# Software Supported Modelling in Pharmacokinetics



[1] CiT GmbH,
Oldenburger Str. 200,
D-26180 Rastede, Germany
r.telgmann@cit-wulkow.de
[2] Freie Universität Berlin,
Department of Mathematics and Informatics,
Arnimallee 6,
D-14195 Berlin, Germany
{kleist, huisinga}@math.fu-berlin.de

**Abstract.** A powerful new software concept to physiologically based pharmacokinetic (PBPK) modelling of drug disposition is presented. It links the inherent modular understanding in pharmacology with orthogonal design principles from software engineering. This concept allows for *flexible* and *user-friendly* design of pharmacokinetic whole body models, data analysis, hypotheses testing or extrapolation. The typical structure of physiologically-based pharmacokinetic models is introduced. The resulting requirements from a modelling and software engineering point of view and its realizations in the software tool MEDICI-PK [9] are described. Finally, an example in the context of drug-drug interaction studies is given that demonstrates the advantage of defining a whole-body pharmacokinetic model in terms of the underlying physiological processes quite impressively: A system of 162 ODEs is automatically compiled based on the specification of 7 local physiological processes only.

## 1 Introduction

Pharmacokinetics is the study of the time course of drug and metabolite levels in different fluids, tissues, and excreta of the body [12]. This includes the investigation and understanding of the processes of absorption, distribution, metabolism, and excretion (ADME). The pharmacokinetic profile of a drug strongly influences its delivery to biological targets, thereby affecting its efficacy and potential side effects. Following studies in the late 1990s indicating that poor pharmacokinetics and toxicity were important causes of costly late-stage failures in drug development, it has been widely perceived that these areas need to be considered as early as possible in the drug discovery process [1]. Today's combinatorial chemistry and high throughput screening methods enlarged the space of drug candidates significantly, creating actual needs for *in silico* pharmacokinetic analysis to support the drug development pipeline. The pharmacokinetics of a compound are

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typically understood, analyzed and interpreted in the context of their underlying ADME processes. However, there is no unique mathematical model for any of these processes; usually a number of different models with different underlying assumptions, parameterization and applicability are concurrent.

To efficiently support *in silico* modelling and simulation in pharmacokinetics, we propose to inherit the inherent modular structure, which is based on the physiological processes, to the software tool. We describe the concepts of modularity and orthogonality as fundamental principles for the design of a virtual lab in pharmacokinetics. The above mentioned design principles have recently been realized successfully in the software tool MEDICI-PK, that is especially designed to fit the needs in pharmacokinetic modelling. Our approach is illustrated by an example from drug-drug interaction studies.

## 2 Mathematical Modelling in Physiologically Based Pharmacokinetics (PBPK)

A physiologically based pharmacokinetic (PBPK) whole body model is a special type of compartmental model, in which the compartments represent anatomical volumes, such as organs or tissues. The compartments are connected in an anatomically meaningful way, to simulate drug exchange via the blood flow. The conceptional representation of a 15 organ PBPK model is shown in Fig. 1. Each

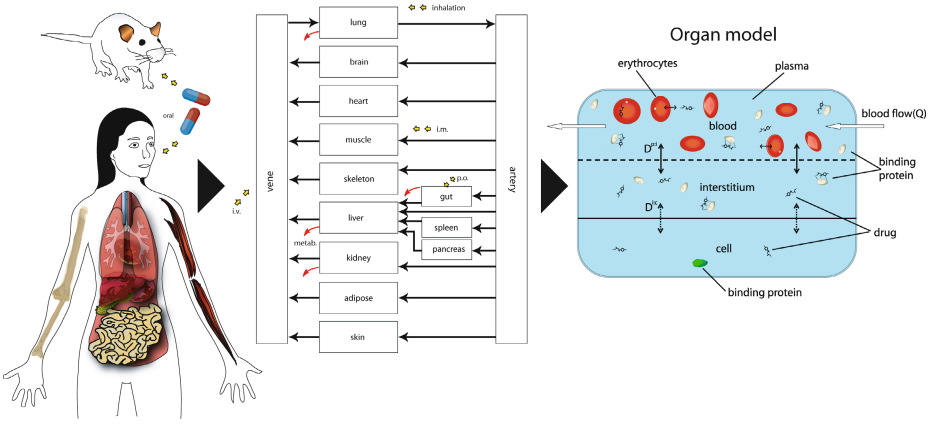


**Fig. 1.** Organ structure of a physiologically based pharmacokinetic model

compartment is further subdivided into the four phases: erythrocytes, plasma, interstitium and cellular space (see Fig. 1). Many physiological processes in pharmacokinetics are accessible for a mechanistic description at this resolution. Typically, following processes are modelled:

