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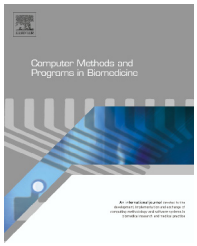

Maxsim2—Real-time interactive simulations for computer-assisted teaching of pharmacokinetics and pharmacodynamics

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ABSTRACT

We developed a computer program for use in undergraduate and graduate courses in pharmacology, pharmacokinetics and pharmacodynamics. This program can also be used in environmental and toxicological studies and preclinical simulation, to facilitate communication between modeling pharmacokineticists and project leaders or other decision-makers in the pharmaceutical industry. The program simulates the drug delivery and transport by means of (I) a six-compartment physiological pharmacokinetic flow model, (II) a system of traditional compartment models, or (III) a target-mediated drug disposition system. The program also can be used to simulate instantaneous equilibria between concentration and pharmacodynamic response, or as temporal delays between concentration and response. The latter is done by means of turnover models (indirect response models). Drug absorption, distribution, and elimination are represented by differential equations, which are described by organ and tissue volumes or other volumes of distribution, blood flows, clearance terms, and tissue-to-blood partition coefficients. The user can control and adjust these parameters by means of a slider in *real time*. By interactively changing the parameter values and simultaneously displaying the resulting concentration–time and/or response–time profiles, users can understand the major mechanisms that govern the disposition or the pharmacological response of the drug in the organism in real time. Schedule dependence is typically seen in clinical practice with a non-linear concentration–response relationship, and is difficult to communicate except *via* simulations. Here, we sought to illustrate the potential advantages of this approach in teaching pharmacology, pharmacokinetics, and pharmacodynamics to undergraduate pharmacy-, veterinary-, and medical students or to project teams in drug discovery/development.

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1. Introduction

Pharmacokinetics (PKs) and pharmacodynamics (PDs) are distinct disciplines within the traditional pharmacology curriculum. Whereas pharmacokinetics looks at how the body handles drugs, pharmacodynamics looks at their effects. Pharmacokineticists and pharmacologists frequently work more or less in isolation of each other, a practice that greatly restricts the detailed understanding of both known and potentially novel drugs. Therefore, an important question is whether teaching students using an approach that deliberately and systematically integrates the activities of these two disciplines will enhance our understanding of drugs, and the efficiency and effectiveness of drug discovery and development.

Pharmacokinetic models are used to describe the time-dependent disposition and absorption of a substance in a living system. For medical purposes, pharmacokinetics can be used to estimate optimal drug dosage regimens in different therapeutic situations, and for other chemicals be used to aid decision-making in the risk evaluation of the working environment. Until now, three main approaches have been used to analyze the concentration–time behavior of drugs. The classical approach employs either (I) a sum of exponentials referred to as empirical models, or (II) compartment models [1]. Although the empirical and compartmental models have the advantage of simplicity and meet the needs of most pharmacokinetic studies, they do not describe a physiological system with large tissue-to-tissue concentration differences, the effect of altered perfusion, membrane resistance or changes in protein binding. The limitations of these classical pharmacokinetic models have led to the need for a more realistic way of modeling, namely, (III) physiological flow models. The general approach in physiological modeling is to define the pharmacokinetic processes by means of physiologically, anatomically, and biochemically meaningful parameters. Every organ is represented by one or more compartments where each vascular tissue compartment is interconnected through the circulatory system as in the body [2].

In this study, we used a physiologically sound base to construct a pharmacokinetic model for use in human clinical simulations as well as for pre-clinical (rat) and veterinary applications (cat, dog, horse). The computer program, which we call Maxsim2, simulates the drug delivery and transport by means of (I) a six-compartment physiologically based pharmacokinetic flow model, (II) a system of traditional compartment models, or (III) a target-mediated drug disposition system [3]. Maxsim2 also can be used to simulate instantaneous equilibria between concentration and pharmacodynamic response, or as temporal delays between concentration and response. We also illustrate the potential advantages of this parallel approach of instantaneous coupling or delay between plasma concentration and pharmacodynamic response, as outlined in [4], in teaching undergraduate/graduate pharmacology, pharmacokinetics, and pharmacodynamics to undergraduate pharmacy-, veterinary-, and medical students or to project teams in drug discovery/development.

2. Model description

2.1. The physiologically based pharmacokinetic model

The physiologically based pharmacokinetic model used for the human clinical simulations is shown in Fig. 1. Models of the rat, cat, dog and horse are also available for veterinary practice. All model parameters, such as organ volumes, blood flows, partition coefficients, intrinsic clearance terms, absorption rate constants, maximum metabolic rates and their Michaelis–Menten constants, and dosing parameters, are available for real-time adjustment during simulations.

The model comprises only six compartments, which is obviously a simplification but serves the purpose of illustrating the multi-compartment distribution of compounds in PBPK-modeling. The largest (in volume) compartment, denoted *M* below, could be interpreted not only to represent muscle tissue but also to contain all other non-specifically modeled tissue such as adipose, bone marrow, *etc*. Plasma protein binding was not an inherent factor in the present version of the model. Work is ongoing to incorporate plasma protein concentrations, affinity parameters, and the total number of binding sites of drug on the protein. These options will be released in a future version of the program.

The system of ordinary differential equations governing the behavior of the physiologically based pharmacokinetic model in Maxsim2 is shown below

$$
\begin{aligned}
V_{Br}\frac{dC_{Br}(t)}{dt} &= Q_{Br}\left(C_B(t)-\frac{C_{Br}(t)}{K_{PBr}}\right), \quad C_{Br}(0)=0\\
V_M\frac{dC_M(t)}{dt} &= Q_M\left(C_B(t)-\frac{C_M(t)}{K_{PM}}\right), \quad C_M(0)=0\\
V_G\frac{dC_G(t)}{dt} &= Q_G\left(C_B(t)-\frac{C_G(t)}{K_{PG}}\right)+f_A K_A A(t), \quad C_G(0)=0\\
\frac{dA(t)}{dt} &= -K_A A(t)+\sum_i d_{oral,i}\delta(t-t_i), \quad A(0)=0\\
V_H\frac{dC_H(t)}{dt} &= Q_{HA}C_B(t)+Q_G\frac{C_G(t)}{K_{PG}}-(Q_{HA}+Q_G)\frac{C_H(t)}{K_{PH}}\\
&\quad -CL_H\frac{C_H(t)}{K_{PH}}, \quad C_H(0)=0\\
V_R\frac{dC_R(t)}{dt} &= Q_R\left(C_B(t)-\frac{C_R(t)}{K_{PR}}\right)-CL_R\frac{C_R(t)}{K_{PR}}, \quad C_R(0)=0\\
V_B\frac{dC_B(t)}{dt} &= -Q_{Br}\left(C_B(t)-\frac{C_{Br}(t)}{K_{PBr}}\right)-Q_M\left(C_B(t)-\frac{C_M(t)}{K_{PM}}\right)\\
&\quad -Q_R\left(C_B(t)-\frac{C_R(t)}{K_{PR}}\right)-(Q_{HA}+Q_G)\left(C_B(t)-\frac{C_H(t)}{K_{PH}}\right)\\
&\quad +d_{inf}(t)+\textstyle\sum_i d_{iv,i}\delta(t-t_i), \quad C_B(0)=0
\end{aligned}
\tag{1}
$$

where V_{ind} denotes volumes, C_{ind} is concentrations, Q_{ind} is flows, K_{Pind} is blood–tissue-partition coefficients, f_A is fraction absorbed, K_A is first-order absorption-rate constant for drug from the GI tract to plasma, *A* is amount of drug in the gut, and CL_{ind} is clearance, respectively. Here *ind* denotes an index identifying the corresponding tissue, where *Br* denotes the brain,

