{aligned}
$$

In general, after the $n^{th}$ dose, we obtain the following theorem 2.2.1.

**Theorem 2.2.1** *To calculate the value of $C(t)$ at any time $t$ after the $n^{th}$ dose we can use the following equation [11]:*

$$C(t) = \frac{D}{V_d} \cdot \frac{1-e^{-k_e n\tau}}{1-e^{-k_e\tau}} \cdot e^{-k_e t} \tag{2.9}$$

*where:*

$n$ = *number of doses,*

$\tau$ = *dosing interval* $[h]$ *and*

$t$ = *time after the* $n^{th}$ *dose.*

Proof:

The concentration during the first dosing interval is given by:

$$C(t) = C_0 \cdot e^{-k_e t}, \quad C_0 = \frac{D}{V_d}.$$

The concentration during the second interval is, using the principle of superposition:

$$C(t) = C_0 \cdot e^{-k_e(\tau+t)} + C_0 \cdot e^{-k_e t} = C_0 \cdot e^{-k_e t}(1 + e^{-k_e \tau}).$$

Let us denote $e^{-k_e \tau}$ by $R$.

The concentration during the third interval is, for the same reasons:

$$C(t) = C_0 \cdot e^{-k_e(2\tau+t)} + C_0 \cdot e^{-k_e(\tau+t)} + C_0 \cdot e^{-k_e t} = C_0 \cdot e^{-k_e t}(R^2 + R + 1).$$

The factor between brackets is the beginning of a geometric series with each term being $R$ times the following term. For the concentration during the $n^{th}$ dose interval we obtain:

$$C(t) = C_0 \cdot e^{-k_e t}(R^{n-1} + R^{n-2} + ... + 1).$$

Using

$$R^{n-1} + R^{n-2} + ... + 1 = \frac{1 - R^n}{1 - R},$$

this can be simplified to give:

$$C(t) = C_0 \cdot \frac{1 - e^{-nk_e\tau}}{1 - e^{-k_e\tau}} \cdot e^{-k_e t}. \quad \square$$

**Corollary 2.2.2** *At steady state, the following equation can be used to describe the drug concentration* $C(t)$ *(e.g. in blood plasma) at any time* $t$ *within the dosing interval* $\tau$*:*

$$C(t) = \frac{D \cdot e^{-k_e t}}{V_d \cdot (1 - e^{-k_e \tau})}. \tag{2.10}$$

Proof:
We consider steady-state to be the state after infinitely many doses. Then $n$ in (2.9):

$$n \to \infty$$

and thus

$$e^{-nk_e\tau} \to 0.$$

This gives (2.10), where the influence of the dose number has disappeared. □

Using corollary 2.2.2, we can describe the maximum plasma concentration $C_{max}$ at steady state (i.e. $t = 0$, then $e^{-k_e t} = 1$) by the following equation:

$$C_{max} = \frac{D \cdot 1}{V_d \cdot (1 - e^{-k_e\tau})} = \frac{D}{V_d \cdot (1 - e^{-k_e\tau})}. \tag{2.11}$$

The minimum plasma concentration $C_{min}$ (i.e. $t = \tau$ in (2.10)) is:

$$C_{min} = \frac{D \cdot e^{-k_e\tau}}{V_d \cdot (1 - e^{-k_e\tau})}. \tag{2.12}$$

We will next derive a frequently used quantity called *average steady-state concentration*. However, we would like to point out that the average steady-state concentration is not a mathematical average, it is not the same as the arithmetic mean of (2.11) and (2.12).

As we mentioned before, steady state occurs when the rate of administered drug amount is equal to the rate of drug elimination. We can approximate the rate of drug administration as the dose $D$ per dosing interval $\tau$, i.e as $\frac{D}{\tau}[\frac{mg}{h}]$. The rate of drug elimination at steady state can be given by the clearance $Cl$ of plasma times the so-called average steady-state concentration, $C_{ss}(\tau)$:

$$\text{Rate of drug elimination} = Cl \cdot C_{ss}(\tau).$$

Thus, at steady state:

$$\frac{D}{\tau} = Cl \cdot C_{ss}(\tau).$$

Rearranging the equation we get the average steady-state concentration $C_{ss}(\tau)$:

$$C_{ss}(\tau) = \frac{D}{Cl \cdot \tau}. \tag{2.13}$$

From equations (2.4) and (2.6)) we have:

$$Cl = \frac{\ln 2 \cdot V_d}{t_{\frac{1}{2}}},$$

then (2.13) changes to

$$C_{ss}(\tau) = \frac{D \cdot t_{\frac{1}{2}}}{\ln 2 \cdot V_d \cdot \tau}. \tag{2.14}$$

Those concentrations depend on the half-life $t_{\frac{1}{2}}$ of the drug under consideration.

We see that the average steady-state levels depend on the given amount of the dose (see (2.14)): the higher the dose - the higher the levels. But the time to achieve steady-state levels does not depend on the given dose amount, it depends on the exponent $-k_e n\tau$ in (2.9), i.e. the larger $k_e$, the smaller the time needed to achieve steady state. Note that the higher the dose, the greater the fluctuations in $C_{max}$ and $C_{min}$ (see equations (2.11), (2.12) and see Figure 2.3).

The difference between the dosing interval $\tau$ and the half-life $t_{\frac{1}{2}}$ can cause 3 different types of average steady-state levels (see (2.14)):

1) If $\tau < t_{\frac{1}{2}}$, greater accumulation occurs, i.e. steady-state levels are higher, but because of (2.12) there is less fluctuation in $C_{max}$ and $C_{min}$ (see Figure 2.8-A);

2) If $\tau > t_{\frac{1}{2}}$, a lower accumulation occurs with greater fluctuation in $C_{max}$ and $C_{min}$ (see Figure 2.8-B);

3) If the dosing interval $\tau$ is much greater than the half-time $t_{\frac{1}{2}}$ of the drug, then $C_{min}$ approaches zero (see (2.12) and Figure 2.8-C). In this case no accumulation will occur and the plasma concentration-time profile will be the same as when administering a series of single doses. In practice, steady-state is often assumed to be reached in 4-5 half-lives. If we assume that a patient is receiving 10 mg doses and half the total amount is

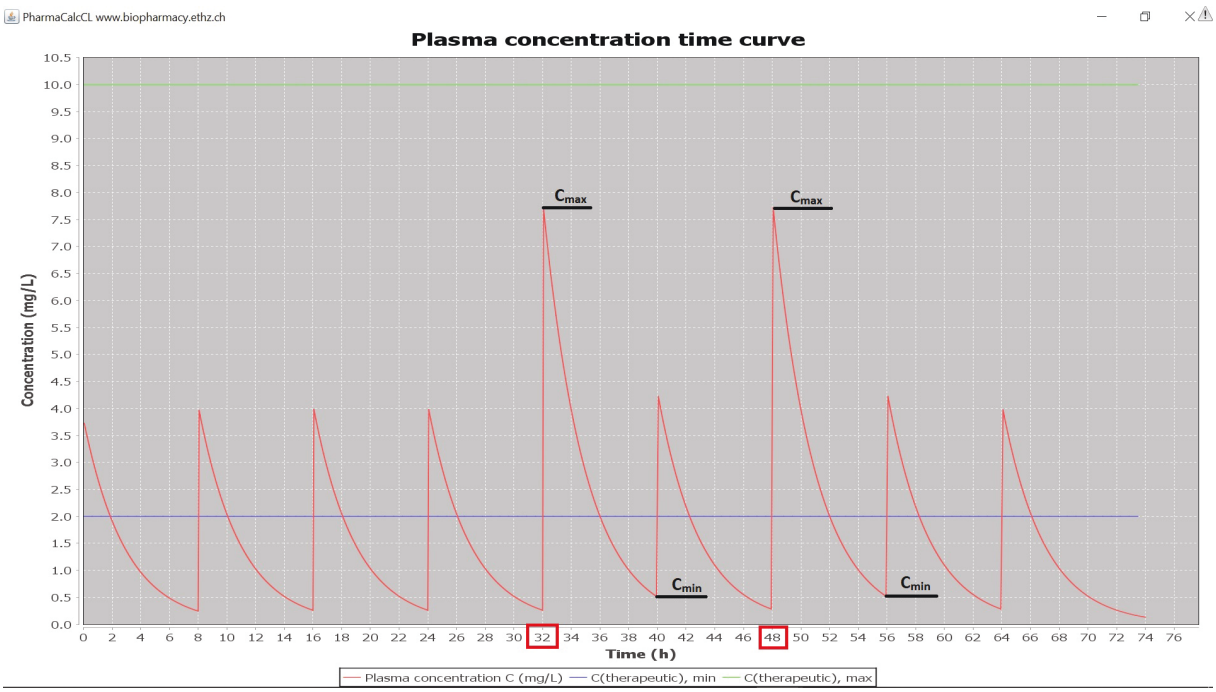



Figure 2.3: Plasma concentration versus time profile of IV doses of the 80 $mg$ gentamicin (dosing interval $\tau$ is each 8 $h$), where $5^{th}$ and $7^{th}$ doses were increased twice (computed in the software PharmaCalcCL (see [5])).

eliminated at each half-life, Table 2.1 shows the time to reach a steady-state concentration in the body.

We remark, that for some drugs it is important to consider its *salt factor* $S$. The salt factor is the proportion of the parent drug contained in the salt, expressed as [12]

$$\frac{\text{weight of parent drug}}{\text{weight basis of the salt}}.$$

Hence, if it is applicable, then $C_0 = \frac{S \cdot D}{V_d}$, which looks similar to (2.2), and we will get instead of (2.10) the following equation with salt factor $S$:

$$C(t) = \frac{S \cdot D \cdot e^{-k_e t}}{V_d \cdot (1 - e^{-k_e \tau})}. \tag{2.15}$$

It is sometimes important to take into account as well the bioavailability $F$, which represents the fraction of an administered dose of unchanged drug that reaches the systemic

| *Dose (mg)* | *Amount in the body (mg)* | *Amount eliminated (mg)* | *Number of half-lives* |
|---|---|---|---|
| 10 | 10 | 5 | 1 |
| 10 | 15 | 7.5 | 2 |
| 10 | 17.5 | 8.75 | 3 |
| 10 | 18.75 | 9.375 | 4 |
| 10 | 19.375 | 9.6875 | 5 |
| 10 | 19.6875 | 9.84375 | 6 |
| 10 | 19.84375 | 9.921875 | 7 |
| 10 | 19.921875 | 9.9609375 | 8 |
| 10 | 19.9609375 | 9.98046875 | 9 |
| 10 | 19.98046875 | 9.990234375 | 10 |
| 10 | 19.99023438 | 9.995117188 | 11 |
| 10 | 19.99511719 | 9.997558594 | 12 |
| ... | ... | ... | ... |

Table 2.1: The table shows the time to reach steady-state concentration in the body, where we assume that a patient is receiving 10 mg doses.

circulation. This will be relevant mainly for extravascular administration.

