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Three Examples Illustrating the Good Performance of an Advanced Mathematical Modeling Method Based on the Theory of Dynamic Systems in Pharmacokinetics

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Abstract

The objective of the current study is to give three examples illustrating the good performance of an advanced mathematical modeling method based on the theory of dynamic systems in pharmacokinetics. The performance of the modeling method considered in the current study is illustrated in the following examples: 1) the first example illustrates the development of a mathematical model of the pharmacokinetic behavior of a drug administered orally; 2) the second example illustrates the determination of a physiologically realistic structure of the mean residence time of a drug administered orally; 3) the third example illustrates the development of a combined parent-metabolite mathematical model.

In all examples, the mathematical models developed successfully fitted to the experimental data.

Introduction

The basic idea behind the modeling method used in the current study may seem rather complicated. Over simplifying, this idea can be explained as follows: Figure 1, (taken from the author's web page http://www.uef.sav.sk/advanced.htm) shows the working example used in the current study. The schematically illustrated drug administration is in the column headed "INPUTS", and the schematically illustrated resulting plasma concentration-time profiles of the drug administered are in the column headed "OUTPUTS". In the working example, the following key assumptions are applied: 1) a single bolus drug dose is administered intravenously to a hypothetical subject (see the first scheme in the column "INPUTS"); 2) a drug is administered by an infusion to a hypothetical subject (see the second scheme in the column "INPUTS"); 3) a drug is administered by repeated multiple bolus doses to a hypothetical subject (see the third scheme in the column "INPUTS"); 4) the drug dose, the site of measurement of the plasma concentration-time profiles of the drug administered, and physiological properties of the body remind unchanged during the working experiment.

By using traditional modeling methods such as compartment methods, significantly different models of the pharmacokinetic behavior of the drug administered are obtained. The reason for this is that compartment methods use only plasma concentration-time profiles of administered drugs. In the working example shown in Figure 1, the resulting plasma concentration-time profiles of the drug administered are different, therefore, the models developed by a compartment method are also different. On the contrary, modeling methods based on the theory of dynamic systems simultaneously uses both: the mathematically described inputs of drugs into the body and plasma (or blood) concentration-time profiles of drugs administered. Models developed in this way are dependent only on physiological properties of the body, and on the ADME properties of the drugs administered. Therefore, the same models are obtained for the pharmacokinetic behavior of the drug administered, irrespective whether the drug is administered by a single-bolus dose, or by an infusion, or by multiple bolus doses, assumed in the working example shown in Figure 1. ADME is a well-known acronym commonly

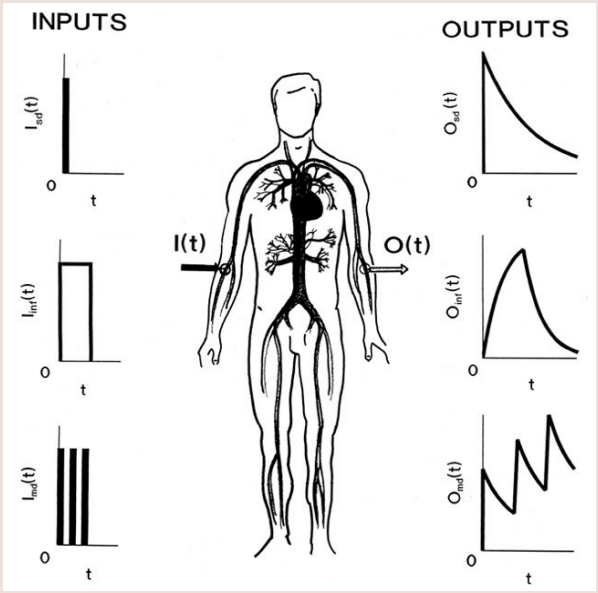

Figure 1: Working example showing schematically an intravenous drug administration to a hypothetical subject in a single bolus dose, by a constant-rate short-time infusion, by repeated multiple bolus doses (the column "INPUTS"). Resulting plasma concentration-time profiles of the drug are schematically shown in the column OUTPUTS.