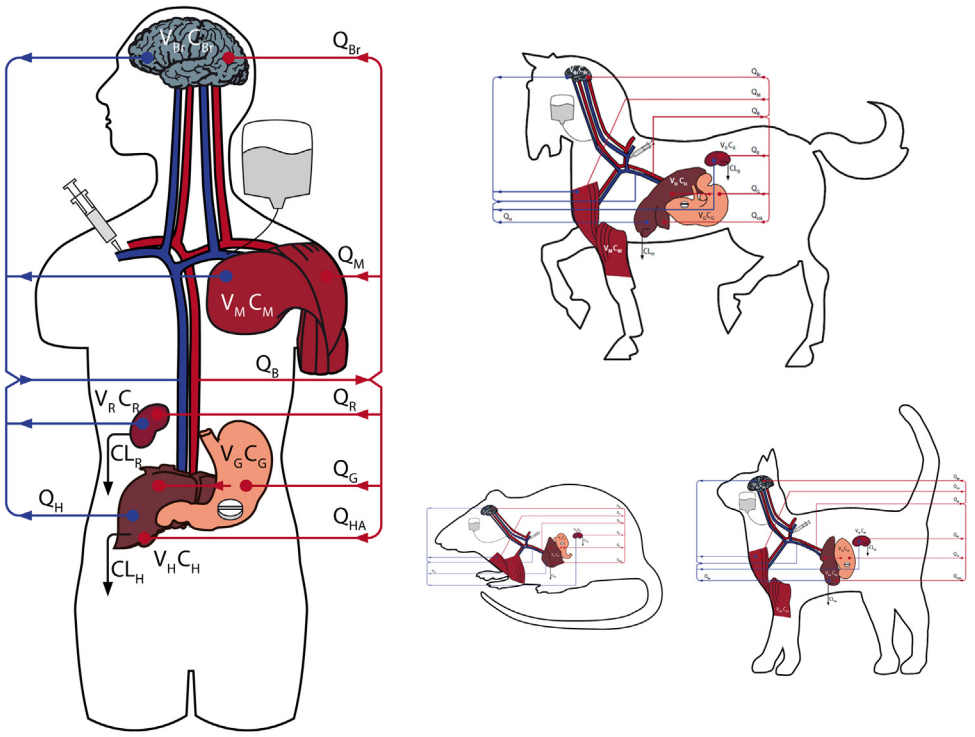

Fig. 1 – Examples of physiologically based pharmacokinetic model schemes used in Maxsim2, covering models of interest for drug development and pharmaceutical applications such as models for human and rat and in veterinary practice such as models for rat, cat, dog, and horse. The V_i denotes organ volumes, Q_i blood flows, K_{Pi} partition coefficients, CL_{iH} intrinsic clearance terms, K_a absorption rate constants, V_{max} maximum metabolic rates and K_m Michaelis–Menten constants, which are all available for real time adjustments. For a detailed description of the nomenclature see the glossary list.

M is muscle, G is gut, H is the liver, HA is the liver (arterial), R is the kidneys, and B is the blood, respectively. Furthermore,

$$d_{oral,i} = \frac{D_{oral,i}}{Mw}$$
$$d_{inf} = \frac{D_{inf}}{Mw} \quad (2)$$
$$d_{iv,i} = \frac{D_{iv,i}}{Mw}$$

where Mw is the molecular weight of the compound and $D_{oral,i}$ and $D_{iv,i}$ are given as amount in grams of compound and D_{inf} is given as amount in grams per time unit. There is also an option to select nonlinear hepatic clearance in which case CL_H is changed from being a parameter to be a function of C_H and two new parameters maximum metabolic rate V_{max} and the Michaelis–Menten constant K_m, *i.e.*, $CL_H = V_{max}/(K_m + C_H)$.

2.2. *One-compartment model*

A schematic diagram of a traditional one-compartment model is shown in Fig. 2.

The differential equation for the one-compartment model in Maxsim2 is

$$V\frac{dC(t)}{dt} = In(t) - Cl\,C(t), \quad C(0) = 0 \quad (3)$$

where V denotes volume of distribution, C is the drug concentration, and Cl is the plasma clearance. The input term $In(t)$ constitutes of three parts given by infusion rate, i.v. bolus doses, and rate of uptake for extravascular administration, respectively,

$$In(t) = d_{inf}(t) + \sum_i d_{iv,i}\delta(t - t_i) + f_A K_A A(t)$$
$$\frac{dA(t)}{dt} = -K_A A(t) + \sum_i d_{ev,i}\delta(t - t_i), \quad A(0) = 0 \quad (4)$$

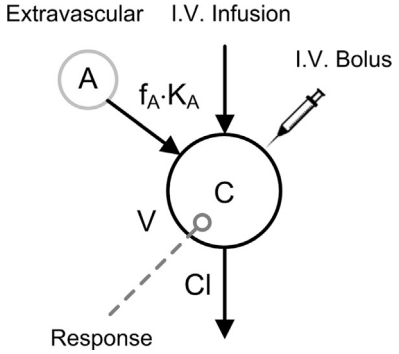

Fig. 2 – The one-compartment disposition model scheme used in Maxsim2. For a detailed description of the nomenclature see the glossary list.

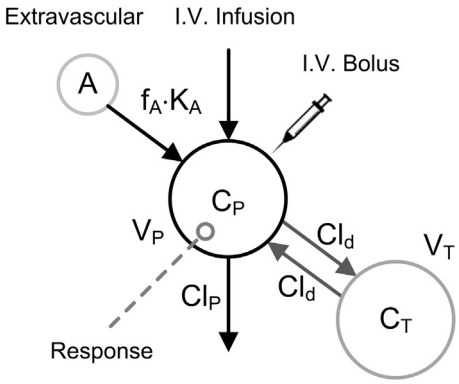

Fig. 3 – The two-compartment disposition model scheme used in Maxsim2. For a detailed description of the nomenclature see the glossary list.

where the lower case *d*s are defined as above and the differential equation governs the elimination of an extravascular (*e.g.*, oral) administrated drug. There is also an option to select nonlinear clearance, in which case Cl is changed from being a parameter to be a function of C and two new parameters, maximum metabolic rate V_{max} and the Michaelis–Menten constant K_m, *i.e.*, $Cl = V_{max}/(K_m + C(t))$.

2.3. Two-compartment model

A schematic diagram of a traditional two-compartment model is shown in Fig. 3.

The system of differential equations for the two-compartment model in Maxsim2 is

$$\begin{aligned} V_P \frac{dC_P(t)}{dt} &= In(t) - Cl_P C_P(t) + Cl_d C_T(t) - Cl_d C_P(t), \quad C_P(0) = 0 \\ V_T \frac{dC_T(t)}{dt} &= -Cl_d C_T(t) + Cl_d C_P(t), \quad C_T(0) = 0 \end{aligned} \tag{5}$$

where V_P and V_T denote plasma volume and tissue volume, respectively, C_P and C_T are the drug concentration in plasma and tissue, respectively, Cl_P is the plasma clearance, and Cl_d is the distributional clearance. The input term $In(t)$ is defined as in Eq. (4) and in case of nonlinear plasma clearance Cl_P is changed from being a parameter to be a function of C_P and two parameters maximum metabolic rate V_{max} and the Michaelis–Menten constant K_m, *i.e.*, $Cl_P = V_{max}/(K_m + C_P(t))$.

2.4. Target mediated drug disposition model

Target mediated drug disposition (TMDD) is also an option in Maxsim2 as shown in Fig. 4. The present version is applicable to a circulating target R available for reaction with the ligand L *via* a second order reaction.

The system of ordinary differential equations governing the behavior of the target mediated drug disposition in Maxsim2 is

$$\begin{aligned} V_C \frac{dC_L(t)}{dt} &= In(t) - Cl_L C_L(t) + Cl_d C_T(t) - Cl_d C_L(t) \\ &\quad -k_{on} V_C C_L(t) C_R(t) + k_{off} V_C C_{RL}(t), \quad C_L(0) = 0 \\ V_T \frac{dC_T(t)}{dt} &= -Cl_d C_T(t) + Cl_d C_L(t), \quad C_T(0) = 0 \\ \frac{dC_R(t)}{dt} &= k_{syn} - k_{deg} C_R(t) - k_{on} C_L(t) C_R(t) \\ &\quad +k_{off} C_{RL}(t), \quad C_R(0) = R_0 \\ \frac{dC_{RL}(t)}{dt} &= k_{on} C_L(t) C_R(t) - (k_{off} - k_{e(RL)}) C_{RL}(t), \quad C_{RL}(0) = 0 \\ \frac{dA(t)}{dt} &= -K_A A(t) + \sum_i d_{oral,i} \delta(t - t_i), \quad A(0) = 0 \end{aligned} \tag{6}$$

where C_L denotes the ligand concentration, C_T is the secondary tissue concentration, C_R is the target concentration, C_{RL} is the receptor–ligand complex concentration, and A is the amount of extravascular drug. The parameters are the central compartment volume, V_C, the secondary tissue compartment volume, V_T, ligand clearance, Cl_L, distributional clearance, Cl_d, receptor–ligand complex second-order on-rate constant and first-order off-rate constant, k_{on} and k_{off}, respectively, basal zero-order receptor (target) synthesis rate, k_{syn}, first-order receptor–ligand complex elimination rate constant, $k_{e(RL)}$, first-order absorption rate constant from the GI tract to plasma, K_A, and fraction absorbed, f_A. The input term $In(t)$ constitutes three parts given by infusion rate, i.v. bolus doses, and rate of uptake for extravascular administration, respectively

$$In(t) = d_{inf}(t) + \sum_i d_{iv,i} \delta(t - t_i) + f_A K_A A(t) \tag{7}$$

Furthermore, k_{syn} is not considered an independent parameter for manipulation (*i.e.*, it is not available in the menu for parameters to be adjusted in Maxsim2), but is in turn parameterized according to $k_{syn} = R_0 k_{deg}$, *i.e.*, changing R_0 or k_{deg} implies a change in k_{syn}.