- Convection of drug molecules by the blood flow
- Binding to macromolecules in plasma and interstitial space

– Distribution into tissue
– Diffusion or active transport across the cellular membrane
– Metabolism or interaction with metabolic networks or signalling pathways etc.

There are many levels of mathematical description for a certain biological process (e.g., each of the physiological processes stated in the above list). To give an example, the process of protein binding (complex formation) between a compound and some macromolecule can be explicitly modelled in terms of the corresponding differential equations derived from the law of mass action. However, often it is assumed that the binding process is fast in comparison to other processes and therefore in dynamical equilibrium (quasi-stationarity). This results in some algebraic equation, often still accounting for saturation effects of the binding process. A further simplification finally results in a linear algebraic equation that is not capable of accounting for saturation effects, however it may be directly parameterized in terms of a frequently generated *in vitro* parameter.

Each mathematical model has its range of applicability and typically requires different knowledge about the process and in particular different input parameters. In broad terms, a chosen model will be a compromise between detailed mechanistic description and required "quality" of the input parameters. At early stages of drug discovery, frequently measured *in vitro* parameters are used to parametrize early PBPK models. Either the parameter can directly be used in the model, or relevant model parameters are estimated through mechanistic equations [3,4,5] from the measured *in vitro* parameters. Typically, the knowledge and the quality of parameters increases along the drug discovery and development process so that adaptation of the model to the current knowledge and parameter quality is possible (and should be aimed for) [10,11].

The characterization of the PBPK model already suggests a modular description of the whole body model, especially in drug discovery. In mathematical terms, a PBPK model constitutes a set of differential/algebraic equations describing the underlying processes. The current status of software development in pharmacokinetics is dominated by either a purely equation based approach—contradicting user-friendliness—or implementing a static model—contradicting flexibility [10]. Instead, the requirements on user-friendliness and flexibility can be fulfilled by the use of sophisticated modular software concepts and structures, as outlined in the next section.

## 3 Modular Software Design

To support the specification of a whole-body pharmacokinetic model, a variety of physiological processes (as mentioned above) and a corresponding collection of different mathematical models have to be regarded. In practice, identical processes in different compartments will be described by identical mathematical models. From a software engineering point of view it is important to encapsulate the mathematical descriptions into modular parts. These modular parts ("models")–collected in a model library–are defined only once and can be reused inside the whole PK model wherever suitable. This prevents redefinition

and rewriting and ensures the even treatment of identical processes wherever wanted. The models are specified in terms of concentrations and parameters, but (a prerequisite for this approach) do not rely on any specific parameter values. This allows for the evaluation of identical mathematical models in different contexts (by means of different parameter sets).

A given topology (like the 15 organs example) combined with a selection of models from the library (one for each physiological process) builds a description of the PBPK model which is still independent of specific values. It may be evaluated for any selection of parameter values. We call this description a 'full body template' (see Fig.2). The parameters to which the models refer can be classified as (i) compound dependent, (ii) species/individual dependent, (iii) dependent on the compound and species or (iv) independent (general parameters). This classification suggests the introduction of four corresponding software objects, each building an orthogonal structure of its own, independent of the 'full body template'.

For the full specification of a PBPK model, a 'full body template' and values of the required parameters given in the mentioned (i)-(iv) parameter objects have finally to be linked (see Fig. 2) - this is realized by the 'simulation object'.