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used in pharmacokinetics. It stands for absorption, distribution, metabolism, and excretion of a drug administered [1].

It is well known that dynamic processes associated with the pharmacokinetic behavior of an administered drug are controlled by several mechanisms and are influenced not only by diverse interactions between the drug administered and a physiological environment but also by various factors [2,3]. Since the pharmacokinetic behavior of an administered drug is a complicated dynamic process, dependent upon a variety of independent factors, several studies described investigations of the pharmacokinetic behavior of administered drugs in the body using advanced modeling methods based on the theory of dynamic systems, see for example, the following studies [4-17] and the references therein. Three examples illustrating a successful use of an advanced modeling method based on the theory of dynamic systems in pharmacokinetics are also given in the current study.

The modeling method used in the current study was developed by Dedík [7,8]. It has been effectively used in several studies; see for example, the studies cited in the previous paragraph. Using the modeling method considered here, investigations of dynamic systems can be performed in a variety ways. In pharmacokinetics, the given modeling method can be advantageously used to investigate the pharmacokinetic behavior of an administered drug in the following way: In the first step of an investigation, an ADME related dynamic system (thereafter only dynamic system) is defined in the complex domain, and is used to mathematically represent static and dynamic aspects of the pharmacokinetic behavior of an administered drug in the body, see, for example, the studies cited in the previous paragraph. In the second step of an investigation, a mathematical model of the dynamic system is developed and point estimates of model parameters are determined in the complex domain, using the non-iterative modeling method published previously [18]. In the third step of an investigation, an optimal model of the dynamic system is selected, using the Akaike information criterion modified for the use in the complex domain [6,19].

Examples

The first example illustrates the development of mathematical models of the pharmacokinetic behavior of pentacaine in healthy volunteers. Pentacaine is a long-acting carbanilate type local anaesthetic [20]. In the comparative study [4], the pharmacokinetic behavior of pentacaine in healthy volunteers was investigated using data collected during the clinical trial of pentacaine. A short description of the comparative study [4] is as follows: Pentacaine was orally administered to healthy volunteers. The modeling program CXT (based on the theory of dynamic systems) [7-10] and modeling program VisSim [21] were employed to develop mathematical models of the pharmacokinetic behavior of pentacaine in the healthy volunteers enrolled in the study [4]. The results obtained revealed that the best approximations of the plasma concentration-time profiles of pentacaine were obtained using the CXT in all healthy volunteers [4] (see Figure 2, taken from the author's previous study [4]).

The second example illustrates a section from the author's previous study [15]. The section shown corresponds to the determination of the physiologically realistic structure of a mean residence time MRT_{po} of a drug administered orally in an immediate release dosage form to a hypothetical subject. The physiologically realistic structure of a mean residence time MRT_{iv} of an intravenously administered drug to a human subject was determined in the previous study by the author [14]. It is described by the following equation:

$$MRT_{iv} = F_{cp} + F_p + F_h + F_o + F_r. \quad (1)$$

Five interconnected structural components related to the pharmacokinetic behavior of an intravenously administered drug to a human subject occur on the right-hand side of Eq. (1). The structural component F_{cp} describes the contribution to MRT_{iv} by the dynamic process associated with the drug dynamic transit [22] in the cardiopulmonary subsystem H_{cp} [23]. (A subsystem of a dynamic system is a part of a dynamic system which itself has characteristics of a dynamic system). The structural component F_p describes the contribution to MRT_{iv} by the dynamic process associated with the drug dynamic transit in the portal-venous subsystem H_p [24]. The structural component F_h describes the contribution to MRT_{iv} by the process associated with the drug dynamic transit in the hepatic-portal subsystem H_p [22,24]. The structural component F_o describes the contribution to MRT_{iv} by the process associated with the drug dynamic transit in the subsystem H_o. The subsystem H_o mathematically represents drug fate and disposition in non-eliminating tissues. If the drug is subject to the enterohepatic circulation (EHC) [25], the structural component F_r describes the contribution to MRT_{iv} by the dynamic process associated with the drug dynamic transit in the subsystem H_r. The subsystem H_r mathematically represents the dynamic process associated with *EHC*, and the structural components F_p and F_0 are as follows:

$$F_p = \frac{Q_h - Cl_h}{Cl_h}\frac{Q_p}{Q_h}MT_p, \quad (2)$$

$$F_h = \frac{Q_h - Cl_h}{Cl_h}MT_h, \quad (3)$$

$$F_o = \frac{Q_o}{Cl_h}MT_o. \quad (4)$$

In Eqs. (2)-(4), Q_p is blood flow in the portal vein, Q_o is blood flow in non-eliminating tissues, Cl_h is the hepatic clearance of the drug administered, MT_p is the mean time of the drug dynamic transit in the portal-venous subsystem, MT_h is the mean time of the drug dynamic transport in the hepatic-portal subsystem, and MT_o is the mean time of the drug dynamic transit in the subsystem H_o, where

$$MT_o = \frac{\sum_{i=1}^{q} Q_i.MT_i}{Q_o}, \quad (5)$$

and MT_i is the mean time of the drug dynamic transit in non-eliminating tissues, the i subscript specifies a tissue [24].

In order to mathematically represent dynamic processes associated with drug fate and disposition after an oral administration, the dynamic system H_{po} was defined, and a circulatory model of the dynamic system H_{po} was developed. The developed circulatory model of the dynamic system H_{po} is diagrammed in Figure 3, which was taken from the previous study by the author [15], preformed under equal condition as the current study. The study cited here can be briefly described as follows: The determination of the physiologically realistic structure of MRT_{po} was performed in the following steps: In the first step, a working example was prepared

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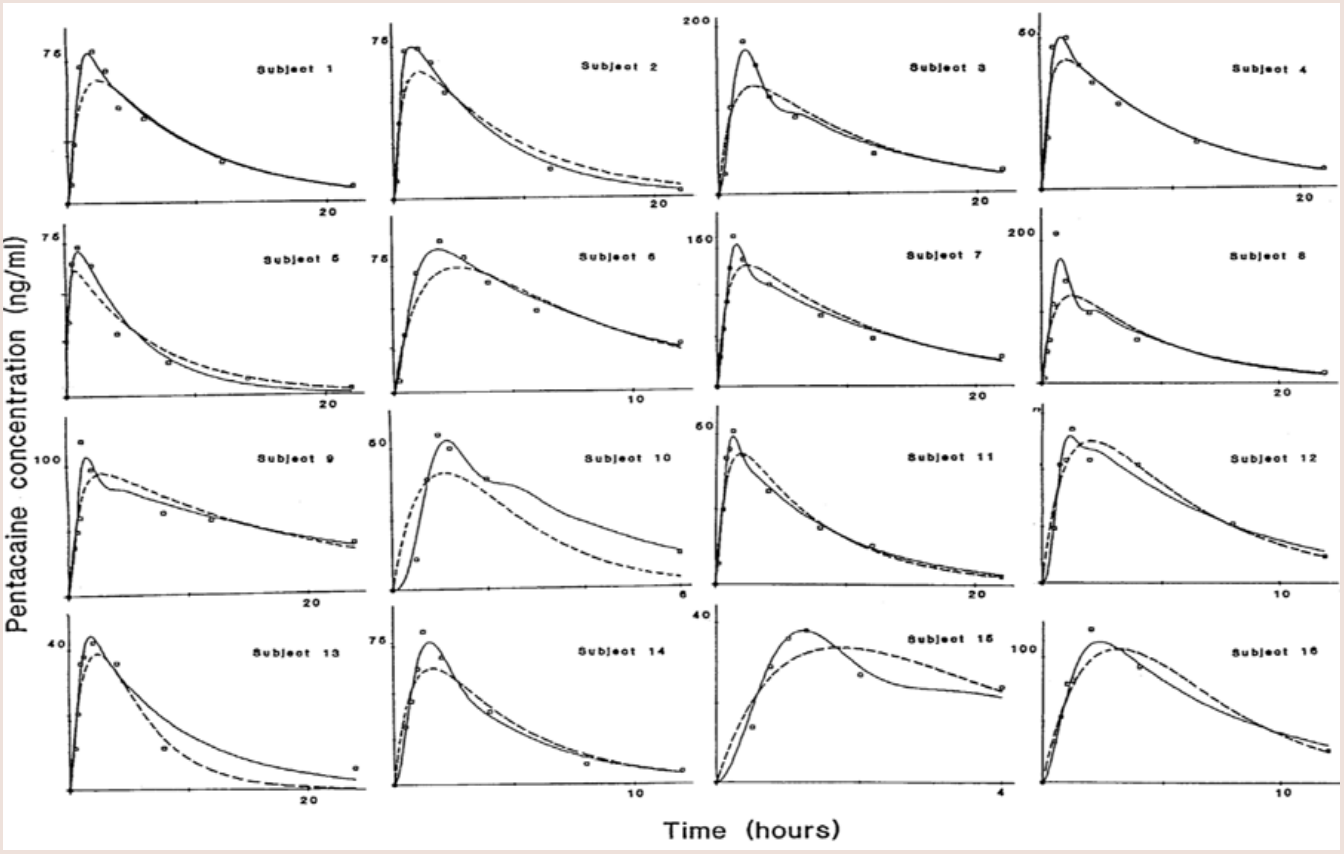