2.5. Pharmacodynamic models

Maxsim2 implements both instantaneous and turnover-driven (indirect pharmacodynamic) response models. The instantaneous response models are the ordinary E_{max} model with a baseline parameter E_0

$$R = E_0 + \frac{E_{max} C^n}{EC_{50}^n + C^n} \tag{8}$$

where EC_{50} and n denote the potency and sigmoidicity factor, respectively. The inhibitory I_{max} model

$$R = E_0 - \frac{I_{max} C^n}{IC_{50}^n + C^n} \tag{9}$$

where I_{max}, IC_{50} and n denote the efficacy parameter, potency and sigmoidicity factor, respectively. Models for capturing temporal differences between plasma concentration and response are primarily turnover-driven. Delays limited by

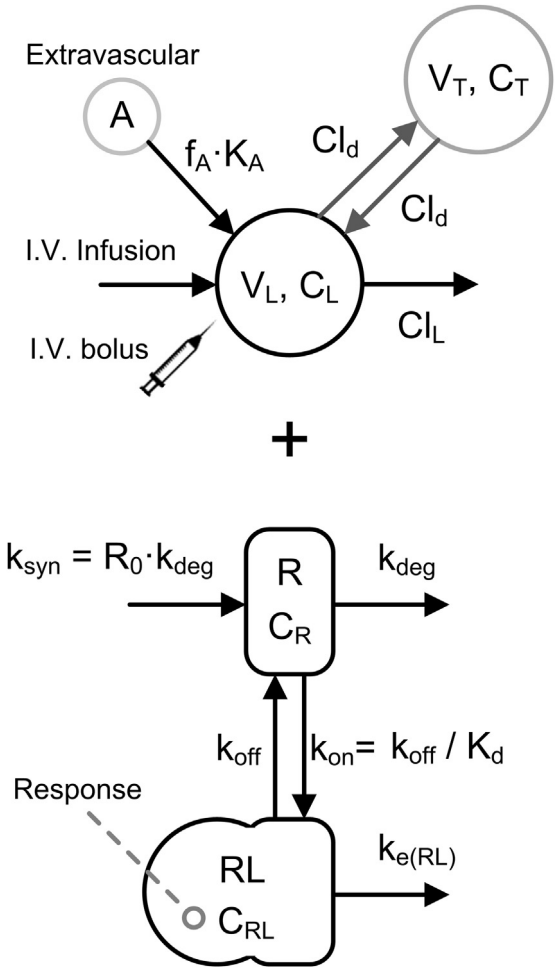

Fig. 4 – (Top) Schematic illustration of the compartmental system with the target-mediated drug disposition model attached. The two-compartment disposition model with unspecific binding (C_T, V_T, Cl_d) collapses into a one-compartment model when the inter-compartmental distribution term is set to zero. Input to the central compartment can be done *via* bolus administration, zero-order constant rate infusion or first-order absorption (K_A). (Bottom) The TMDD system is activated when the target baseline concentration R_0 is set to a value greater than zero. Ligand (L) and target (R) react *via* a second-order rate process (k_{on}) resulting in the formation of a ligand–target complex (RL). The latter can then be degraded back into L and R or irreversibly lost *via* $k_e(RL)$. The turnover of the circulating target occurs by means of a zero-order production (turnover rate $R \cdot k_{deg}$) and first-order loss (k_{deg}). For a detailed description of the nomenclature see the glossary list.

receptor-binding on/off rates are captured and can be simulated by the TMDD system (Fig. 4). The turnover (indirect) response models are inhibition of production

$$\frac{dR(t)}{dt} = k_{in} I(C) - k_{out} R(t), \quad R(0) = R_0$$
$$I(C) = 1 - \frac{I_{max} C^n}{IC_{50}^n + C^n} \tag{10}$$

inhibition of the loss term

$$\frac{dR(t)}{dt} = k_{in} - k_{out} I(C) R(t), \quad R(0) = R_0$$
$$I(C) = 1 - \frac{I_{max} C^n}{IC_{50}^n + C^n} \tag{11}$$

stimulation of the production term

$$\frac{dR(t)}{dt} = k_{in} S(C) - k_{out} R(t), \quad R(0) = R_0$$
$$S(C) = 1 + \frac{S_{max} C^n}{SC_{50}^n + C^n} \tag{12}$$

and stimulation of the loss term

$$\frac{dR(t)}{dt} = k_{in} - k_{out} S(C) R(t), \quad R(0) = R_0$$
$$S(C) = 1 + \frac{S_{max} C^n}{SC_{50}^n + C^n} \tag{13}$$

2.6. *Software design and numerical algorithms*

The current version of the program (version 2.0, www.maxsim2.com) is written in C++ using external libraries and routines such as wxWidgets, CVODE, and Boost. The wxWidgets library provides tools for designing and implementing the graphical user interface of Maxsim2 (http://www.wxwidgets.org) and CVODE is a well-recognized numerical solver for stiff and non-stiff ordinary differential equations developed at the Lawrence Livermore National Laboratory (http://computation.llnl.gov/casc/sundials). Boost provides high-level platform-independent C++ libraries facilitating programming productivity and maintenance (http://www.boost.org). The source code for Maxsim2 is written for cross platform deployment. The current version is available for Windows XP and higher and for Mac OS X. The pharmacokinetic and pharmacodynamics models implemented in Maxsim2 and the program's capability to accurately compute corresponding numerical solutions for different dosing regimens have been successfully validated by comparing simulation results with independent implementations of these models and their simulations in Mathematica (http://www.wolfram.com).

3. Applications of Maxsim2 in undergraduate teaching

The Maxsim2 program has been frequently used over the past two years to teach pharmacy students, and in a course in pharmacokinetics in the medical, toxicological and veterinary curriculum at our institutions. Generally the program is introduced during the first course week, when each student gets the computer lab instructions and program. A mid-course question and answer session is followed by a mandatory summary session at the end of the course. This saves the teacher's time and gives the student a more flexible working environment. All students also have to submit a written report before the final examination. We think that the introduction of interactive simulation, facilitating the mix of theory and practice,

has been very rewarding in terms of improvement of the student's ability to learn and understand new concepts as noted by several others [5–9].

The following are several examples of assigned conceptual exercises regarding the interplay between physiology and pharmacokinetics, or more clinically oriented tasks of maintaining therapeutic drug concentrations in patients and domestic animals during varying pathological and physiological conditions after single or multiple doses.

3.1. Single dose administration

This exercise was divided into three different sections. In the first part, students familiarize themselves with the Maxsim2 program and the type of problems put forward. Students are then confronted with problems dealing with single i.v. injection or first-order absorption using the human PBPK model. With the simulator, they can study the impact of changes in the absorption rate constant, bioavailability (intrinsic clearance), and drug interactions, on the blood and tissue concentration time profiles. They are also expected to obtain a firm grasp of some of the physiological factors governing the disposition of a drug during single dose kinetics. Fig. 5 provides a presentation of the concentration–time plot of drug in plasma at two different clearance (left) and volume (right) settings.

3.2. Oral and intravenous dosing

In this exercise, students demonstrate the impact of a change in intrinsic hepatic clearance Cl_{iH} in the human PBPK model on the plasma concentration–time course after oral and intravenous infusion regimens, respectively. This simulation highlights the meaning of the first-pass effect and perfusion-rate (blood flow rate) limited clearance (Fig. 6).

3.3. Multiple dosing

The second part of the exercise deals with multiple dosing of different drugs using the human PBPK model. Currently, we have compiled data on the pharmacokinetics parameters and tissue-to-blood partition coefficients of several model drugs: digoxin, morphine, methadone, theophylline, salicylic acid, pethidine, and aminoglycosides. In this part of the exercise, the user should be able to develop a dosage regimen from knowledge of the pharmacokinetics of the drug and evaluate a dosage regimen, *e.g.*, ordinary tablet or prolonged-release formulation, from a pharmacokinetic point of view. The aim is also to make the student familiar with how a change in either of the absorption rate constant K_A, the bioavailability F or f_a, the clearance Cl, or the tissue-to-blood partition coefficient $K_{p,i}$ affect the concentration time course during steady state.

An example of a simulation can be seen in Fig. 7, where a patient receives several doses of theophylline. The student can study the impact of a sustained-release dosage form (absorption rate constant K_A small) given to an asthmatic patient, which is represented by the less fluctuating curve. When the absorption becomes the rate-limiting step for the plasma kinetics it also impacts the time to steady-state (lower simulation in Fig. 7 with $K_A < 0.05\,h^{-1}$). Although the time to steady-state is prolonged, the average concentration at steady-state is still the same.

The user may also simulate a scenario with variable dosing intervals, in this case a drug given twice a day, at 8:00 A.M. and 2:00 P.M. (Fig. 8).

3.4. Physiologically based pharmacokinetic (PBPK) models and its advantage in teaching situations

The goal of the PBPK option is to integrate physiological principles and pharmacokinetic concepts. To achieve this goal each pharmacokinetic parameter, *e.g.*, clearance or volume of distribution, is now treated as a variable instead of as a constant. The user studies the impact of changes in the tissue-to-blood partition coefficients, organ blood flows, organ volumes and clearances, on the time-course of drug in the body. Changes in tissue (brain, gut, renal, hepatic and skeletal muscle tissue) uptake and organ blood flows are of particular interest in making the user confident with factors that govern either the time to reach steady-state, or the drug concentration level in blood or tissues at equilibrium.