Remark: if $S$ and $F$ play a role, then in most equations $D$ must be replaced with $S \cdot F \cdot D$, in particular in equations (2.1) and (2.9) till (2.14).

## 2.3 Intravenous infusion

Intravenous infusion is used when it is necessary to direct the drug solution into the blood circulation gradually, either for therapeutical reasons (long-term infusion) or when because of technical reasons the high amount of solution can not be injected entirely (short-term infusion). The rate $R$ $[\frac{mg}{h}]$, which is needed to direct the drug solution into the organism, is as a rule assumed to be constant and it is expressed by ratio: $R = \frac{D}{T}$, where $T$ is a certain end time of the given infusion. The model illustration is shown in Figure 2.4.

**Theorem 2.3.1** *In case of long-term infusion, for the single-compartment model, the*

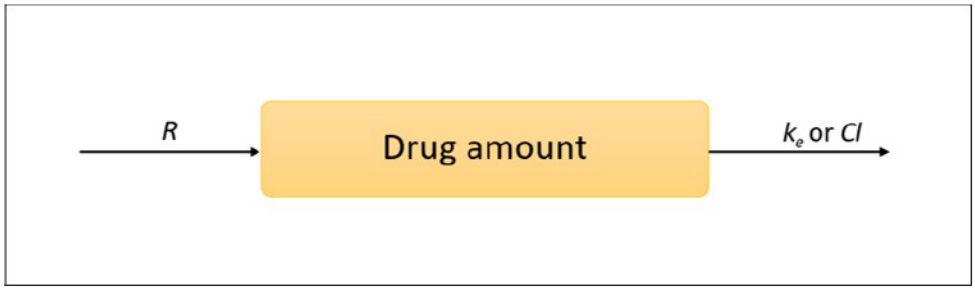



Figure 2.4: Scheme for one-compartment IVI (intravenous infusion). $R$ is infusion rate constant, $k_e$ is elimination rate constant and $Cl$ is total plasmatic clearance (drawn in PowerPoint).

*time-concentration equation is the following with first-order reactions:*

$$C(t) = \frac{R}{k_e V_d}(1 - e^{-k_e t}). \tag{2.16}$$

Proof:

The differential equation for $C(t)$ is [11]:

$$\frac{dC(t)}{dt} = \frac{R}{V_d} - k_e \cdot C(t).$$

Using Laplace transforms (see [21]), it can be integrated to give (2.16). In fact, the Laplace transforms is an very complicated integral transform. Thus, to make the proof more simple for the readers, now we are going to proof that the derivative of (2.16) satisfies the differential equation for $C(t)$, i.e., that

$$\frac{dC(t)}{dt} = \frac{d\left(\frac{R}{k_e V_d}(1 - e^{-k_e t})\right)}{dt} = \frac{R}{V_d} - k_e \cdot C(t).$$

Differentiating the expression for $C(t)$ in (2.16),

$$\frac{dC(t)}{dt} = \frac{d\left(\frac{R}{k_e V_d}(1 - e^{-k_e t})\right)}{dt},$$

we get

$$\begin{aligned}\frac{dC(t)}{dt} &= \frac{R}{k_e V_d}\cdot\frac{d(1-e^{-k_e t})}{dt}\\ &= \frac{R}{k_e V_d}\cdot(0+k_e e^{-k_e t})\\ &= \frac{R}{k_e V_d}\cdot k_e e^{-k_e t}\\ &= \frac{R}{V_d}\cdot e^{-k_e t}.\end{aligned}$$

On the other hand, if $C(t)$ equals the expression in (2.16), then:

$$\begin{aligned}\frac{R}{V_d}-k_e\cdot C(t) &= \frac{R}{V_d}-k_e\cdot\frac{R}{k_e V_d}(1-e^{-k_e t})\\ &= \frac{R}{V_d}-\frac{k_e R}{k_e V_d}+\frac{k_e R}{k_e V_d}\cdot e^{-k_e t}\\ &= \frac{R}{V_d}\cdot e^{-k_e t}. \quad \square\end{aligned}$$

As it is perceptible from the equation (2.16), during the long-term infusion performed by constant rate, the drug concentration in the distribution area is getting closer to a definite value - the plateau concentration, i.e. the steady state concentration $C_{ss}$. In this case

$$e^{-k_e t}=0,$$

thus from (2.16) we get:

$$C_{ss}=\frac{R}{k_e V_d}. \tag{2.17}$$

Alternatively, we can show this formula for $C_{ss}$ similarly as we have done for multiple doses before equation (2.13). As the rate of infusion equals the rate of elimination at steady state

$$R=k_e\cdot V_d\cdot C_{ss},$$

then we have the steady state concentration $C_{ss}$, which is defined as the ratio of infusion rate constant $R$ to the total plasmatic clearance $Cl$:

$$C_{ss}=\frac{R}{k_e V_d}=\frac{R}{Cl}, \tag{2.18}$$

notice the similarity with (2.13).

As for multiple doses steady-state is achieved, which denotes a definite dynamical balance between the intake rate of the drug by the infusion and its removal by the elimination processes, where the amount of the drug discharged from the distribution area equals the amount of the drug incoming into the distribution area per time unit. Concurrently, gradually increased drug concentration during the infusion leads to increased rate of the elimination. The increase in concentration per time unit is getting lower and lower till the drug intake rate draws level with its elimination.

Since the value of the total plasmatic clearance $Cl$ during the infusion is usually constant and it is affected by functional condition of the elimination organs, the used infusion rate constant $R$ actually determines the maximal drug concentration, which can be reached in distribution area for the stated circumstances, see (2.18). The question whether a therapeutical effect can be reached or not during the long-term infusion depends on the infusion rate and how long we infuse the drug over a long period. Because effect of $A_C$, which depends on period length.

On the other hand the formula (2.16) shows that time to approach steady state concentration $C_{ss}$, does not depend on the infusion rate at all, but only on the elimination constant of the corresponding drug for a given individual. E.g. if we express the time in units of half-life, we see that min. 4-5 elimination half-lifes are necessary to obtain a drug concentration in the distribution area, which deviates less than 6% or 3% from steady state. If we give observed half-life values of majority drugs, which are usually bigger than 1h, the time to achieve steady state of the drug is relatively long during the long-term infusion, i.e. 4 to 5 hours.

In clinical conditions the infusion time is limited till a certain end time $T$, during which the drug dose is inserted into blood circulation with the total value $D$. The

concentration $C_T$, which we will reach during the time $T$, equals:

$$C_T = \frac{D}{Cl \cdot T} \cdot (1 - e^{-k_e T}). \tag{2.19}$$

As soon as we finish infusion, the drug elimination stops being compensated by its intake, thus the drug concentration immediately starts to decrease exponentially like for a single infusion:

$$C_{t>T} = C_T \cdot e^{-k_e(t-T)}. \tag{2.20}$$

We end the section with an example for illustration of formula (2.16). We have from the SPC given in [23] that the infusion of $80\,mg$ gentamicin should be given for 30 to 60 minutes. From pervious example we calculated $k_e$, but $V_d$ value was given in [23] as $17.5\,l$ for a $70\,kg$ patient. From the mean of the proposed infusion times we can find out $R$ as follows:

$$R = 80 \cdot \frac{60}{45} = 106.67\,mg/h.$$

Thus, for the calculation of formula (2.16) we have all values. In Excel we calculated concentration change for each 1 hour, as we can see in Figure 2.5.

Remark: if salt factor $S$ and bioavailability $F$ play a role, then $D$ must be replaced with $S \cdot F \cdot D$ in the equation (2.19).

## 2.4 Extravascular drug application

Extravascular drug application is a drug administration by any other route than the intravenous route. Extravascular drug application is represented in practice in different forms. According to occurrence frequency first of all is oral administration, further examples are subcutaneous and intramuscular injection.

However, from the point of view of pharmacokinetic models of the compartment type model, it is not essential through what specific route the drug is administered to the organism. At this level of drug modeling, it is crucial that in extravascular mode

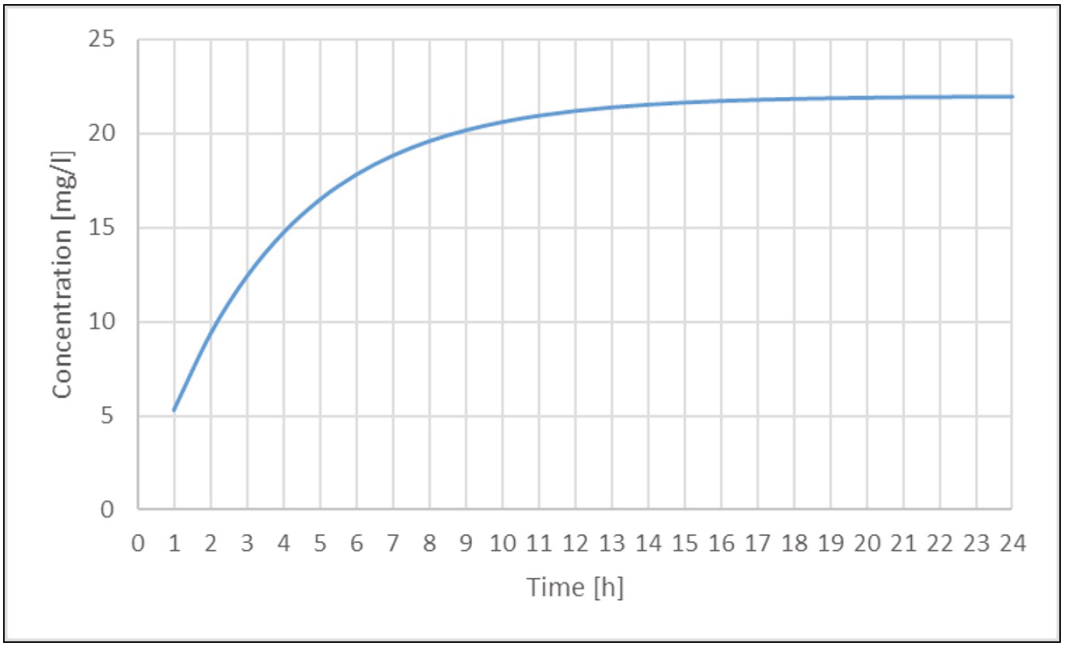



Figure 2.5: Plasma concentration versus time profile of 80 $mg$ gentamicin administered in infusion form (according to values given in [23]).

of administration, unlike intravascular application, the drug must overcome a certain biological barrier to get into the systemic circulation that we consider to be an integral part of the distribution area. This process is called absorption of the drug from the application site. During this process, however, some losses may occur, so that part of the administered drug will not reach the distribution area (incomplete absorption). These losses should be taken into account especially when given orally.