Figure 2: Plasma concentration-time profiles of pentacaine (stars). Approximation by the model developed by a compartment method (dotted line). Approximation by the model developed by a method based on system approach (full line).

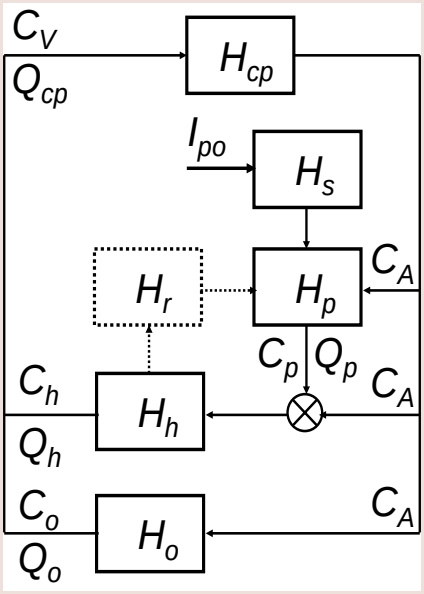

Figure 3: The circulatory model of the dynamic system H_{po} which mathematically represents dynamic dynamic process of drug fate and disposition after an oral drug administration. *Ipo* is oral drug administration. *D* is the drug dose, *t* is time. C_A is the concentration-time profile of the drug in arterial blood. C_V is the concentration-time profile of the drug in venous blood. H_{cp} is the cardiopulmonary subsystem. H_p is the portal-venous subsystem. H_h is the hepatic subsystem. H_o is the subsystem representing non-eliminating tissues. H_r is the subsystem representing the enterohepatic cycling. C_p is the concentration-time profile of the drug in the subsystem H_p. C_h is the concentration-time profile of the drug in the subsystem H_h. C_o is the concentration-time profile of the drug in the subsystem H_o. Q_{cp}, Q_p, Q_h, Q_o are the blood flows through the subsystems specified by a subscript. The symbol ⊗ denotes a summation operator.

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and used to schematically illustrate the drug dynamic transit [22] in the body after an oral administration to a hypothetical subject. In the second step, the following simplifying assumptions were made: a) the drug was uniformly distributed in the body; b) the drug was eliminated mainly by hepatic excretion; c) the drug was not bound to plasma proteins or tissues; d) the drug was completely dissolved in the stomach, and emptied into the duodenum; e) no barriers to the distribution (or elimination) of the drug existed. In the third step, a circulatory model of the dynamic system H_{po} was developed. In the fourth step, the following equation was derived for the description of MRT_{po} in the Laplace (s) domain:

$$MRT_{po} = \frac{\lim_{s\to 0} \frac{dH_{po}(s)}{ds}}{\lim_{s\to 0} H_{po}(s)}, \quad (6)$$