Physiologically based pharmacokinetic models might be useful in both pharmacology and toxicology to address questions such as: to what extent is a particular region or organ exposed to a specific drug during a given dosing schedule? Can the obtained concentration–time profile provide any clues to toxicological effects? or How does multiple dosing influence the time course of exposure to chemicals in different tissues or organs?

3.5. Target-mediated drug disposition

Target-mediated drug disposition is covered in a series of lectures in a pharmacokinetics course followed by a full day computer lab. One of the introductory exercises is to study and describe the impact of an increase in dose of the ligand (*e.g.*, antibody) concentration–time course in plasma (Fig. 9). In Fig. 10 we illustrate the impact of a change in the target level expression, R_0, on the concentration–time course of ligand (antibody).

3.6. Veterinary application: theophylline pharmacokinetics in cat and horse

In this example, the student has to consider the pharmacokinetic parameters deciding the average steady-state concentration and the time to reach steady state by means of a PBPK model of each species. A horse is being treated with theophylline $5\,mg\,kg^{-1}$ BID for recurrent airway obstruction. The therapeutic window is narrow and the half-life in horses (about 18 h) is more than twice the half-life in cats (about 8 h). The dose per kg body weight is the same in cats and horses. The veterinarian thinks the horse might be overdosed. The questions the student must answer are what may have caused this reflection? Is it appropriate to give the same dose per kg to a horse and a cat (given the therapeutic window in plasma)?

This exercise compares the concentration–time course following repeated doses of theophylline in a cat of 4 kg and in a horse of 500 kg body weight. Theophylline is a xanthine derivative and has a variety of pharmacological effects, including

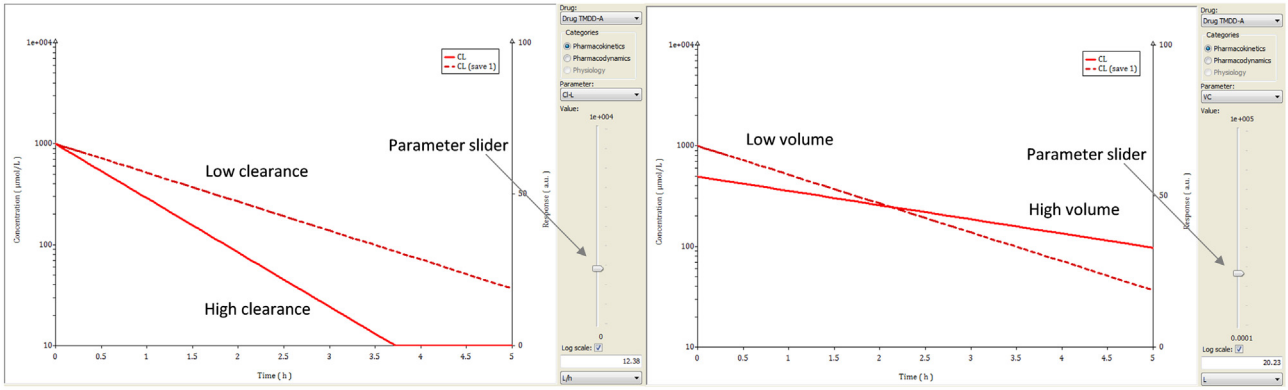

Fig. 5 – (Left) Semi-logarithmic plot of the plasma concentration–time course of test compound X in the human PBPK model after an i.v. bolus dose in two different individuals with different clearance values. Note that the compound displays one-compartment kinetics (mono-exponential decline) and that the half-life is shorter in the subject with higher clearance. The area-under-the concentration time curve AUC is also lower when clearance is higher. (Right) Semi-logarithmic plot of the concentration–time course of test compound X after an i.v. bolus dose in two different individuals with different volumes of distribution. The area-under-the concentration time curve AUC is equal in the two subjects since clearance is unaffected. Data taken from case study PK1 in [1].

relaxation of bronchial smooth muscles. The most important adverse effect is cardiac stimulation with resulting arrhythmias. In veterinary medicine, theophylline is especially used as a bronchodilating drug. In cats, theophylline might be used to treat asthma. In horses, the drug has been used to treat recurrent airway obstruction (RAO). The simulated dose is 5 mg kg^{-1} twice daily for 9 days both for the cat and the horse. The oral bioavailability is high and similar in both species. The simulated plasma concentration–time courses in horse and cat are shown in Fig. 11. Students assess the mean concentration at steady-state, the time to reach steady state, the parameter(s) that determines the average steady-state

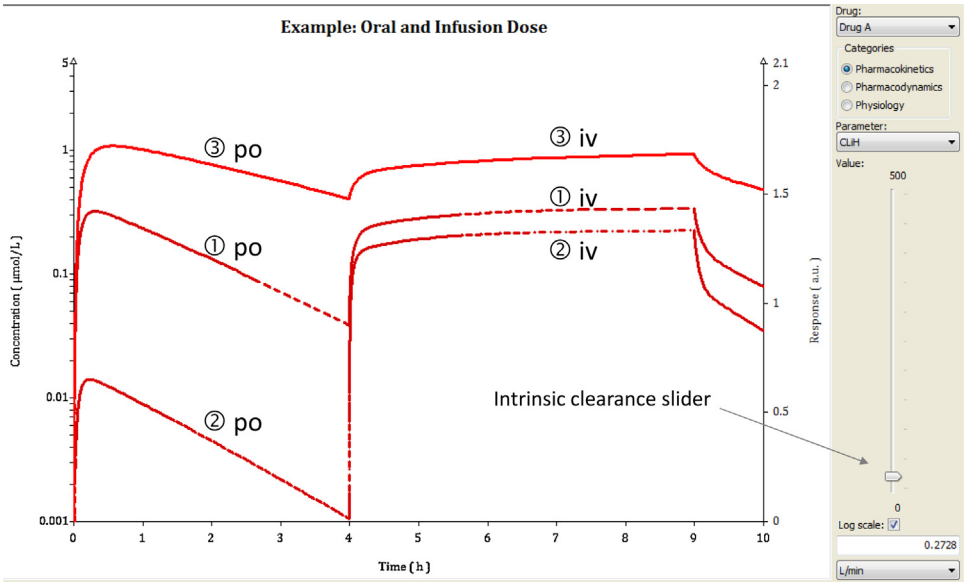

Fig. 6 – Simulation 1: Semi-logarithmic plot of the concentration–time course of test compound X after an oral dose followed by a 5 h constant rate i.v. infusion dose starting at 4 h. Note that the compound displays multi-compartment kinetics (two-exponential decline) after the constant rate infusion using a PBPK model. The peak of the oral curve occurs in the same concentration range as the steady-state concentration upon i.v. dosing. The terminal half-lives after oral and i.v. dosing fall in parallel. Simulation 2: Increase in hepatic intrinsic clearance. The area under the oral curve decreases as hepatic intrinsic clearance increases due to the first-pass effect observed after oral dosing. This is not seen after intravenous dosing, in which the plasma concentration lowers until it reaches perfusion-rate-limited elimination (hepatic blood flow-rate limited clearance). Simulation 3: Decrease in hepatic intrinsic clearance. The area under the oral and i.v. curves increases as hepatic intrinsic clearance decreases. The terminal half-lives increase and fall in parallel. The time to steady-state t_{ss} and the time to the maximum plasma concentration t_{max} after oral dosing increase.