Notice that the administered drug amount into the organism by intravenous (100 % drug reaches system circulation) and extravascular way (some part of the drug yields due to elimination, degradation ect.) is different. That differency is described by the *bioavailability* ($F$) - it refers to the degree and rate at which an administered drug is absorbed by the body's circulatory system, the systemic circulation. It can be computed

as

$$F = \frac{A_{C_{(e.v.)}}}{A_{C_{(i.v.)}}}, \tag{2.21}$$

where $A_{C_{(e.v.)}}$ is the $A_C$ of the extravascular drug application, $A_{C_{(i.v.)}}$ is the $A_C$ of the intravascular drug application, both determined from corresponding blood samples.

For these reasons bioavailability $F$ of the drug becomes an important quantitative indicator. Therefore, the fact that the bioavailability of the drug may not be complete (i.e. 100 %) for various reasons, must be taken into account when formulating pharmacokinetic models, describing the movement of the drug in the organism, after extravascular administration.

A block diagram of a single-compartment pharmacokinetic model with extravascular application of the drug is shown in Figure 2.6. From the diagram it can be seen that the loss of the drug from the site of application is achieved in two concurrently running processes by absorption into the distribution area and by losses prior to entering the distribution area. Both of these processes summarize the process of disappearing of the drug from the site of absorption. For the rate constants characterizing these processes, therefore, we define:

$$k_d = k_a + k_l$$

where $k_d$ is the rate constant of the disappearance of the drug from the site of application.

We can look at the disappearance of the drug from the application point as to elimination from a single-compartment model. The time course of this process is described, like in (2.1), with a monoexponential expression. As the volume of distribution of the site of absorption is hard to determine, the expression is given in drug amount, instead of drug concentration.

$$N_A(t) = D \cdot e^{-k_d t}, \tag{2.22}$$

where:

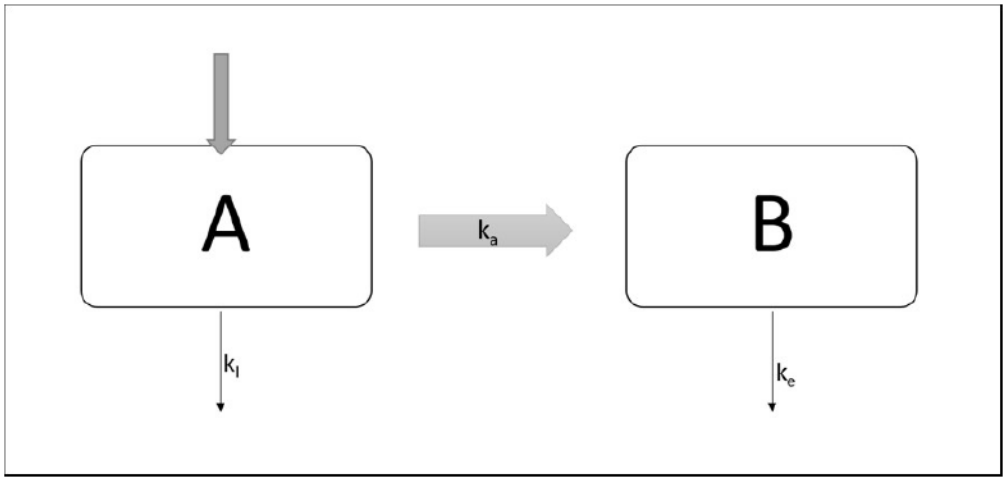



Figure 2.6: A block diagram of a single-compartment pharmacokinetic model with extravascular application of the drug at its incomplete availability: A-application site, B-distribution area, $k_a$-absorption rate constant, $k_l$-rate constant of loss processes, $k_e$-elimination rate constant (drawn in PowerPoint).

$N_A(t)$ $[mg]$ = the drug amount at application point,

$D$ $[mg]$ = the given dose of the drug,

$k_d$ $[h^{-1}]$ = the rate constant of the disappearing drug from the application point.

From the therapeutical point of view we are mostly interested in time course concentration change in the distribution area. The time course concentration is given in the next theorem.

**Theorem 2.4.1** *The time course concentration for extravascular application in the central compartment is given by:*

$$C(t) = F \cdot \frac{C_0 \cdot k_d}{k_d - k_e} \cdot \left(e^{-k_e t} - e^{-k_d t}\right). \tag{2.23}$$

Proof:

We use here the same method as for proving (2.16). Now, we try to proof if the derivative

of (2.23) satisfies the following differential equation [4]:

$$\frac{dC(t)}{dt} = F \cdot k_d \cdot C_A(t) - k_e \cdot C(t),$$

where $C_A(t)$ is expressed as:

$$C_A(t) = \frac{N_A(t)}{V_d}.$$

Differentiating (2.23) we get:

$$\begin{aligned}
\frac{dC(t)}{dt} &= \frac{d\left(F \cdot \frac{C_0 \cdot k_d}{k_d - k_e} \cdot \left(e^{-k_e t} - e^{-k_d t}\right)\right)}{dt} \\
&= F \cdot \frac{C_0 \cdot k_d}{k_d - k_e} \cdot \left(k_d e^{-k_d t} - k_e e^{-k_e t}\right) \\
&= F \cdot \frac{C_0 \cdot k_d}{k_d - k_e} \cdot \left(k_d e^{-k_d t} - k_e e^{-k_d t} + k_e e^{-k_d t} - k_e e^{-k_e t}\right) \\
&= F \cdot \frac{C_0 \cdot k_d}{k_d - k_e} \cdot (k_d - k_e) \cdot e^{-k_d t} + F \cdot \frac{C_0 \cdot k_d}{k_d - k_e} \cdot (e^{-k_d t} - e^{-k_e t}) \cdot k_e \\
&= F \cdot C_0 \cdot k_d \cdot e^{-k_d t} - F \cdot \frac{C_0 \cdot k_d}{k_d - k_e} \cdot (e^{-k_e t} - e^{-k_d t}) \cdot k_e \\
&= F \cdot k_d \cdot C_0 \cdot e^{-k_d t} - k_e \cdot C(t)\,. \quad \square
\end{aligned}$$

Unlike with intravenous infusion, the drug concentration ascends as far as possible till a certain maximum, then again descends (see Figure 2.7).

**Lemma 2.4.2** *Time of maximum concentration $t_{max}$ depends only on the values of the rate constants $k_d$ and $k_e$ according to the formula:*

$$t_{max} = \frac{1}{k_d - k_e} \cdot \ln \frac{k_d}{k_e}. \tag{2.24}$$

Proof:

The $t_{max}$ is the $t$ for which $C'(t)$ is zero. Using (2.23):

$$\begin{aligned}
C'(t) &= F \cdot \frac{C_0 \cdot k_d}{k_d - k_e} \cdot (-k_e e^{-k_e t} - (-k_d) e^{-k_d t}) \\
&= F \cdot \frac{C_0 \cdot k_d}{k_d - k_e} \cdot (k_d e^{-k_d t} - k_e e^{-k_e t}).
\end{aligned}$$

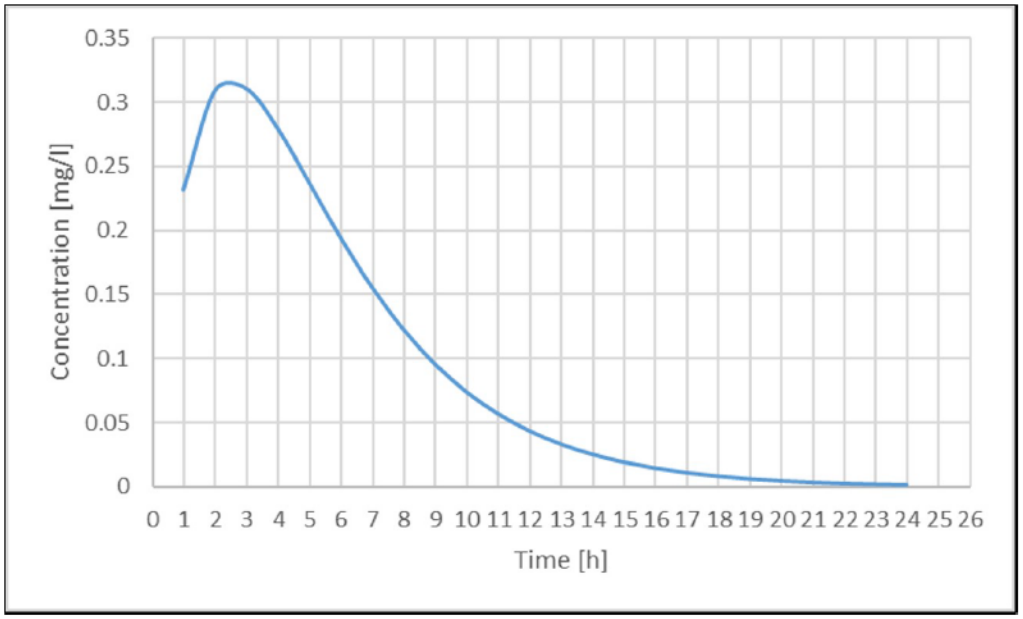



Figure 2.7: Plasma concentration versus time profile of i.m. administered 80 $mg$ gentamicin for the central compartment. $k_d$ value is hypothetically taken twice more than $k_e$ value (inspired from [13]) and computed in Excel.