The models address the concentration of a compound by fixed terms (e.g. "Comp1", "Comp2"). They are independent of an actual compound selection,

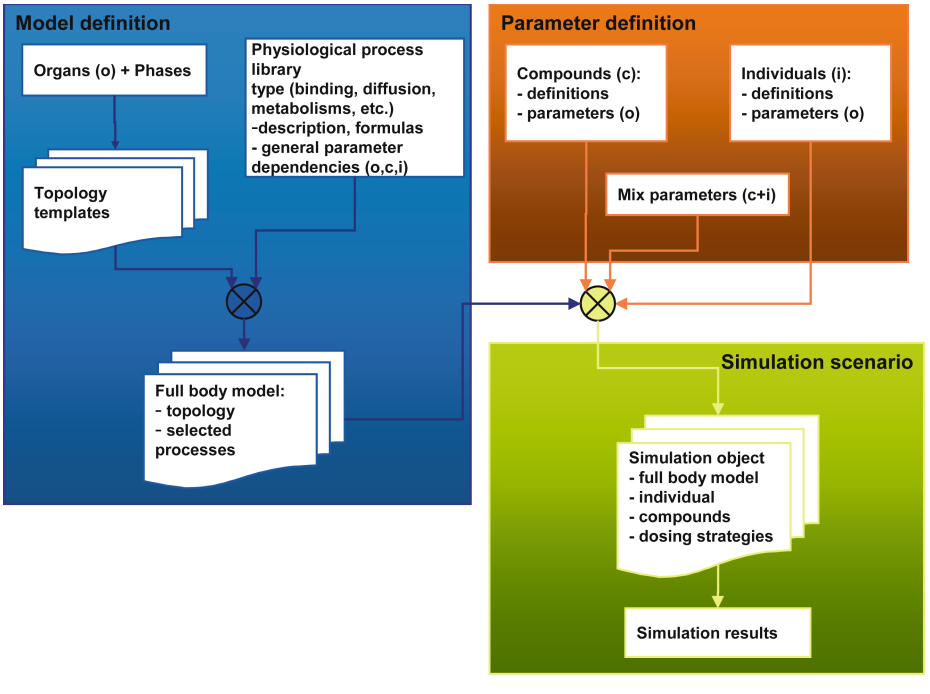


**Fig. 2.** Schematic illustration of the orthogonal approach to software supported pharmacokinetic modelling

which makes it necessary to assign the actual selection of compounds to these expressions. Models which consider only one compound need no assignment, since this is internally handled, however, multi-compound models (e.g. needed in metabolism models for interactions between compounds) necessitate explicit mapping of the terms addressing the different compound concentrations. For instance, the simple metabolism model

$$V\frac{\mathrm{d}}{\mathrm{d}t}C^{(1)} = k_1 C^{(1)} - k_2 C^{(1)} C^{(2)}$$
$$V\frac{\mathrm{d}}{\mathrm{d}t}C^{(2)} = -k_1 C^{(1)} + k_2 C^{(1)} C^{(2)}$$

will be evaluated for two compounds A and B only if the mapping between compounds (A, B) and concentration terms ($C^{(1)}$, $C^{(2)}$) is performed, e.g., compound A to $C^{(1)}$ and compound B to $C^{(2)}$. This has to be done inside the 'simulation object' where the 'full body template' and the compound(s) are specified. As soon as all missing mappings are defined, the PBPK model is completed.

When starting the simulation, the resulting differential equation system is automatically generated, including the assignment of all compound-specific parameter values and species-specific physiological parameter values to the respective processes. An example from drug-drug interaction studies is given in the next section that illustrates the modular and orthogonal concept and illuminates the advantage of defining a whole-body PBPK model in terms of underlying physiological processes quite impressively.

## 4 Examples

Some drugs are administered as so-called pro-drugs that are metabolized into active compounds by liver enzymes. One example is Oseltamivir, better known as Tamiflu [8]. Tamiflu is the main antiflu medicine recommended by the World Health Organization (WHO) [2]. In anticipation of a flu pandemic, the WHO suggests that countries should stockpile enough Tamiflu to allow the treatment of at least a quarter of their population. At present time, however, the supplies of Tamiflu are enough to cover about 2% of the world population only. Recently, Hill et al. [7] highlighted a way to effectively double the supplies of Tamiflu: When administered with a second drug, called probenicid, Tamiflu excretion into the urine is stopped. As a result, only half of the normal doses of Tamiflu are needed. This "wartime tactic" could be used to double power of scarce resources of Tamiflu in case of a flu pandemic [2].