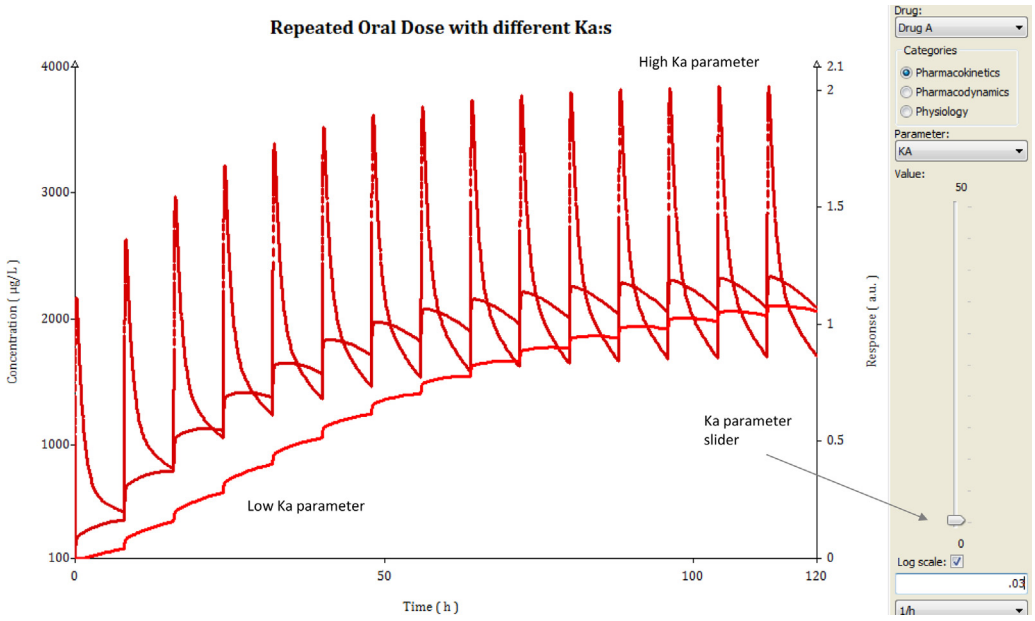

Fig. 7 – Concentration–time course of test compound X after three oral formulations. The curve with the fastest absorption displays the highest fluctuation. When the absorption-rate constant K_A is decreased the fluctuations between peak and trough decrease. When K_A is decreased further so absorption becomes the rate-limiting step, then the time to steady-state is governed by the absorption rate. Still the average concentration at steady-state is the same. A PBPK disposition model was used.

concentration, and the time to reach steady state. They are also asked which primary pharmacokinetic parameter(s) differ between horse and cat (as the half-life differs) based on a per kg body weight scale.

3.7. *Veterinary application: nimesulide hypothermia in dogs – schedule dependence*

In this exercise, students are asked to design a dosage regimen that lowers the exposure to the drug but still keeps the response at an acceptable level without too much fluctuation in the hypothermic response. Fig. 12 contains two simulations suggested in Toutain et al. [10]. Each regimen provides the same total plasma exposure (same total dose). If the total hypothermic response is summed up, the area under the response–time course of 2.5 mg bid is greater and the hypothermic response contains fewer fluctuations than the once daily dose of 5 mg. The figure shows that the once daily 5 mg dose causes less hypothermia per day than does 2.5 mg bid. The drug response is dependent on the dose schedule.

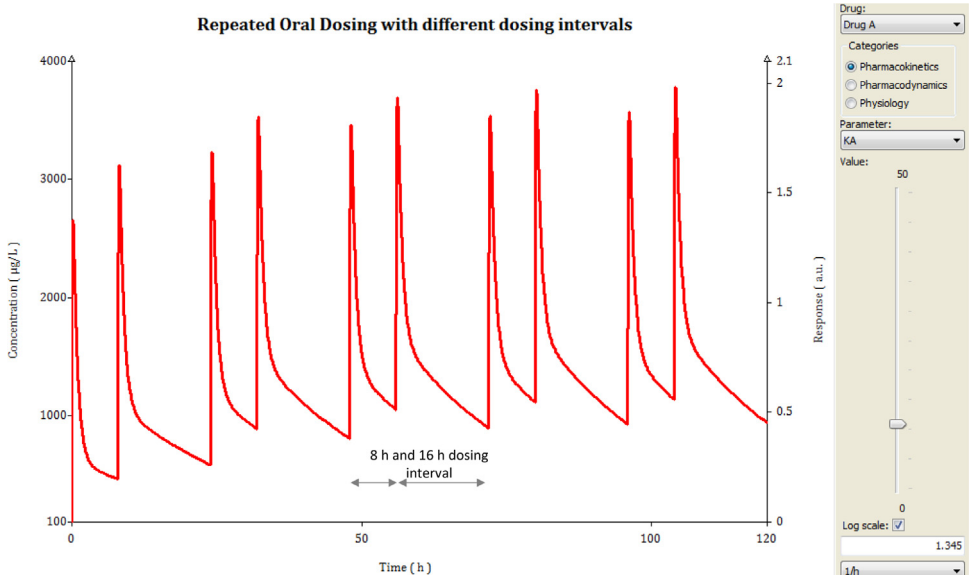

Fig. 8 – Simulation of the time-course of compound X with an 8 and 16 h dosing interval. A PBPK disposition model was used.

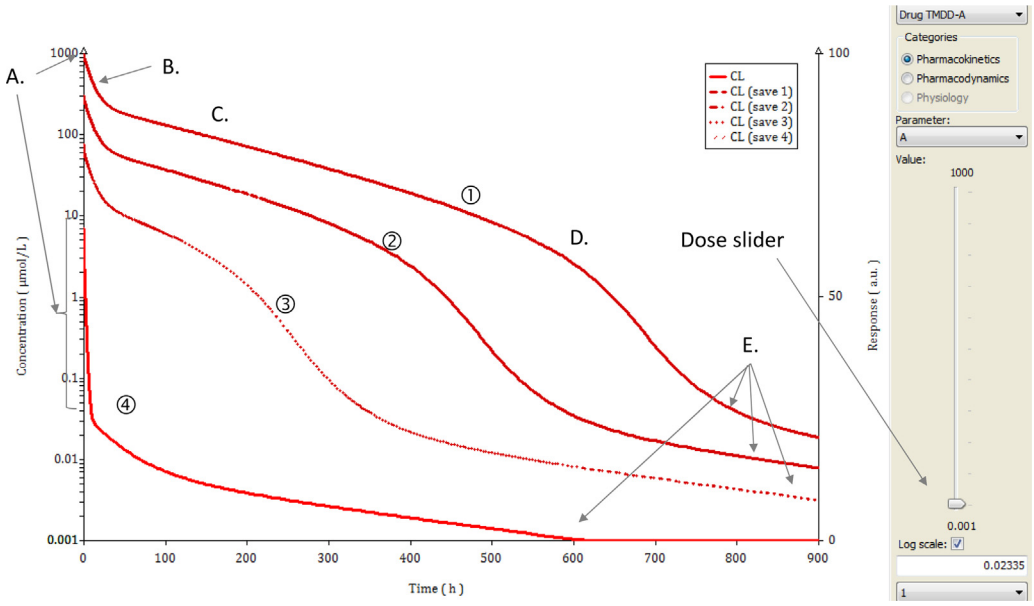

Fig. 9 – Impact of a change in the dose-slider on the concentration–time course of ligand (antibody) at four different dose levels. Note how the disposition of ligand displays a complicated multi-phasic concentration–time course at the different dose levels. The upper curve displays an initially rapid drop (within 1 h (A) shown for the highest and lowest doses) followed by a slower decline due to distribution (phase B). Phase C is primarily linear elimination and phase D represents the target mediated disposition. Phase E is the terminal linear phase governed by elimination of the ligand–target complex. Note how the initial phase A increases as the ligand dose decreases. Phase A is due to the second-order reaction between ligand and target. Unspecific binding is represented by a peripheral compartment attached to the central ligand compartment *via* a first-order process (Fig. 4, top).

Fig. 13 shows three simulations based on temperature data in three individual dogs where only the EC_{50} value has been changed and the consequences that has on the hypothermic time course. Again the students are asked to explain why the three simulated curves differ so much and how can this be tackled in a population. Students are also requested to draw the relationship between target concentration range (what concentration is required for a certain target effect) and the pharmacodynamic determinants of that target range, such as potency, efficacy and the sigmoidicity factor. This gives a better understanding of how inter-individual pharmacodynamics differences impact the target effect and how potency affects the intensity, and in particular, the duration of response. Another task is to draw the corresponding concentration–response relationships provided potency is the only difference between the subjects.

3.8. *Pharmacological application: clinical significance of potency differences-schedule dependence*

This exercise tries to elucidate the complexity within the questions of potency and powerfulness. In addition to the Maxsim2-tasks, the students are expected to construct two ordinary concentration–response curves out of the peak responses obtained during the exercise – one for the drug with low efficacy and one for that with high efficacy (full agonist). The assumption is that there is a rapid equilibrium between plasma concentration and the diuretic effect.

How efficiently a diuretic exerts its effect is greatly influenced by the condition of the kidneys, in that the individual dosage regimen may diverge. The dose is also influenced by the variation of the duration of drug effect. In this exercise, a patient is treated with two different diuretics (A and B), which are considered to be powerful. However, the dosing regimen does not seem to have any effect and a tenfold increase of the dose is given (10–100 mg). The pharmacokinetic parameters are the same for Drugs A and B, which means that the plasma exposure profiles of the two compounds are similar. The system parameters k_{in} and k_{out} are assumed to be the same for the drugs. Drug A gives a maximal drug-induced (E_{max}) response of 4 arbitrary units (au), with an EC_{50} of 7 and an n (Hill coefficient) of 0.4. The corresponding parameters for drug B are 10 au (E_{max}), 12 (EC_{50}) and 2.7 (n), respectively. The result of the exercise is presented in Fig. 14.

The student is expected to reflect about potency (EC_{50}) and maximum effect, steepness of response-curve and consequences when increasing the dose to a patient, and also about what the Hill coefficient actually means. By examining peak responses to doses other than 10 and 100 mg, the student should eventually construct concentration (dose)–response curves (for drug A and B). If correctly done, the student should from the curves get the same maximum, EC_{50} and n values as presented originally.