If $C'(t) = 0$, then

$$\begin{aligned}
F \cdot \frac{C_0 \cdot k_d}{k_d - k_e} \cdot (k_d e^{-k_d t} - k_e e^{-k_e t}) &= 0 \Leftrightarrow \\
k_d e^{-k_d t} - k_e e^{-k_e t} &= 0 \Leftrightarrow \\
\ln(k_d e^{-k_d t}) &= \ln(k_e e^{-k_e t}) \Leftrightarrow \\
\ln(k_d) + \ln(e^{-k_d t}) &= \ln(k_e) + \ln(e^{-k_e t}) \Leftrightarrow \\
\ln(k_d) - k_d t &= \ln(k_e) - k_e t \Leftrightarrow \\
-k_d t + k_e t &= -\ln(k_d) + \ln(k_e) \Leftrightarrow \\
k_d t - k_e t &= \ln(k_d) - \ln(k_e) \Leftrightarrow \\
t(k_d - k_e) &= \ln\left(\frac{k_d}{k_e}\right) \Leftrightarrow \\
t &= \frac{\ln(\frac{k_d}{k_e})}{k_d - k_e} \Leftrightarrow
\end{aligned}$$

$$t_{max} = \frac{1}{k_d - k_e} \cdot \ln \frac{k_d}{k_e}. \quad \square$$

On the other hand, maximum concentration value is directly proportional to the drug amount, which is administered to the bloodstream, as shown by the lemma below:

**Lemma 2.4.3**

(2.25) $$C_{max} = \frac{F \cdot D}{V_d} \cdot \left(\frac{k_d}{k_e}\right)^{\frac{k_e}{k_e - k_d}}.$$

Proof:

To find $C_{max}$ we replace $t$ in (2.23) with $t_{max}$ from (2.24) and compute:

$$C_{max} = F \cdot \frac{C_0 \cdot k_d}{k_d - k_e} \cdot (e^{-k_e t_{max}} - e^{-k_d t_{max}}), \quad t_{max} = \frac{1}{k_d - k_e} \cdot \ln \frac{k_d}{k_e}.$$

Hence,

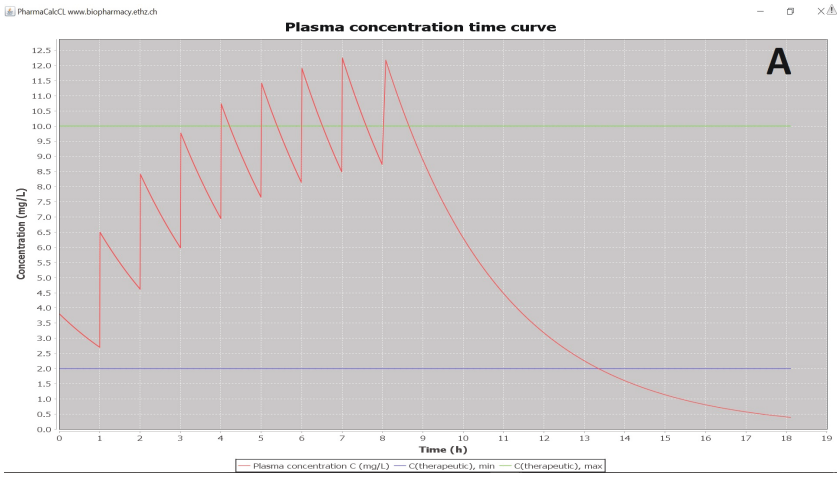
$$\begin{aligned}
e^{-k_e t_{max}} - e^{-k_d t_{max}} &= e^{-k_e \frac{\ln\left(\frac{k_d}{k_e}\right)}{k_d - k_e}} - e^{-k_d \frac{\ln\left(\frac{k_d}{k_e}\right)}{k_d - k_e}} \\
&= e^{-\frac{k_e}{k_d - k_e} \cdot \ln\left(\frac{k_d}{k_e}\right)} - e^{-\frac{k_d}{k_d - k_e} \cdot \ln\left(\frac{k_d}{k_e}\right)} \\
&= e^{\ln\left(\left(\frac{k_d}{k_e}\right)^{-\frac{k_e}{k_d - k_e}}\right)} - e^{\ln\left(\left(\frac{k_d}{k_e}\right)^{-\frac{k_d}{k_d - k_e}}\right)} \\
&= \left(\frac{k_d}{k_e}\right)^{-\frac{k_e}{k_d - k_e}} - \left(\frac{k_d}{k_e}\right)^{-\frac{k_d}{k_d - k_e}} \\
&= \left(\frac{k_d}{k_e}\right)^{-\frac{k_e}{k_d - k_e}} \cdot \left(1 - \left(\frac{k_d}{k_e}\right)^{\frac{k_e}{k_d - k_e} - \frac{k_d}{k_d - k_e}}\right) \\
&= \left(\frac{k_d}{k_e}\right)^{-\frac{k_e}{k_d - k_e}} \cdot \left(1 - \left(\frac{k_d}{k_e}\right)^{-1}\right) \\
&= \left(\frac{k_d}{k_e}\right)^{-\frac{k_e}{k_d - k_e}} \cdot \left(1 - \frac{k_e}{k_d}\right) \\
&= \left(\frac{k_d}{k_e}\right)^{-\frac{k_e}{k_d - k_e}} \cdot \left(\frac{k_d - k_e}{k_d}\right).
\end{aligned}$$

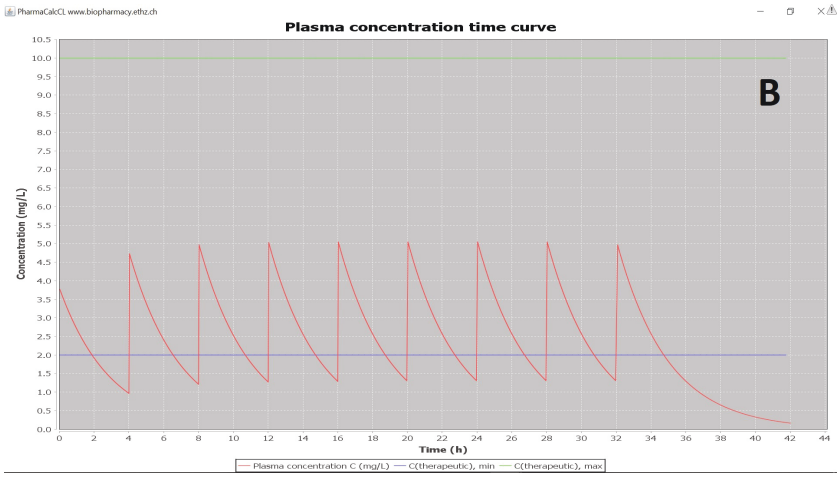
We computed that

$$e^{-k_e t_{max}} - e^{-k_d t_{max}} = \left(\frac{k_d}{k_e}\right)^{-\frac{k_e}{k_d - k_e}} \cdot \left(\frac{k_d - k_e}{k_d}\right).$$

Now, finally we can compute $C_{max}$ following:

$$\begin{aligned} C_{max} &= F \cdot C_0 \cdot \frac{k_d}{k_d - k_e} \cdot \left(\frac{k_d}{k_e}\right)^{-\frac{k_e}{k_d - k_e}} \cdot \frac{k_d - k_e}{k_d} \\ &= \frac{F \cdot D}{V_d} \cdot \left(\frac{k_d}{k_e}\right)^{\frac{k_e}{k_e - k_d}} . \quad \square \end{aligned}$$



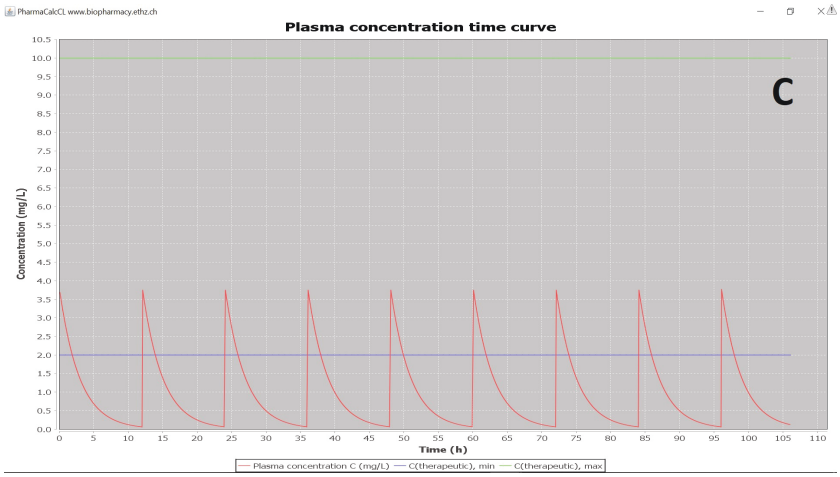




Figure 2.8: Difference between the dosing interval $\tau$ and the half-life $t_{\frac{1}{2}}$ for $80\,mg$ gentamicin (computed in the software PharmaCalcCL (see [5])).

# Chapter 3

# Two-compartmental models

In this chapter we discuss about two-compartmental models. We will consider single dose injection and infusion. We give mathematical proofs of pharmacokinetic equations. The description in this chapter is based on the book [13].

This model consists of two compartments, where the drug is administered into the central compartment and it is reversibly connected with the peripheral compartment (see Figure 3.2). The intensity of the reversible transfer of the drug between the two compartments is expressed by the rate constants $k_c$ and $k_p$. Excretion of the drug from the central compartment, which is most often supposed, is characterized by the rate constant $k_{e(c)}$, while excretion from the peripheral compartment is characterized by the rate constant $k_{e(p)}$. All these rate constants are overall denoted as microconstants.

Already decades ago, it was observed that the time course of concentration decline of intravenously administered drugs in the blood plasma in the first period immediately after the injection is considerably steeper than would be expected assuming a one-compartment model. For this reason, two-compartment open models began to be widely used. The term open model means that the administered drug amount, after its metabolism, is eliminated by an excretory mechanism.