Here, *in silico* modelling and simulation could help to better understand and possibly further optimize the co-administration effects. Motivated by the above example, we want to illustrate how the previously introduced software concepts –realized in MEDICI-PK–can be used to efficiently model the phenomena of pro-drug administration and drug-drug interaction. Our aim is to illustrate the power of our orthogonal and modular approach by establishing complex pharmacokinetic models. It is explicitly not our aim to reproduce experimental data; this is work in progress.

The starting point is the definition of the building blocks in our PBPK model. This is done in terms of the relevant physiological processes like: (a) i.v. absorption, (b) linear protein binding, (c) passive diffusion, (d) tissue distribution (according to [6]), (e) saturable metabolism, (f) renal excretion. Each of the processes (modules) is defined in a 'model basis' by a corresponding mathematical equation. For instance, the processes of saturable metabolism is defined by

$$v_{\text{meta}} = \frac{V_{\text{max}}^{\text{meta}} C_u}{K_{\text{m}}^{\text{meta}} + C_u}, \tag{1}$$

with maximum reaction velocity $V_{\text{max}}^{\text{meta}}$ and Michaelis-Menten constant $K_{\text{m}}^{\text{meta}}$. The concentration of unbound drug is denoted by $C_u$. The process of excretion is specified by

$$v_{\text{excr}} = \left( \text{Q}_{\text{GF}} + \frac{V_{\text{max}}^{\text{ren}}}{K_{\text{m}}^{\text{ren}} + C_u} \right) (1 - \text{F}_{\text{re-abs.}}) \cdot C_u \tag{2}$$

The parameter $V_{\text{max}}^{\text{ren}}$ denotes the maximum velocity of the saturable active tubular excretion process with Michaelis-Menten constant $K_{\text{m}}^{\text{ren}}$. $\text{Q}_{\text{GF}}$ and $\text{F}_{\text{re-abs.}}$ are the glomerular filtration rate and the fraction, that is passively reabsorbed. The renal excretion has been modelled as a function of three processes: (i) passive glomerular filtration (efflux), (ii) active tubular secretion (efflux) and (iii) passive reabsorption. Metabolic clearance in the kidney has been neglected. In total, seven local processes have been defined to model the whole body pharmacokinetics of the three compounds.

The overall PBPK model is then defined by the 'full body template' that links the local physiological process modules on the organ level. For efficiency, it is possibe to define a generic organ structure, which is taken as a default for the initialization of the entire list of organ models. Subsequent individual modifications are possible in order to model organ specific processes, like e.g., excretion by the kidneys. Next, we specify the physiological parameters of the considered species, in our case a 250 g weighting male rat. These values are later needed to fill the model parameters. Finally, we specify the compound-specific data. Motivated by the Tamiflu example, we consider three compounds named A, B, and C; a pro-drug, an active metabolite and a competitive inhibitor for the secretion (of compound B).

At this stage, the three constituents are completely independent. The PBPK model is specified in terms of parameters, however, no actual numerical values are assigned in the model. Only if we map the specific numerical values of the parameters (corresponding to the compound and the species of interest), we obtain a fully specified and ready to simulate so-called 'simulation object'. The advantage of this orthogonal specification and data management is a large flexibility. The same PBPK model can be used for different species and compounds, while the same species database can be used in studies of different models etc. We now demonstrate how to user-friendly and efficiently set up a model for three compounds interacting in a way motivated by the Tamiflu example in three steps. An overview over the necessary modelling steps to be performed is given in Table 1.