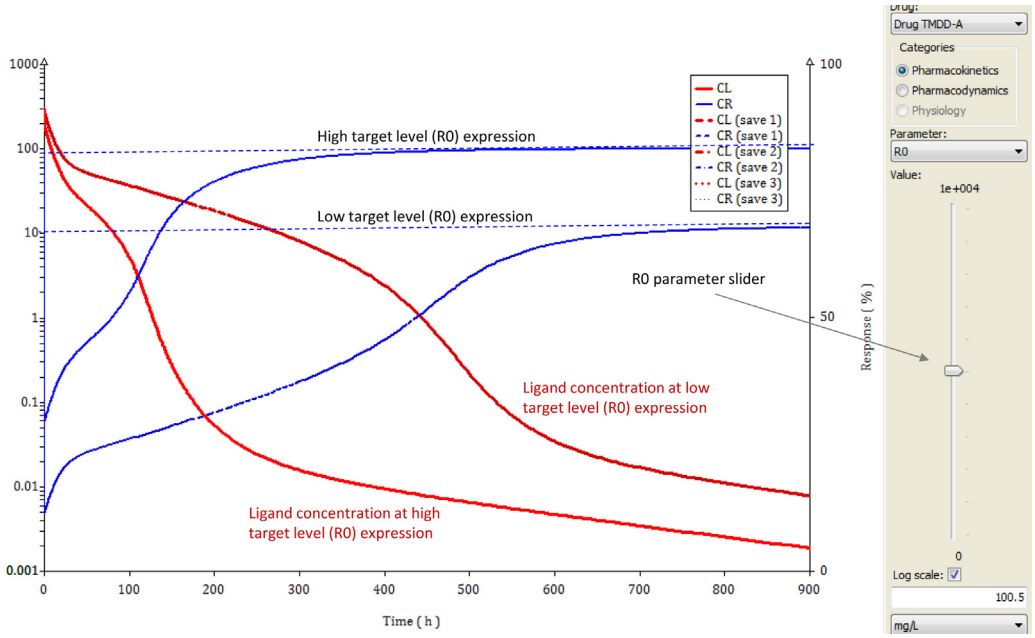

Fig. 10 – Impact of a change in the target level expression (R_0) on the concentration–time course of ligand (antibody) at two different target levels. Note how the disposition of ligand (red curve) displays a complicated multi-phasic concentration–time course at the different dose levels. The upper red curve displays an initially rapid drop (within 1 h (A) shown for the highest and lowest doses) followed by a slower decline due to distribution (phase B). Phase C is primarily linear elimination and phase D represents the target mediated disposition. Phase E is the terminal linear phase governed by elimination of the ligand–target complex and will not be affected by target expression. Unspecific binding is represented by a peripheral compartment attached to the central Ligand compartment *via* a first-order process (Fig. 4, top). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

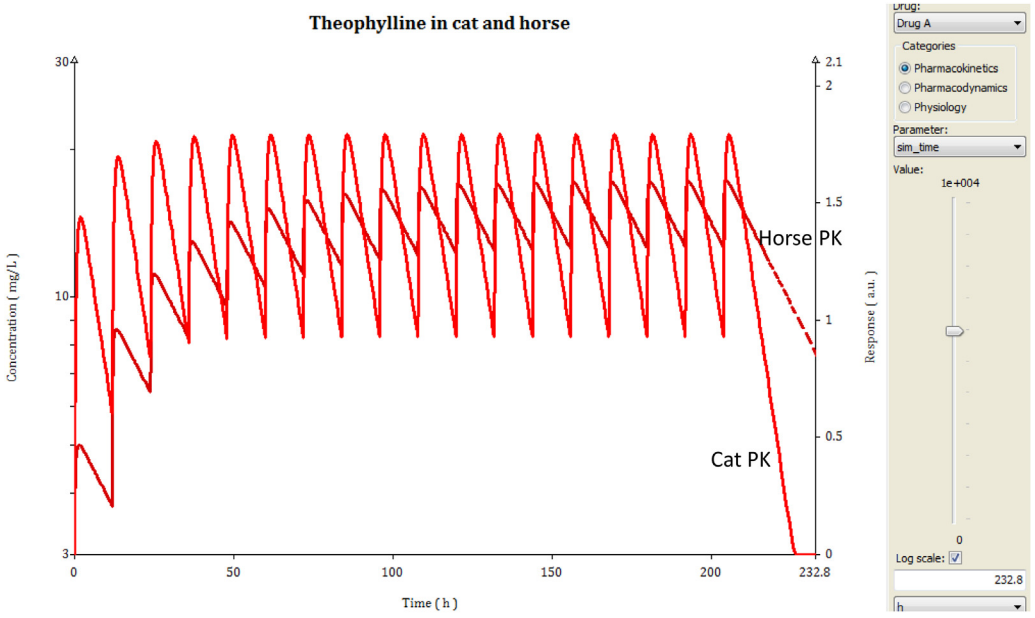

Fig. 11 – Semi-logarithmic plot of the concentration–time course of theophylline in cat and horse plasma after repeated oral doses of 5 mg/kg. Note that the average concentration is similar but the half-lives differ, which also impacts the time to steady-state. PBPK disposition models for cat and horse were used.
Data on theophylline are taken from Riviere and Papich [13].

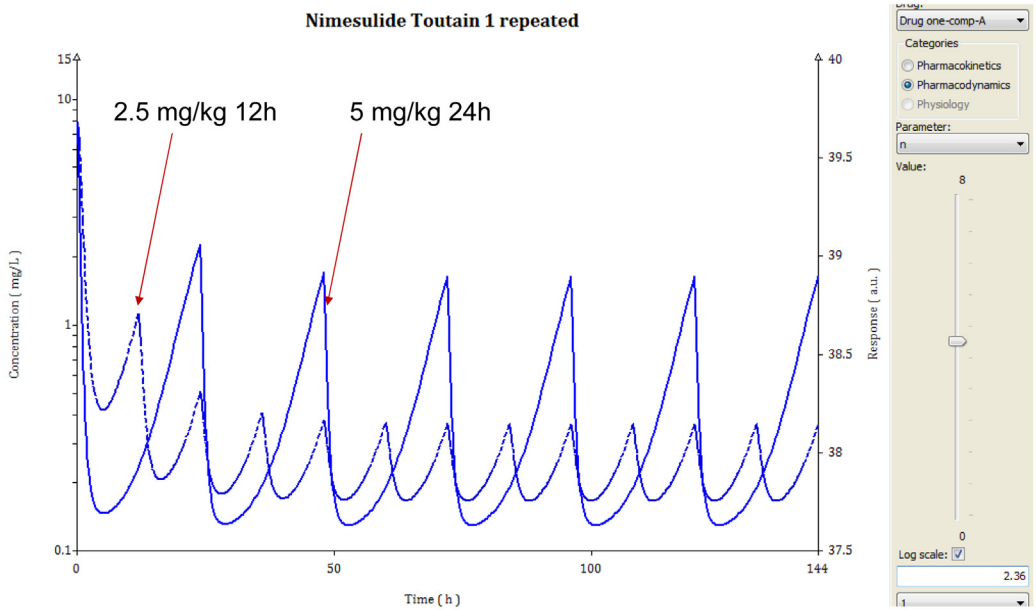

Fig. 12 – Linear (right hand axis) plot of the response–time course of body temperature in dogs after repeated oral doses of 5 mg kg^{-1} 24 h^{-1} and 2.5 mg kg^{-1} 12 h^{-1}. Data were simulated from mean parameters obtained from eight dogs. Visual inspection of the simulations suggests superiority of the 2.5 mg kg^{-1} 12 h^{-1} dosage regimen. For a detailed description of the underlying kinetic and dynamic model structures see Toutain et al. [10].