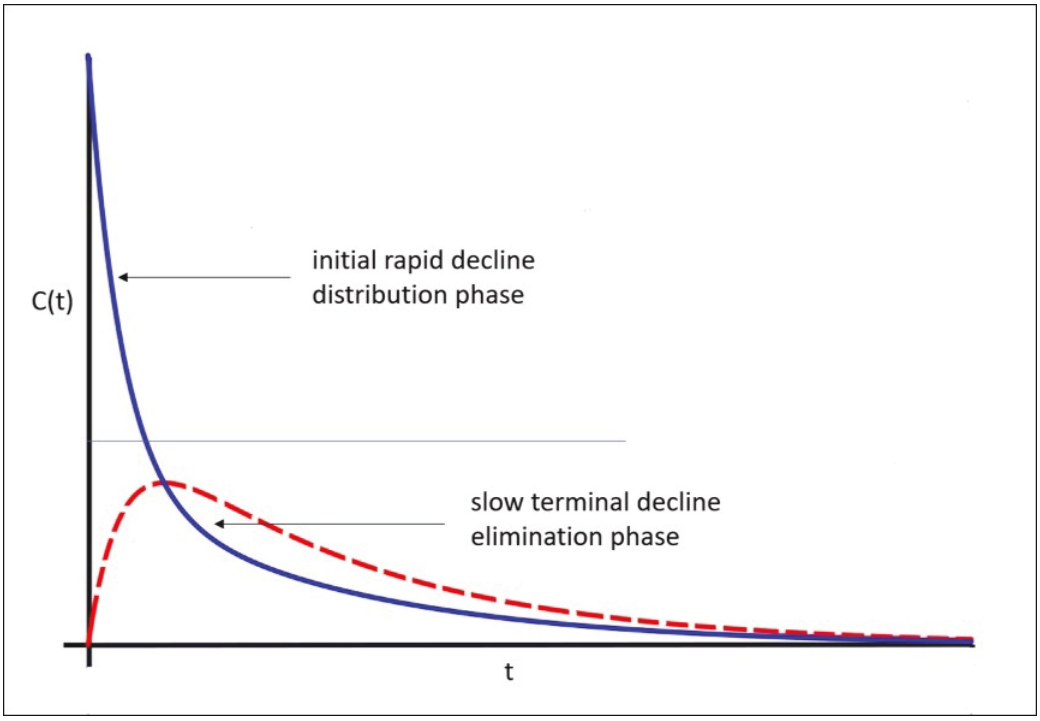



Figure 3.1: Changes in the drug concentrations in the central (plasma), blue curve, and peripheral (tissues) compartment, red dash curve, after IV bolus of a drug that fits two-compartment model (the picture is taken from [7] and modified in Paint).

## 3.1 Single dose injection

The time course of the decline in drug concentration, after intravenous injection, in the central compartment of the two-compartment model is represented by a two-phase concentration curve (see Figure 3.1). Immediately after the injection there is a very rapid decline, which in the subsequent period is going over in a slower decline. The rapid decline immediately after the injection is only partially caused by the drug secretion, it is also caused by the transfer of the drug to the peripheral compartment, which occurs in parallel with the elimination. This is the so-called distribution phase, however, it only takes place until the drug concentrations in both compartments are balanced. Then, the

so-called elimination phase begins, in which drug secretion from the central compartment continues, but movement of the drug molecules between the compartments prevails, unlike the distribution phase, in the opposite direction. The concentration of the drug in the peripheral compartment is no longer increasing, because at the moment of concentration balance the maximum is reached. On the contrary, it gradually declines in proportion to how the excretion discharges the central compartment. Each amount of drug that is excreted from the central compartment is partially replaced by the passage of a certain amount from the peripheral compartment. This also causes the decline in the drug concentration in the central compartment to be slower in the elimination phase than would correspond to the rate of drug elimination.

Mathematically the time course in the central compartment can be expressed by biexponential dependence:

$$C(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}, \tag{3.1}$$

where:

$\alpha$ and $\beta$ = hybrid first order constants for rapid distribution phase and slow elimination phase respectively,

$A$ and $B$ are additional coefficients defined as:

$$A = \frac{\alpha - K_p}{\alpha - \beta} \cdot \frac{D}{V_{d(c)}}, \qquad B = \frac{K_p - \beta}{\alpha - \beta} \cdot \frac{D}{V_{d(c)}} \tag{3.2}$$

where:

$K_p$ = elimination constant for peripheral compartment,

$D$ = injected dose,

$V_{d(c)}$ = distribution volume of the drug in the central compartment.

$\alpha$, $\beta$ and $K_p$ can be determined experimentally from the decay of plasma concentration. $V_{d(c)}$ is determined from $C_0$.

Due to the reversible connection between the central and peripheral compartments, the $\alpha$ and $\beta$ constants in this dependence are not simple rate constants that would express

the intensity of a single pharmacokinetic process, as we have seen in a one-compartmental pharmacokinetic model. On the contrary, these parameters characterize the course of actions that are the result of several pharmacokinetic processes. For this reason, they are also the function of all microconstants describing the model. To distinguish them, they are therefore often referred to as hybrid constants. The $\alpha$ hybrid constant characterizes the intensity of the drug concentration decline in its distribution phase, which is also referred to as the $\alpha$-phase, whereas the $\beta$ hybrid constant expresses its intensity in the elimination phase, also referred to as the $\beta$-phase. Because hybrid constants characterize processes of a more complex nature, their clinical significance is greater than that of individual microconstants. In practical pharmacotherapy we are much more interested in how intensive the blood plasma concentration of the drug declines than the intensity of elimination, so that we can determine the appropriate dosing frequency accordingly.

In the general case where the elimination of the drug is not located in a single compartment, alongside with the $\alpha$ and $\beta$ hybrid constants we can only evaluate the rate constants of the total elimination of the drug (elimination constants) from the individual compartments. These constants are defined as:

$$K_c = k_c + k_{e(c)} \qquad K_p = k_p + k_{e(p)} \tag{3.3}$$

where:

$K_c$ = elimination constant for central compartment,

$K_p$ = elimination constant for peripheral compartment,

$k_c$ = rate of transfer from central to peripheral compartment,

$k_p$ = rate of transfer from peripheral to central compartment,

$k_{e(c)}$ = rate of elimination from central compartment,

$k_{e(p)}$ = rate of elimination from peripheral compartment.

In variants with exclusive excretion from the central or peripheral compartment, either $k_{e(c)}$ or $k_{e(p)}$ equals zero. The elimination rate constants therefore have a variable

interpretation depending on which variant of the two-compartmental pharmacokinetic model is appropriate.

A widely used variant with exclusive excretion from the central compartment has its merits. The central compartment volume, determined by the pharmacokinetic analysis, largely exceed the volume of blood plasma. In view of rapid exchange with some tissues, therefore, it is assumed that the central compartment contains not only extracellular fluid, but also highly perfused tissues, including major elimination organs (like liver, kidneys, lungs). This automatically implies the idea of localizing the overall elimination into the central compartment. However, in situations where the question of excretion from central or from peripheral compartment is more or less subject to certain speculations, it is much more realistic to note that instead of the rate constants of the intercontinuous transfer, we determine rather the values of the rate constants of the total drug elimination (i.e. $K_c$ and $K_p$) from both compartments.

Comparison of all three variants of the two-compartmental pharmacokinetic model, however, shows that there are definitely characteristics of this model whose value is invariant for all three variants. In literature, for such characteristics, the name model-independent parameters is used. The existence of such parameters makes it possible to bypass excretion compartments specification. These are parameters that can be expressed by formulas in which no microconstants emerge. These include:

**1. The half-lives of the distribution and elimination phases** of the concentration decline of the drug given by the formulas:

$$t_{\frac{1}{2}}(\alpha) = \frac{\ln 2}{\alpha} \approx \frac{0.693}{\alpha}, \qquad t_{\frac{1}{2}}(\beta) = \frac{\ln 2}{\beta} \approx \frac{0.693}{\beta}; \tag{3.4}$$

notice the similarity with (2.3). Both $t_{\frac{1}{2}}(\alpha)$ and $t_{\frac{1}{2}}(\beta)$ are biological half-lives. In case of two-compartment kinetics, we can not interpret biological half-life as the time at which the drug concentration drops to half as for a one-compartment model.

**2. The apparent initial concentration of the drug** in the central compartment

$C_0(t = 0)$ and from that the derived **distribution volume of the central compartment** $V_{d(c)}$. Values of these parameters after a rapid intravenous injection are determined by the formulas:

$$V_{d(c)} = \frac{D}{C_0} \tag{3.5}$$

notice the similarity with (2.2).

The concentration of the drug in the central compartment is called "apparent" concentration. Because, there are several reasons. At first, we can not inject the whole does instantly. It takes some definite time to administer injection dose, which depends on the volume of the injection. Thus, immediate intravenous injection is actually short-term, rapid infusion. Secondly, the equation (3.5) was derived assuming an immediate and even dispersion of the entire administered dose in the central compartment, which is de facto unrealistic. The dispersion of drug molecules in the central compartment has more likely gradual character, which is also in line with the concept of volume distribution as a function of time. Thirdly, notice that, before the drug enters the systemic circulation, first it must pass through the small pulmonary circulation, where drug can yield to biotransformation. It can cause that, a smaller amount of the administered drug will flow into the systemic circulation. Therefore, to obtain more realistic values for "apparent" concentration (also volume of distribution), it is recommended to consider each intravenous injection as a short-term rapid infusion.

**3. The area under the curve** of the drug concentration in the central compartment $A_C$ and from that derived **the total plasma clearance** $Cl$. In the two-compartmental model the clearance $Cl$ is computed same as in (2.8), i.e.:

$$Cl = \frac{D}{A_C}.$$

**Lemma 3.1.1** *In the two-compartment model, the $A_C$ parameter satisfies:*

$$A_C = \frac{A}{\alpha} + \frac{B}{\beta}. \tag{3.6}$$

Proof:

$$\begin{aligned} A_C = \int_0^\infty (A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}) dt &= \int_0^\infty A \cdot e^{-\alpha t} dt + \int_0^\infty B \cdot e^{-\beta t} dt \\ &= \left[ A \cdot \frac{e^{-\alpha t}}{-\alpha} \right]_0^\infty + \left[ B \cdot \frac{e^{-\beta t}}{-\beta} \right]_0^\infty \\ &= A \left( \frac{e^{-\infty}}{-\alpha} - \frac{e^0}{-\alpha} \right) + B \left( \frac{e^{-\infty}}{-\beta} - \frac{e^0}{-\beta} \right) \\ &= A \left( 0 - \frac{1}{-\alpha} \right) + B \left( 0 - \frac{1}{-\beta} \right) \\ &= \frac{A}{\alpha} + \frac{B}{\beta}. \quad \square \end{aligned}$$

The $A_C$ value is given by all four parameters of the biexponential dependence (see (3.1)), to obtain them it is not needed to specify from which compartment the drug is excreted. Here, $A_C$ is not obtained from an integration rule, but for other compartmental models this is in general needed.