In Eq. (6), $H_{po}(s)$ is the transfer function [4-17] of the dynamic system H_{po}. In the last step, the physiologically realistic structure of MRT_{po} was determined, using Eq. (6), the circulatory model of the dynamic system H_{po} developed, the previously published method [5,8], and all assumptions concerning the pharmacokinetic behavior of the drug administered. The determined physiologically realistic structure of MRT_{po} is described by the following equation:

$$MRT_{po} = MT_s + MT_p + MT_h + MRT_{iv}. \quad (7)$$

The right-hand side of Eq. (7) comprises four interconnected structural components involved in the pharmacokinetic behavior of the orally administered drug. MT_s is the mean time of the drug dynamic transit [22] in the subsystem H_s, *i.e.* in the subsystem mathematically representing the following dynamic processes: disintegration of a drug formulation, liberation of a drug from a drug formulation, drug dissolution, hepatic and intestinal first-pass effects (if present), and gastric emptying; MT_p is the mean time of the drug dynamic transit in the portal subsystem H_p, MT_h is the mean time of the drug dynamic transit in the hepatic-portal subsystem H_h. MRT_{iv} in Eq. (7) is the same as that in Eq. (1). The sum of the mean times $MT_s + MT_p + MT_h$ in Eq. (7) is total mean time of the drug dynamic transit from the gastrointestinal tract to the blood circulation, see Figure 3. Assuming that *EHC* [25] was not present, the following equation was developed for the description of the structural component F_r:

$$F_r = f_r \frac{Q_h Cl}{Q_h f_r Cl}(MT_h + MT_p + MT_r). \quad (8)$$

The sum of the mean transit times $MT_s + MT_p + MT_h$ in Eq. (8) is total mean time of the drug dynamic transit from the gastrointestinal tract to the blood circulation, see Figure 3.

The third example illustrates the development of a combined mathematical model of the dynamic process of the formation of 7-hydroxymethotrexate (7OH-MTX) from methotrexate (MTX) in patients undergoing treatment for psoriasis with MTX [26]. The chemotherapeutic agent methotrexate (MTX) is widely used in tumor therapy for different forms of leukemia, as well as for the therapy of patients with arthritis and/or psoriasis [26-29]. In the study [26], MTX was administered to psoriatic patients in a single oral dose of 15 mg once per week, and the investigation of pharmacokinetics and pharmacodynamics of MTX was performed in the early phase (3 months) after the start of therapy of psoriatic patients with MTX. In the current study, combined models for MTX and 7OH-MTX are developed Figure 4a, Figure 4b, Figure 4c, using data kindly provided by the authors of the study [26]. The development of the models started with the definition of the dynamic systems *H* in the complex domain. Thereafter, the transfer functions *H(s)* (*s* is the Laplace variable) of the dynamic systems *H* were derived by relating the Laplace transforms