3.9. *Pharmacological application: clinical significance of potency differences*

Most students easily grasp the definition of the EC_{50} value, but in many examples that a student may encounter, either from published studies or in teaching exercises, much focus is put on drug potency and its correlation to the EC_{50} value, without considering drug efficacy. When they later learn about the concept of partial and full agonists, some students reflect over the validity of EC_{50} as a pure and simple parameter for describing potency. This exercise tries to elucidate the complexity within the questions of potency and efficacy. In addition to the Maxsim2-tasks, the students are expected to construct two ordinary dose–response curves out of the peak responses

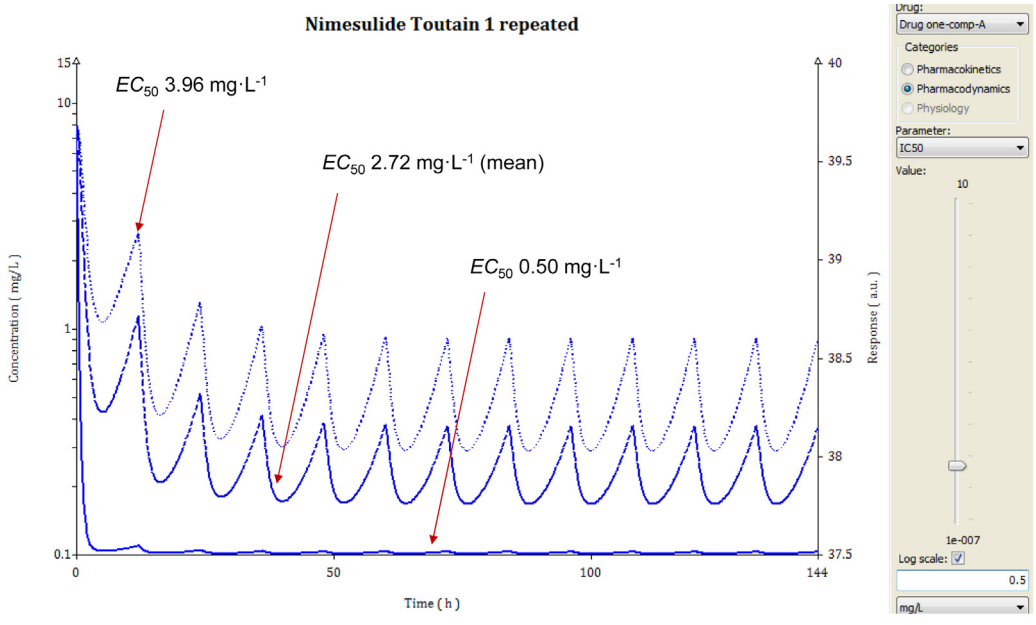

Fig. 13 – Linear (right hand axis) plot of the response–time course of body temperature in dogs after repeated oral doses of 2.5 mg kg^{-1} 12 h^{-1}. Data were simulated from low potency value (EC_{50} = 3.96 mg L^{-1}, upper curve), mean potency in the eight dog population (EC_{50} = 2.72 mg L^{-1}, middle curve) and a high potency value (EC_{50} = 0.50 mg L^{-1}, bottom curve). Visual inspection of the simulations demonstrates the impact of a change with respect to intensity and duration of response [10].

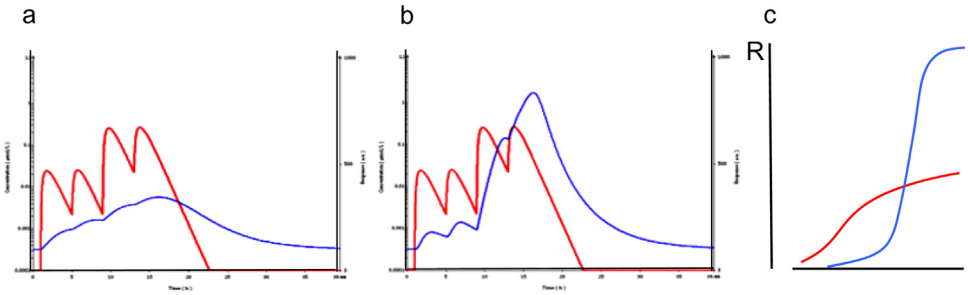

Fig. 14 – Semi-logarithmic plot of the concentration–time course (red line) and linear plot of response–time (blue line: excretion of sodium ions in urine) of two diuretics (a, b) after two repeated doses of 10 mg and two successive doses given of 100 mg. The evaluation of the maximum responses to a number of randomly chosen doses (D) should result in the curves in (c). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

obtained during the exercise – one for the drug with low efficacy and one for that with high efficacy ('the full agonist').

In this case, two agonists are evaluated according to secretagogic pancreatic potency; *e.g.*, pilocarpine and carbachol. A dose–response assessment is performed (10–2000 mg). The pharmacokinetic parameters are very much the same for drug A and B. The system parameters k_{in} and k_{out} are considered to be the same for the drugs. Drug A gives a maximal response of 2 arbitrary units (au) with an EC_{50} of 50 mg and with a Hill coefficient of 0.9. The corresponding parameters for drug B are 4 au, 100 mg and 1.0, respectively

The student is expected to reflect about potency (EC_{50}) and maximum effect, steepness of response-curve, and consequences when increasing the dose to a patient. By examining peak responses to other doses than 10 and 100 mg, the student should eventually construct dose–response curves (for drug A and B). If this is done correctly, the curves should yield different maximum, and ED_{50} values from those presented originally (Fig. 15).

3.10. *Clinical significance of nonlinear concentration–response curves – schedule dependence*

Schedule dependence is the result of a nonlinear concentration–response relationship. Since many drugs display a saturable effect relationship (Sigmoidal or Hill-type of relationship), schedule dependence is an important topic to tackle for an overall understanding of the consequences on the clinical outcome when designing a dosing regimen. A good understanding can easily be reached by practicing simulations. Fig. 16 demonstrates the relationship between concentration and time, and pharmacological response and time, when a dose of 120 mg is given as a single dose or separated into three dosing occasions (3× 40 mg). In this case, the integral of the pharmacological response is >50%) greater with the separated dosing regimen; a typical example of dose-schedule dependence. The split regimen not only results in a lower peak-to-trough variability but also an extended pharmacological utility of the medicine.

4. Discussion

Computer models have become common and important supportive tools in university courses [5]. The advantages are apparent. The models are relatively cheap and individually accessible tools that allow for problematizing of course contents. The integration of these models with supervision performed in dialog with the student creates an almost ideal learning situation [6]. However, technology-based learning (TBL) has its disadvantages. Examples of drawbacks are that

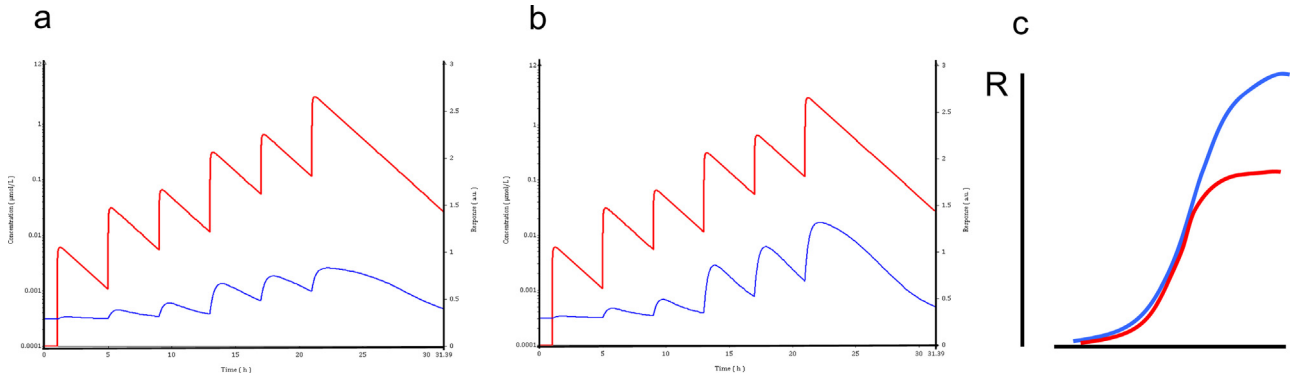

Fig. 15 – Semi-logarithmic plot of the concentration–time course (red line) and linear plot of response–time (blue line: excretion of sodium ions in urine) of two secretagogues (a, b) after oral doses of 10, 20, 100, 200, 1000 and 2000 mg. The evaluation of the maximum responses to a number of randomly chosen doses should result in the curves in (c), where the red dose–response curve relates to the system presented in (a) and the blue dose–response curve to the system in (b). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

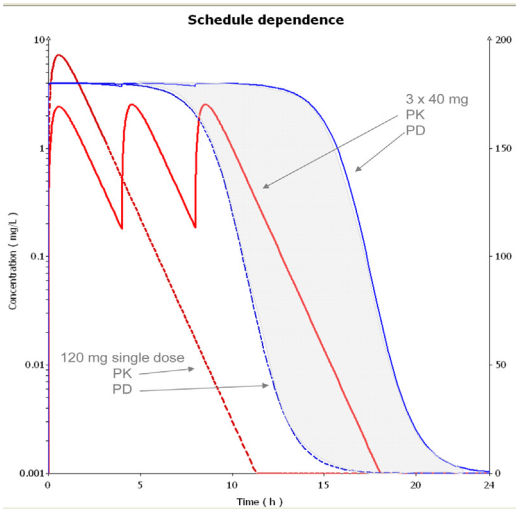

Fig. 16 – Semi-logarithmic plot of the concentration–time courses (red curves and left axis) and the corresponding response–time courses (blue curves and right hand axis) following a single 120 mg dose and 3 × 40 mg separated by 4 h. The shaded area is the extra clinical value from splitting the 120 mg into three separated doses – dose–schedule dependence. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Data taken from Wright et al. [12].

some students still have low computer literacy and that students may become frustrated by course material and technology, resulting in less engagement. Students' appreciation of TBL has been noted to decrease for several reasons, one of which is the course leader's ignorance of software.