**4. Fractional clearance** $k_f$ of the drug is defined as the ratio of total plasma clearance $Cl$ and volume of the central compartment $V_{d(c)}$. It can also be expressed as a function of both hybrid constants $\alpha$, $\beta$ and elimination constant $K_p$.

**Lemma 3.1.2** *There holds:*

$$k_f = \frac{Cl}{V_{d(c)}} = \frac{\alpha \cdot \beta}{K_p} \tag{3.7}$$

Proof:

$$\begin{aligned} k_f &= \frac{Cl}{V_{d(c)}} \\ &= \frac{\frac{D}{A_C}}{V_d} \\ &= \frac{D}{V_d} \cdot \frac{1}{\frac{A}{\alpha} + \frac{B}{\beta}} \\ &= \frac{D \cdot \alpha \cdot \beta}{V_d (A\beta + B\alpha)} \end{aligned}$$

$$
\begin{aligned}
&= \frac{D \cdot \alpha \cdot \beta}{V_d \cdot \frac{D}{V_d}\left(\frac{\beta(\alpha - K_p)}{\alpha - \beta} + \frac{\alpha(K_p - \beta)}{\alpha - \beta}\right)} \\
&= \frac{\alpha \cdot \beta}{\frac{K_p(\alpha - \beta)}{\alpha - \beta}} \\
&= \frac{\alpha \cdot \beta}{K_p}. \quad \square
\end{aligned}
$$

This parameter shows how large the relative proportion of the volume of the central compartment is cleared from the drug per unit of time, therefore $k_f$ has units $h^{-1}$. Likewise, it is far more appropriate to interpret the elimination constant as fractional clearance, comparison with (2.6).

**5. The volume of distribution computed from the area under the curve of the drug concentration** is normally calculated according to the next formula:

$$V_d(area) = \frac{D}{\beta \cdot A_C}. \tag{3.8}$$

It is often also called the *apparent volume of distribution*. By using the equations (2.7) and (3.4), the equation (3.8) can be modified to:

$$V_d(area) = \frac{D}{\beta \cdot A_C} = \frac{D}{\frac{\ln 2}{t_{\frac{1}{2}}(\beta)} \cdot \frac{D}{Cl}} = \frac{Cl \cdot t_{\frac{1}{2}}(\beta)}{\ln 2} \approx 1.44 \cdot Cl \cdot t_{\frac{1}{2}}(\beta). \tag{3.9}$$

It is evident that, this is the volume, which is cleaned of the drug in about 1.5 biological half-lives. This parameter is often advantageously used to re-determine the total plasma clearance based on the formula:

$$Cl = \beta \cdot V_d(area), \tag{3.10}$$

following from (2.8) and (3.8). This makes it possible to bypass the model variant dependent formula:

$$Cl = k_c \cdot V_{d(c)} \tag{3.11}$$

and which is also valid only, if the drug is exclusively excreted from the central compartment.

**6. Time of onset of the maximum concentration of drug** $t_{max}$ in the peripheral compartment:

$$t_{max} = \frac{1}{\alpha - \beta} \cdot \ln \frac{\alpha}{\beta}; \tag{3.12}$$

notice the similarity with (2.24) and proof is also analogous. It is the only parameter that characterizes the processes in the peripheral compartment, which is independent of the two-compartment model variant. However, it should be kept in mind that the maximum drug concentration in the peripheral compartment occurs when the drug concentration equals the concentration in the central compartment.

## 3.2 Infusion

The central compartment of the two-compartmental pharmacokinetic model plays an important role in infusion drug administration, which fully reflects the two-phase nature of the drug movement. At the beginning, the concentration of the drug in the central compartment is rather slower than in the one-compartment model (distribution phase) at a constant rate of infusion. At this stage, part of the administered drug moves from central to peripheral compartment, until the concentrations in both compartments are equalized. In the second phase, due to the reversal of the concentration gradient, the concentration in the central compartment increases a little faster, comparing to the one-compartment model.

Nevertheless, to achieve steady-state concentration in a two-compartment model, as it was with a single-compartment model, is needed a sufficiently long infusion time. It is also shown in the mathematical expression of the time course of changes in drug concentration in the central compartment:

$$C(t) = \frac{R}{Cl} - \frac{\alpha - K_p}{\alpha(\alpha - \beta)} \cdot \frac{R}{V_{d(c)}} \cdot e^{-\alpha t} - \frac{K_p - \beta}{\beta(\alpha - \beta)} \cdot \frac{R}{V_{d(c)}} \cdot e^{-\beta t} \tag{3.13}$$

The steady state concentration $C_{ss}$ is given by the ratio of infusion rate $R$ and total plasma

clearance $Cl$, as it was with the single-compartment pharmacokinetic mode. To achieve steady state concentration $C_{ss}$, it is necessary to assess the hybrid constant $\beta$ according to the number of past half-lives, due to the two-phase kinetics. After the short-term infusion, the drug concentration in the central compartment starts decrease like two-phase of the intravenous injection.

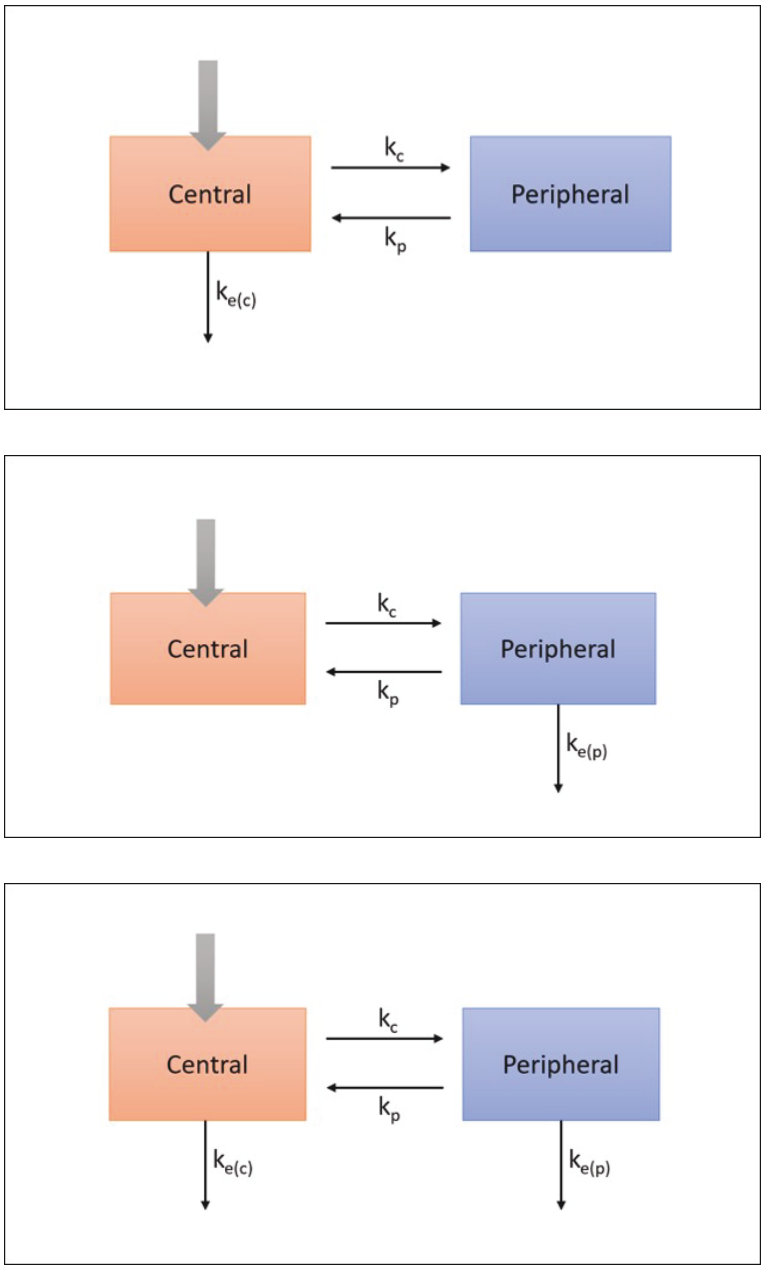



Figure 3.2: Variants of two-compartment open model: A) with exclusive excretion from the central compartment; B) with exclusive excretion from the peripheral compartment; C) with excretion from the both compartments. $k_c$, $k_p$, $k_{e(c)}$ and $k_{e(p)}$ are first-order rate constants: $k_c$ is rate of transfer from central to peripheral compartment, $k_p$ is rate of transfer from peripheral to central compartment, $k_{e(c)}$ is rate of elimination from central compartment, $k_{e(p)}$ is rate of elimination from peripheral compartment (drawn in PowerPoint).

# Chapter 4

# Approximation of the AUC

In practice, the drug concentration is measured at certain discrete points in time, the moments when blood samples are taken, and an integration rule is often used to estimate $A_C$ (though in some cases it can be computed exactly, for example when holds (3.6)). There are many methods, which are used to numerically approximate definite integrals. In this chapter we will describe in some detail the *Trapezoidal rule* and *Simpson's rule* to estimate $A_C$. We will compare them on numerical experiments in MATLAB [18].