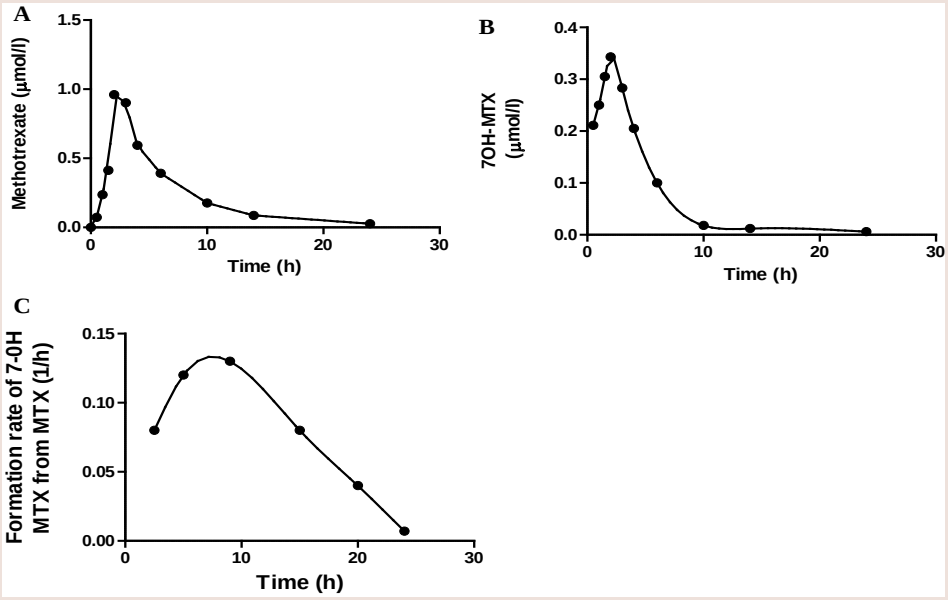

Figure 4: a) Plasma concentration-time profile of orally administered methotrexate to a patient with psoriasis. **b)** Plasma concentration time profile of 7-hydroxymethotrexate in a patient with psoriasis and approximation of the profile with a model developed by a method based on system approach. **c)** Formation rate of 7-hydroxymethotrexate from orally administered methotrexate to a patient with psoriasis.

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of the blood concentration-time profiles of 7OH-MTX ($C_{7OH-MTX}(s)$) to the Laplace transforms of the blood concentration-time profiles of MTX ($C_{MTX}(s)$) :

$$H(s) = \frac{C_{7OH-MTX}(s)}{C_{MTX}(s)}. \quad (9)$$

Employing the models developed, the following quantities were determined: metabolic ratios, mean times of the formation dynamic process of 7OH-MTX from MTX, and rates of the formation dynamic process of 7OH-MTX from MTX. The results obtained revealed that the metabolic ratio were approximately constant (0.67, 0.58, 0.59) during the first three months of the treatment of the patients with psoriasis with MTX. However, the mean times of the dynamic process of the formation of 7OH-MTX increased, from the value of 9.35 h (after the first dose of MTX) to the value of 15.59 h (after thirteenth dose of MTX). The formation rates of 7OH-MTX from MTX decreased from a maximal value of about 0.06 (1/h) after the first MTX dose to a maximal value of about 0.031 (1/h) after the thirteenth MTX dose, see Table 1.

Discussion

The current study presented three examples of an advantageous use of the modeling method based on the dynamic systems theory in pharmacokinetics. The details of the modeling method used, were not presented, they are beyond the scope of the current study. Instead, the reader interested in the details of the modeling method used was referred to the following studies [4-17]. The current study wonted to inspire readers and help them to become familiar with an advanced modeling method based on the theory of dynamic systems.

A few examples describing the successful use of a modeling method based on the theory of dynamic systems in pharmacokinetics can be found in the full-text articles available for free on the Internet: http://www.uef.sav.sk/advanced.htm.

Advantages of the modeling method based on the theory of dynamic systems over the traditional modeling methods used in pharmacokinetics were described in detail in the previous studies [4-17] authored and/or Co authored by the author of the current study.

Note

The research work of the author in the 6FP-Project "EU-Network of excellence BioSim "Biosimulation a new tool in drug development" and the 7FP-Project "EU-Network of Excellence, Virtual Physiological Human" led to the preparation of the current study.

Table 1:

	First MTX dose	Fifth MTX dose	Thirteenth MTX dose
Metabolic ratio	0.67±0.08*	0.58±0.05	0.59±0.09
Mean formation time time of 7OH-MTX from MTX (h)	9.35±1.79	9.90±1.02	15.59±2.214

*SD
MTX – methotrexate

During the preparation of the current study, the author participated in the Action BM1204 of the COST program entitled: An integrated European platform for pancreas cancer research: from basic science to clinical and public health interventions for a rare disease.

Concluding Remarks

J. G. Wagner in his earlier study wrote: modern view of pharmacokinetics must include both linear and nonlinear systems. The current study and also the previous studies authored and/or coauthored by the author of the current study are in line with the idea presented by Wagner in his earlier study [30].

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