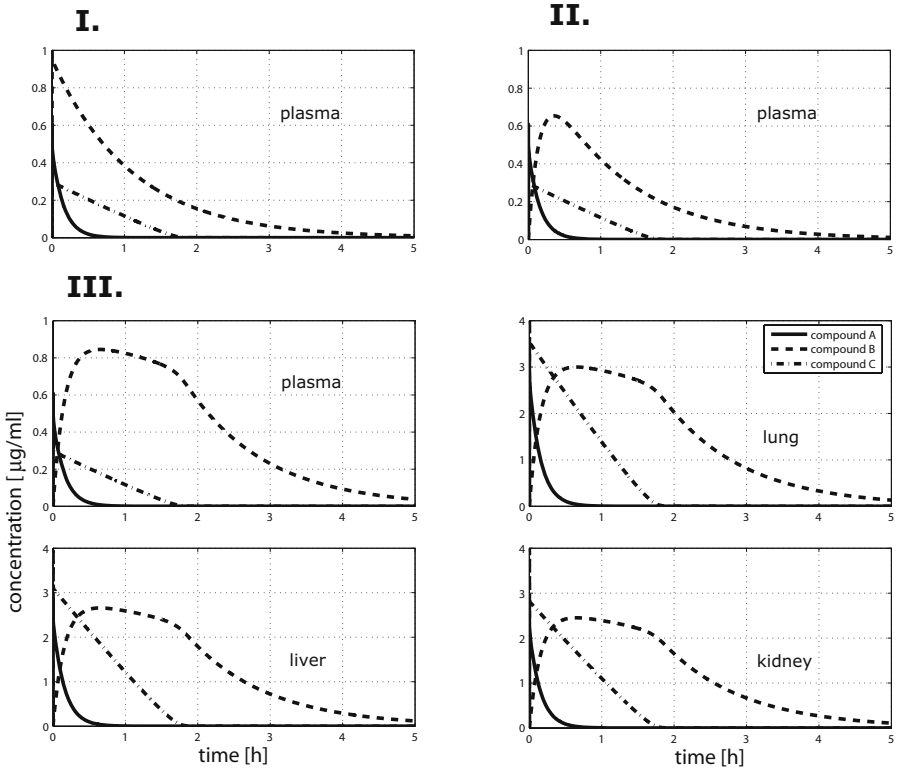


**Fig. 3.** Simulation results as concentration vs. time profiles in venous plasma for (**I.**) *independent pharmacokinetics* (top left) and (**II.**) *conversion of pro-drug A to B* (top right). The simulation results for (**III.**) *competition for tubular excretion* of compounds B and C are shown in the middle and bottom panels. The middle left and right panels shows the concentration vs. time profiles in the venous plasma and interstitial space of the lung, while the bottom panels show the profiles in the cellular space of the liver (bottom left) and kidney.

**Independent pharmacokinetics.** To start with, the pharmacokinetics of the three compounds A, B and C are simulated independently. This is easily performed by creating a 'simulation object', which links the full body model, the species data (rat) and the respective compound data. As a consequence, MEDICI-PK automatically generates a set of model equations for each compound. In this example we have identical models for the three compounds. The resulting pharmacokinetic profiles are shown in Fig. 3 (top left panel) for an intravenous administration of 2 mg/(kg bodyweight) of each compound (modelling details in Table 1). Compounds A, B and C show very different pharmacokinetic profiles. This is due to their distinctive distribution characteristics in the various tissues and due to their different elimination characteristics. While compound C is eliminated in an almost constant

fashion, compound A and B are eliminated in an exponential fashion. Plasma levels of compound B are substantially higher than plasma levels of compound A and C respectively. This is because compound B is mainly distributed in the plasma, with significantly lower concentrations in the interstitium and cellular space.

**Table 1.** Brief overview over the performed simulations

| description | interactions | dosing |
|---|---|---|
| independent pharmacokinetics | - | A: 2[mg/kg body weight] i.v.<br>B: 2[mg/kg body weight] i.v.<br>C: 2[mg/kg body weight] i.v. |
| conversion of pro-drug A to active metabolite B | $A \rightarrow B$ | A: 2[mg/kg body weight] i.v.<br>C: 2[mg/kg body weight] i.v. |
| conversion of pro-drug A to B competition for active tubular excretion between B and C | $A \rightarrow B \downarrow\vdash C$ | A: 2[mg/kg body weight] i.v.<br>C: 2[mg/kg body weight] i.v. |