## 4.1 Trapezoidal rule

The trapezoidal rule is a numerical method used to approximate any definite integral of the form

$$\int_a^b f(x)dx.$$

The region under the graph of the function $f(x)$ is approximated by a trapezoid (see Figure 4.1) and its area is calculated, giving the following approximation [15]:

$$\int_a^b f(x)dx \approx (b-a)\left[\frac{f(a)+f(b)}{2}\right].$$

**Lemma 4.1.1** *The size of the area of the trapezoid in Figure 4.2 is given by*

$$(b-a)\frac{f(a)+f(b)}{2}.$$

Proof (see Figure 4.2):

From figure we can see that total area of trapezoid $S$ equals:

$$S = S_1 + S_2.$$

$S_1$ is defined as:

$$S_1 = (b-a)\cdot f(b).$$

For $S_2$ we have:

$$S_2 = \frac{(b-a)\cdot(f(a)-f(b))}{2}.$$

Then,

$$\begin{aligned} S &= S_1 + S_2 \\ &= (b-a)\cdot f(b) + \frac{(b-a)\cdot(f(a)-f(b))}{2} \\ &= \frac{2\cdot(b-a)\cdot f(b) + (b-a)\cdot f(a) - (b-a)\cdot f(b)}{2} \\ &= \frac{(b-a)\cdot f(b) + (b-a)\cdot f(a)}{2} \\ &= (b-a)\left[\frac{f(a)+f(b)}{2}\right]. \quad \square \end{aligned}$$

We can even better approximate the integral by dividing $[a,b]$ into subintervals and applying the trapezoidal rule to each subinterval, and summing the gained results. Let $x_k, 0 \le k \le n$, be a partition of $[a,b]$ such that $a = x_0 < x_1 < \ldots < x_{n-1} < x_n = b$ and $\Delta x_k$ be the length of the $k$-th subinterval ($\Delta x_k = x_k - x_{k-1}$), then

$$\int_a^b f(x)dx \approx \sum_{k=1}^{n} \frac{f(x_{k-1})+f(x_k)}{2}\Delta x_k.$$

If all $\Delta x_k$ are equal (i.e. $\Delta x_k = \frac{b-a}{n}$), then we obtain

$$\int_a^b f(x)dx \approx \frac{b-a}{n}\left[\frac{f(x_0)}{2} + \sum_{k=1}^{n-1} f(x_k) + \frac{f(x_n)}{2}\right].$$

As the resolution of the partitioning increases (that is, for larger $n$), the approximation becomes more accurate.

## 4.2 Simpson's rule

The essence of the method consists in approximating the function on the segment $[a, b]$ by an interpolation polynomial of the second degree $p_2(x)$, with interpolation points $a$, $b$ and $\frac{a+b}{2}$ [2]. Hence we consider the approximation of the function graph on the segment by a parabola (see Figure 4.3).

**Theorem 4.2.1** *Simpson's formula is the integral for the second degree interpolation polynomial on the segment* $[a, b]$*:*

$$\int_a^b f(x)dx \approx \int_a^b p_2(x)dx = \frac{b-a}{6}\left[f(a) + 4f\left(\frac{a+b}{2}\right) + f(b)\right], \tag{4.1}$$

where $f(a)$, $f(\frac{a+b}{2})$ and $f(b)$ are the values of the function at the corresponding points (at the ends of the segment and in its middle).

Proof [9]: Let $p_2(x)$ be the quadratic function interpolating at the points $(a, f(a))$, $(b, f(b))$ and $((a+b)/2, f((a+b)/2)$. We have

$$\begin{aligned}
\int_a^b p_2(x)dx &= \int_a^b (c_2x^2 + c_1x + c_0)dx \\
&= \left[\frac{c_2x^3}{3} + \frac{c_1x^2}{2} + c_0x\right]_a^b \\
&= \frac{c_2b^3}{3} + \frac{c_1b^2}{2} + c_0b - \frac{c_2a^3}{3} - \frac{c_1a^2}{2} - c_0a \\
&= \frac{b-a}{6}\left[\frac{2c_2(b^3-a^3)}{b-a} + 3c_1\frac{b^2-a^2}{b-a} + 6c_0\right].
\end{aligned}$$

The first term between brackets, $\frac{2c_2(b^3-a^3)}{b-a}$, can be simplified using

$$(b-a)(a^2+b^2+(a+b)^2) = a^2b + b^3 + b(a+b)^2 - a^3 - ab^2 - a(a+b)^2$$

$$
\begin{aligned}
&= b^3 - a^3 + a^2b + a^2b + 2ab^2 \\
&+ b^3 - ab^2 - a^3 - 2a^2b - ab^2 \\
&= 2(b^3 - a^3).
\end{aligned}
$$

Thus, summarizing,

$$\int_a^b p_2(x)dx = \frac{b-a}{6}\left[c_2(a^2+b^2+(a+b)^2) + 3c_1(b+a) + 6c_0\right].$$

Because $p_2(x)$ interpolates at the points $(a, f(a)), (b, f(b))$ and $((a+b)/2, f((a+b)/2)$, we have

$$
\begin{aligned}
&f(a) = c_2a^2 + c_1a + c_0, \\
&f\left(\frac{a+b}{2}\right) = c_2\left(\frac{b+a}{2}\right)^2 + c_1\left(\frac{b+a}{2}\right) + c_0, \\
&f(b) = c_2b^2 + c_1b + c_0
\end{aligned}
$$

and

$$
\begin{aligned}
f(a) + 4f\left(\frac{a+b}{2}\right) + f(b) &= c_2a^2 + c_1a \\
&+ c_2(a+b)^2 + 2c_1(a+b) + c_2b^2 + c_1b + 6c_0 \\
&= c_2\left(a^2 + (a+b)^2 + b^2\right) \\
&+ c_1(a + 2a + 2b + b) + 6c_0,
\end{aligned}
$$

which completes the proof. □

As with the trapezoidal formula, we will get a more accurate result if the segment $[a, b]$ is divided into $m$ subintervals, and we use each of these formulas in combination. For simplicity, we take an equidistant partition. Since we take a midpoint in each subsection, we actually have $2m$ subsections of length $\frac{b-a}{2m}$, $a = x_0 < x_1 < x_2 < ... < x_{2m-1} < x_{2m} = b$. Now we apply an approximate formula on the pairs of neighboring subsections, so that the middle point is a point with an odd index. We get the following formula [10]

$$\int_a^b f(x)dx \quad \approx \quad \frac{b-a}{6m}\left[f(a) + 4f(x_1) + f(x_2)\right] + \frac{b-a}{6m}\left[f(x_2) + 4f(x_3) + f(x_4)\right] +$$

$$+...+ \quad \frac{b-a}{6m}\left[f(x_{2m-2}) + 4f(x_{2m-1}) + f(x_b)\right],$$

respectively

$$\begin{aligned}\int_a^b f(x)dx \quad &\approx \quad \frac{h}{3}[f(a) + 2[f(x_2) + f(x_4) + ... + f(x_{2m-2})] + 4[f(x_1) + f(x_3) + \\ &+...+ \quad f(x_{2m-1})] + f(b)].\end{aligned}$$

This defines Simpson's rule.

## 4.3 Computations in MATLAB

For computations in MATLAB [18] we used the first example, which was given for equation (2.1), where we calculated values for $C_0 = 4.57\, mg/l$ and $k_e = 0.277\, h^{-1}$. Using these values we calculated the size of the area under the curve till $10^{th}$ hour (see Figure 2.1 analytically) following:

$$\begin{aligned}\int_0^{10} C_0 e^{-k_e t} dt &= C_0 \left[\frac{e^{-k_e t}}{-k_e}\right]_0^{10} \\ &= \frac{C_0}{-k_e}(e^{-k_e t} - 1) \\ &= \frac{4.57}{-0.277}(e^{-0.277 \cdot 10} - 1) \\ &= 15.4644\,.\end{aligned}$$

In MATLAB we computed the size of the area under the curve till $10^{th}$ hour for both Trapezoidal and Simpson's rule. Results are 15.5631 and 15.4649 respectively, where number of intervals were $n = 10$.

MATLAB code for Trapezoidal rule is:

```
function [int]=Trapezoidal(Fvalues,n,a,b)
%
int=Fvalues(1)/2;
for k=2:n+1
```

```
int=int+Fvalues(k);
end
int=int-Fvalues(n+1)/2;
int=int*(b-a)/n;
```

MATLAB code for Simpson's rule is:

```
function [int]=Simpson(Fvalues,n,a,b)
%
int=Fvalues(1);
for k=2:2:n
int=int+4*Fvalues(k)+2*Fvalues(k+1);
end
int=int-Fvalues(n+1);
int=int*(b-a)/(3*n);
```

Testscript for both rules:

```
a=0;
b=10;
n=10;
C0=4.57;
ke=0.277;
xvalues(1)=a;
xvalues(11)=b;
for k=2:n+1
xvalues(k)=xvalues(k-1)+(b-a)/n;
end
for k=1:n+1
Fvalues(k)=C0*exp(-ke*xvalues(k));
end
```

Next, we tried compute with lesser number of intervals, i.e. $n = 5$. Results were 15.8579 and 14.8479 respectively. From this, we can say that if area is divided into more intervals - more accurate results we get.

Also, from results we can see that the Simpson's rule is more accurate than Trapezoidal rule. It can be explained e.g. by the difference between theoretical errors. The error for Trapezoidal rule is expressed following [14]:

$$error = -\frac{(b-a)^3}{12n^2} f''(\xi),$$

where $n$ is number of intervals and $\xi$ is some number between $a$ and $b$.
For Simpson's rule it follows [25]:

$$error = -\frac{1}{90}\left(\frac{b-a}{2}\right)^5 f^{(4)}(\xi).$$

The errors are asymptotically proportional to powers of $(b-a)$, i.e. for Trapezoidal rule it is $(b-a)^3$ and for Simpson's rule it is $(b-a)^5$. Therefore, Simpson's rule is more accurate.