We believe Maxsim2 addresses many of these drawbacks by its flexibility. The user-friendly software can be maneuvered at easily accessible levels, as well as at more advanced ones. In addition, since Maxsim2 can address problems at varying levels, it is less likely to cause student attrition. The simplicity of the program commands likely overcomes another pedagogic issue as well, which is that students often focus on succeeding in handling the software package and do not reflect on the meaning of the results. To succeed in understanding the meaning of results it is important to analyze the different components of a task and how they are synthetized by giving the student reinforcing feedback in a well-structured manner so that ability and knowledge of the learner develops in accordance with course goals [8]. Maxsim2 integrates detailed tasks with reflecting information, which leads to fewer such problems. Moreover, students can work in small groups, which stimulate more thorough theoretical discussions than are possible during traditional seminars and workshops.

We believe that Maxsim2, centered on real-time interactivity through 'the slider' concept, offers several advantages. The major one is that it gives the student an idea of the physiological determinants that govern the disposition of a drug, and also how pharmacokinetic parameters are related to each other. Maxsim2 takes this one step further and integrates exposure with pharmacological responses. It demonstrates more clearly that target engagement is a conglomerate of dose, clearance, potency and system properties. This can easily be studied without equations at the undergraduate level. By elaborating these models, the student realizes that parameters like clearance, volume of distribution, and bioavailability are variables and not constants, as they are usually regarded. Furthermore, because it is an interactive program, Maxsim2 gives a quick answer in '*real time*' to a certain question, rather than the traditional way of solving a problem by hand calculator. Experiments that previously have taken days to carry out *in vivo* can now easily be simulated in real-time within seconds and the student instantly observes the impact of a parameter change on the concentration–time or response–time course(s). Another important advantage of this type of teaching aid is that it forces the student to participate more actively in problem-solving than the methods commonly used. Students may also feel that they are 'in charge of' drug therapy of the hypothetical patient, which may motivate them to discuss and test new alternative methods in drug therapy.

Maxsim2 was written to simulate the impact of different modes of administration on the disposition of a specific drug, and how a change in the physiology affects the pharmacokinetics during single and multiple dosing. So far, the students' response has been that the program saves time and makes the learning process of pharmacokinetics and pharmacodynamics more attractive. The program also allows the user complete control over design, monitoring, and adjustment of each dosage regimen. It makes the communication to a small conference room or a large auditorium easy and direct. The program is adaptable to many different situations, for example simulating varying dosing intervals, self-administration of drugs at a certain concentration level, drug interactions, nonlinearities, and target-mediated drug disposition. Furthermore, the program involves less mathematics to explain a particular relationship, and the stresses more of the biological or physiological approach to pharmacokinetics and pharmacodynamics. These are important factors since pharmacokineticists and pharmacologists today are oriented more toward the physiological approach [11].

In pharmacology courses addressing general principles, teachers often tend to discuss pharmacological parameters in an isolated way, rather than in their full context. This tendency may result in lack of a holistic perspective [7]. One obvious example is when the meaning of an EC_{50}-value is introduced. The students learn, without actually understanding the meaning of it that this is the agonist concentration that results in a half maximum response (potency). However, to fully grasp the significance of the parameter, both E_{max} (full or partial agonism) and the Hill coefficient need to at least be considered. Maxsim2 provides excellent opportunities for students to increase their understanding of the pharmacological significance of different parameters. By practically applying the parameters in Maxsim2 models, the importance for functional effects can be simulated. A further dimension of the interplay is provided by the Maxsim2-simulated response being the composite result of both pharmacokinetic and pharmacodynamic parameters and variables. The understanding of the Maxsim2 simulation may be further elucidated if responses are presented and analyzed in conventional dose–response diagrams. The Maxsim2 software has

the advantage of allowing the user to adapt the exercises to a suitable level, and the given examples are beneficially preceded by exercises dealing with just simple demonstrations of, for instance, the significance of differences in potency (variation of only the EC_{50} value) or the Hill coefficient (variation of only n).

Another advantage of the Maxsim2 software is its presentation of the responses, in which the plasma concentration–time and the response–time courses will be displayed. This is one aspect of dose administration that often is neglected in pharmacology teaching, and it highlights how changes of dosage regimens actually affect the patient. However, the impact of some parameters may be more clearly demonstrated in traditional dose–response diagrams. This may be plotted separately, and here the user can see how a large value of the Hill coefficient compresses the curve. The combination of the two ways of displaying data, as well as of the user's hands-on analyses, greatly aids a complete understanding of drug effects in the body. In this way, Maxsim2 enables student-centered learning by a phenomenographic approach [9].

Yet another advantage of the Maxsim2 software is that experiments that earlier have been ethically or practically difficult to perform *in vivo* can now easily be carried out in sequence in a very short time and at a low cost. Work with the program has generated many new ideas on further development for example modeling drug–drug interactions, modeling of inter-species scaling and plasma protein interactions. However, this can only come about with the participation of a larger group of critical users using the program and gradually refining and improving its structure.

A fully functional limited-in-time trial version of the software can be downloaded at www.maxsim2.com.

Conflict of interest

None declared.

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Glossary

Glossary

A: amount of drug in the GI tract (*e.g.*, mg, μmol)
C_L: ligand concentration (*e.g.*, $\mu g\,L^{-1}$, $\mu mol\,L^{-1}$)
C_P: plasma concentration (*e.g.*, $\mu g\,L^{-1}$, $\mu mol\,L^{-1}$)
C_R: target concentration (*e.g.*, $\mu g\,L^{-1}$, $\mu mol\,L^{-1}$)
C_T: peripheral compartment concentration (*e.g.*, $\mu g\,L^{-1}$, $\mu mol\,L^{-1}$)
C_{RL}: receptor–ligand complex concentration (*e.g.*, $\mu g\,L^{-1}$, $\mu mol\,L^{-1}$)
Cl_d: inter-compartmental distribution term (*e.g.*, $L\,min^{-1}$, $mL\,min^{-1}$)
Cl_L: ligand clearance (*e.g.*, $L\,min^{-1}$, $mL\,min^{-1}$)
Cl_P: plasma clearance (*e.g.*, $L\,min^{-1}$, $mL\,min^{-1}$)
D_{iv}: intravenous bolus dose (*e.g.*, mg, μmol)
D_{inf}: intravenous infusion dose (*e.g.*, mg, μmol)
D_{oral}: oral (extravascular) dose (*e.g.*, mg, μmol)
EC_{50}: potency (*e.g.*, $\mu g\,L^{-1}$, $\mu mol\,L^{-1}$)
E_{max}: efficacy parameter for stimulatory drug action (arbitrary units)
E_0: baseline response (arbitrary units)
f_A: fraction absorbed (used as extent of bioavailability for compartment models)
GI: gastro-intestinal
IC_{50}: potency (*e.g.*, $\mu g\,L^{-1}$, $\mu mol\,L^{-1}$)
I_{max}: efficacy parameter for inhibitory drug action (arbitrary units)
In(t): input rate from either a bolus dose, extravascular administration or constant rate infusion (*e.g.*, $\mu g\,min^{-1}$, $\mu mol\,min^{-1}$)
K_A: first-order absorption rate constant from the GI tract to plasma or blood (*e.g.*, min^{-1}, h^{-1})
k_{deg}: first-order fractional receptor turnover rate constant (*e.g.*, min^{-1}, h^{-1})
$k_{e(RL)}$: first-order receptor–ligand complex elimination rate constant (*e.g.*, min^{-1}, h^{-1})
K_m: Michaelis–Menten constant (*e.g.*, $\mu g\,L^{-1}$, $\mu mol\,L^{-1}$)
k_{off}: receptor–ligand complex first-order off-rate constant (*e.g.*, min^{-1}, h^{-1})
k_{on}: receptor–ligand complex second-order on-rate constant (*e.g.*, $\mu mol\,L^{-1}\,min^{-1}$, $\mu g\,L^{-1}\,h^{-1}$)
K_{pi}: tissue-to-blood partition coefficient

k_{syn}: zero-order receptor turnover rate constant (*e.g.*, $\mu g\,min^{-1}$, $\mu mol\,h^{-1}$)
n: Hill coefficient also called the sigmoidicity parameter
PD: pharmacodynamics
PK: pharmacokinetics
Q_i: blood flow where *i* denotes brain, GI tract, skeletal muscle, *etc.* (*e.g.*, $L\,min^{-1}$, $mL\,min^{-1}$)
R_0: target baseline concentration (*e.g.*, $\mu g\,L^{-1}$, $\mu mol\,L^{-1}$)
V_C: central compartment (*e.g.*, L, mL)
V_i: tissue volume where *i* denotes brain, GI tract, skeletal muscle, *etc.* (*e.g.*, L, mL)
V_{max}: maximum metabolic rate (*e.g.*, $\mu g\,min^{-1}$, $\mu mol\,h^{-1}$)
V_T: tissue compartment volume (*e.g.*, L, mL)