**Conversion of pro-drug A to B.** We next demonstrate how to link the pharmacokinetics of compound A and B. In physiological terms, we want to model the conversion of compound A into compound B in the liver (see Table 1). Given the 'full body template' from the first simulation scenario, this requires only a single change, namely the adaptation of the metabolism model chosen for compound B in the liver. We define the so-called multi-compound metabolism model

$$v_{\text{meta}} = -\frac{V_{\max}^{(1)} C_u^{(1)}}{K_{\text{m}}^{(1)} + C_u^{(1)}} + \frac{V_{\max}^{C_2} C_u^{(2)}}{K_{\text{m}}^{(2)} + C_u^{(2)}}$$

and subsequently map B to $C^{(1)}$ and A to $C^{(2)}$ in the 'simulation object'. Assuming no i.v. administration of compound B, the simulation results are shown in Fig. 3 (top right panel) for intravenous administration of 2 mg/(kg body weight) of compound A and C.

While the simulation of non-interacting compounds based on the same PBPK model can be solved by successive simulation of a single compound at a time, the consideration of (dynamic) interactions requires to establish a joint model for the interacting compounds. In MEDICI-PK, this is automatically generated exploiting the described software concept. This will become even more obvious in the next case.

**Competition for active tubular excretion.** Finally, we want to include the drug-drug interactions between compound B and C (modelling details in Table 1). In physiological terms, compound C will compete with compound B for active excretion. Given the 'full body template' from the second simulation scenario, this again requires only a single change. We modify eq. (2) to include the competition by

$$v_{\mathrm{CL_{ren}}}^{(1)} = \left( \mathrm{Q_{GF}} + \frac{V_{\max}^{(1)}}{K_{\mathrm{m}}^{(1)}(1 + \frac{C_u^{(2)}}{K_{\mathrm{m}}^{(2)}}) + C_u^{(1)}} \right) \left( 1 - \mathrm{F_{re-abs.}}^{(1)} \right) \cdot C_u^{(1)}$$

$$v_{\mathrm{CL_{ren}}}^{(2)} = \left( \mathrm{Q_{GF}} + \frac{V_{\max}^{(2)}}{K_{\mathrm{m}}^{(2)}(1 + \frac{C_u^{(1)}}{K_{\mathrm{m}}^{(1)}}) + C_u^{(2)}} \right) \left( 1 - \mathrm{F_{re-abs.}}^{(2)} \right) \cdot C_u^{(2)}$$

As with the case of Oseltamivir-Probenicid competitive inhibition, uni-directed inhibition can be achieved by greatly diverging $K_{\mathrm{m}}$ values (factor $10^4$) for compounds B and C. After mapping B to $C^{(1)}$ and C to $C^{(2)}$ in the 'simulation object', the simulation is performed; the results are shown in Fig. 3 (middle and bottom panels) for intravenous administration of 2 mg/(kg body weight) of compound A and C. This example nicely illustrates the phenomenon of extended drug exposition of compound B (active metabolite) as a result of a drug-drug interaction.

In our physiological context (Fig. 1), a total of 162 ordinary differential equations is necessary to simulate the pharmacokinetics of the three compounds, including drug-drug interactions; – on the basis of the presented concepts, MEDICI-PK generates these equations from seven user-defined local physiological models only!

## 5 Conclusion and Outlook

Considerable progress has been made in the development of *in silico* models to predict and understand the pharmacokinetics of new compounds, in particular in early drug discovery. As a result, modelling and simulation is possible prior to any *in vivo* experiments, solely based on *in vitro* data. We present the principles and concepts of a software design that efficiently allows to build up PBPK models in terms of the underlying physiological processes, combining user-friendliness and flexibility. These principles and concepts are the basis of the software tool MEDICI-PK that has been used to illustrate our approach.

We believe that the combination of *in vitro* experiments and *in silico* modeling has the potential to drastically increase the insight and knowledge about relevant physiological and pharmacological processes in drug discovery. In anticipation of modelling not only the distribution of the drug in the body, but also its effect (disease modelling), one future challenge will be the combination of pharmacokinetics and effect related metabolic networks or signalling pathways for a better understanding of the disease dynamics. An example would be the treatment-induced selective pressure on viral dynamics. The presented concepts, realized in MEDICI-PK, are powerful and flexible enough to also support these future tasks.

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