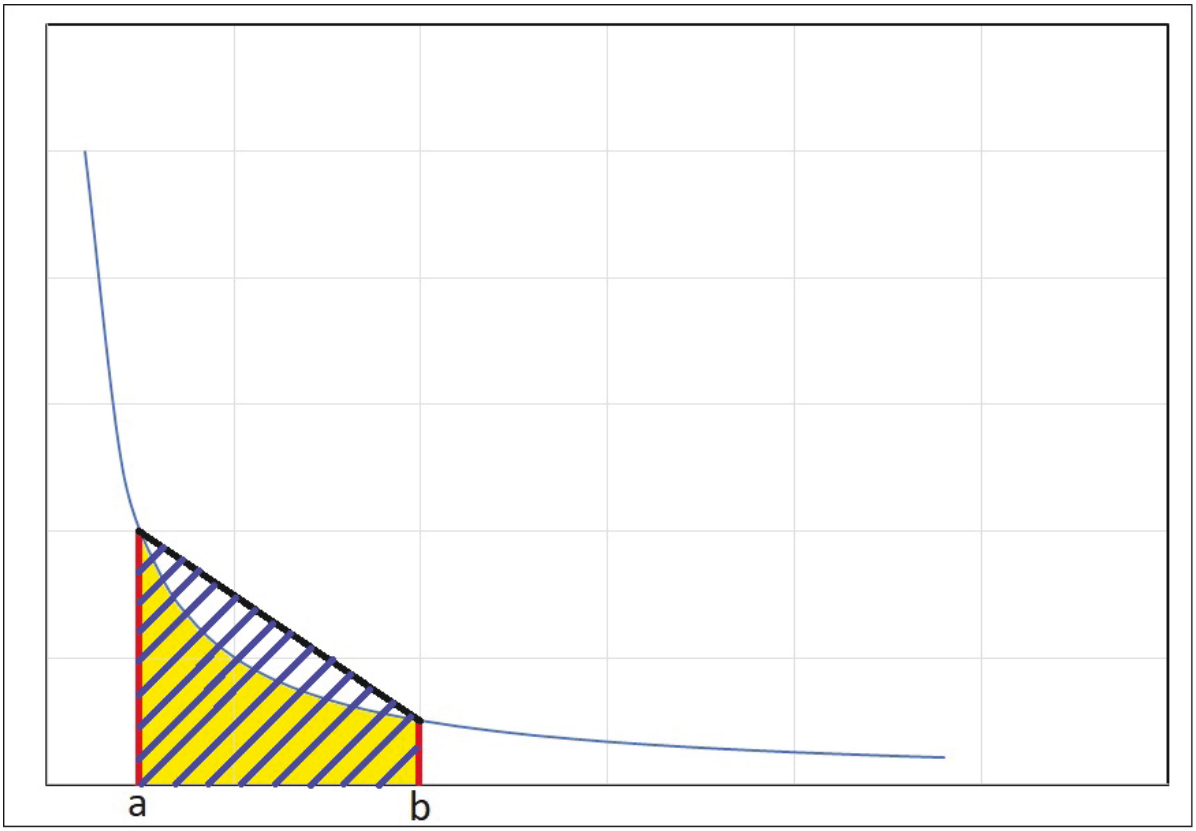



Figure 4.1: An illustration of the Trapezoid Method to Approximate a definite integral of the $f(x) = \frac{1}{x}$ function. The yellow area represents the region under the graph. The striped area represents the approximating trapezoid (computed in Excel and reworked in Paint).

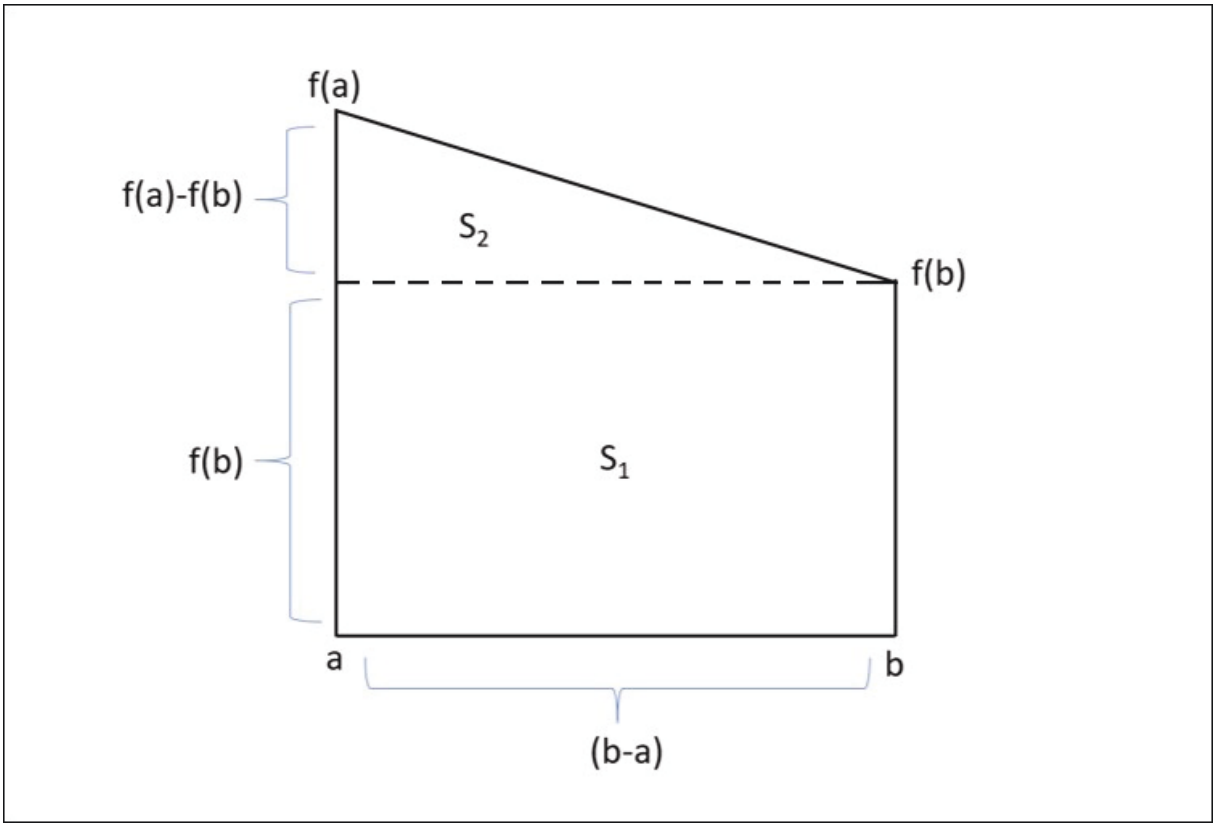



Figure 4.2: An illustration of trapezoid (drawn in PowerPoint).

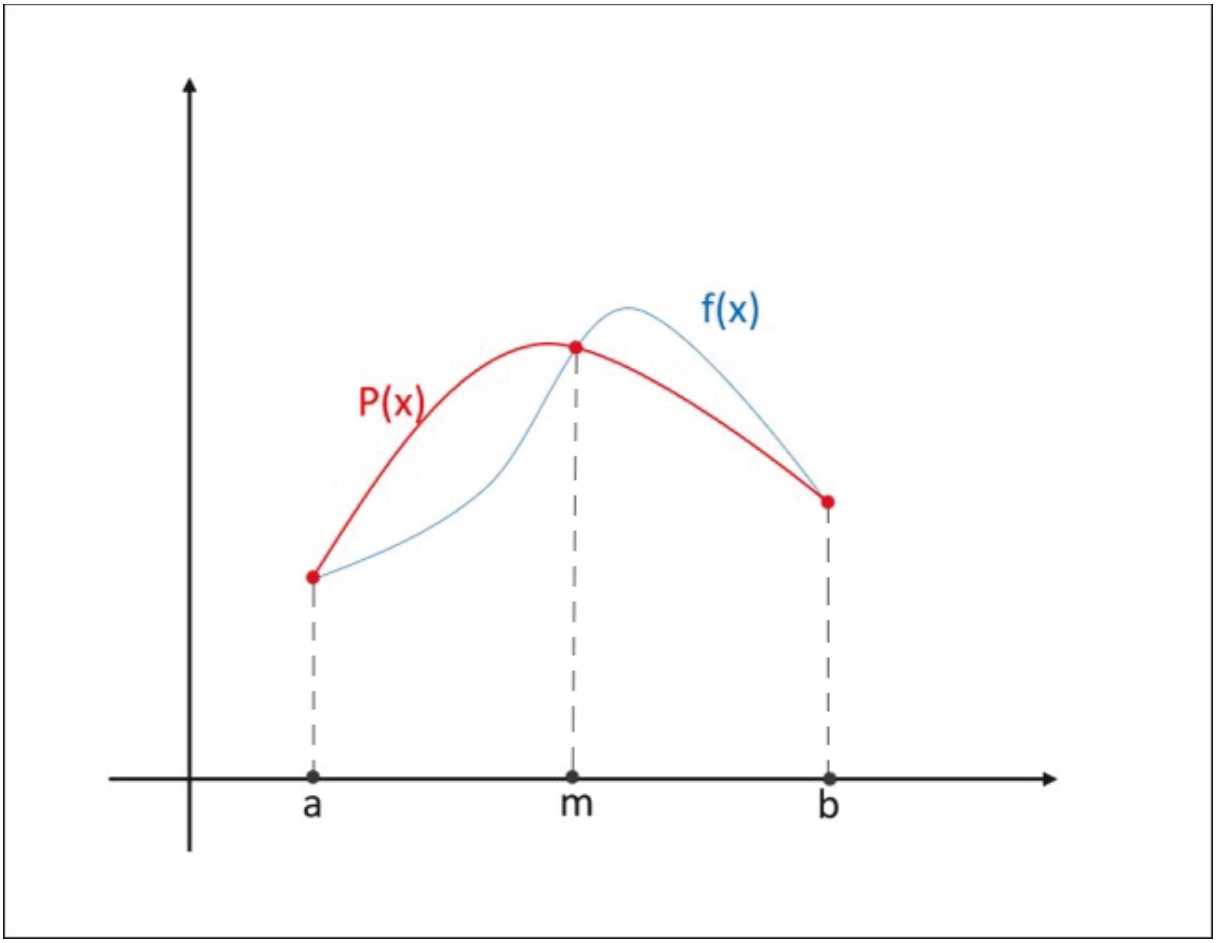



Figure 4.3: The essence of the method is the approximation of the function $f(x)$ (blue graph) by the quadratic polynomial ${}_2(x)$ (red), $m = \frac{a+b}{2}$ (drawn in PowerPoint).

# Conclusion

In our thesis we described pharmacokinetic processes and models. Theoretical knowledges were partially copied from [13] and [4], where was well explained and connected. But we managed to complement the theoretical knowledges and prove pharmacokinetic equations, which are not often given in standard books. We believe that to know origins of these equations could help in deeper understanding of their importance and functioning. It could help for example in our future researches in this field to better understand pharmacokinetic computations and improve complicated equations. We performed numerical experiments in the software PharmCalcCl, which is used for pharmacokinetics simulations, and MATLAB, where we showed difference between numerical methods with real data (i.e. not fictional). We demonstrated that approximation of $AUC$ can be strongly dependent on the used integration rule, especially with a small number of blood samples.

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