

# COMPUTER AIDED MODELLING IN PHARMACOKINETICS AS A TOPICAL ISSUE

Michael Wulkow\* and Regina Telgmann, CiT GmbH,  
Oldenburger Str. 200, Rastede, 26180, Germany, m.wulkow[at]cit-wulkow.de

Modeling and simulation in pharmacokinetics has turned into the focus of pharmaceutical companies and academic research, driven by the emerging consensus that *in silico* predictions, combined with *in vitro* data, have the potential to significantly increase insight into pharmacokinetic processes. Pharmacokinetics is the study of the time course of drug and metabolite levels in different fluids, tissues and excreta of the body. This includes the investigation and understanding of the processes of adsorption, distribution, metabolism and excretion (ADME) at the different stages of the drug discovery process:

- Early drug discovery: prioritize drug candidates and indicate critical pharmacokinetic properties
- Preclinical drug design: analyze *in vivo* data from animal studies, predict the PK in other species and in man and support dose finding for first-time-in-man studies
- Clinical phases: use modeling to understand and interpret clinical data and extrapolate to different scenarios like dosing schemes.

The pharmacokinetic profile of a drug strongly influences its delivery to biological targets, thereby affecting its efficacy and potential side effects. To support *in silico* methodology adequately, software tools are needed which do not only facilitate the solving of equations but also take over the ballast of repeated implementation of known and structurally equal working steps without preventing the input of open modeling ideas. In fact, such software (that does not mean purely equation based standard solvers) has to allow the modeling of ideas that go beyond the current knowledge – otherwise it would not be called innovative. The reasons for this claim will be explained in the lecture.

At first, there is no single established model underlying PK, and it will remain out of reach in the foreseeable future. The medical benefits of a drug depend not only on its biological effect at the target protein but also on its life-cycle within the organism – from its absorption into the blood, distribution to tissue and its eventual breakdown or excretion by the liver and kidneys. Pharmacokinetics (PK) is the study of the drug–organism interaction and comprises a number of physiological phenomena, which are modeled differently (i.e. using different model complexity and thus parameter dependency) at different stages. For example, at early stages (when not much data are available for candidates under consideration) the protein binding might be described by a fuP, B:P dependent basic model. Later it might be replaced by detailed description based on plasma and interstitial albumin concentrations or any other new insight from actual research. This structure holds for all processes in a PK model. Typically, following processes are modeled:

- 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 signaling pathways etc.

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 parameterize early PBPK models. Either the parameter can directly be used in the model, or relevant model parameters are estimated through mechanistic equations 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.

Next, 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 conceptual representation of a 14 organ PBPK model is shown in Fig. 1. Each compartment is further subdivided into the four (or more) sub compartments (phases): erythrocytes, plasma, interstitial and cellular space (also shown in Fig. 1).

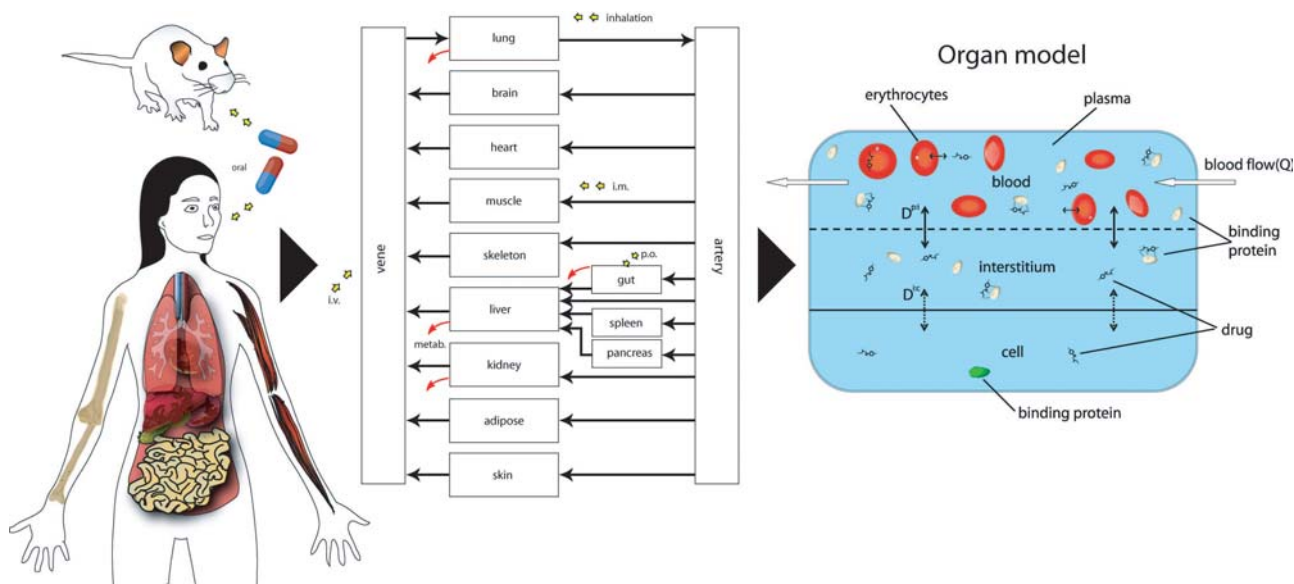


Figure 1: Organ structure of a physiologically based pharmacokinetic model

Such a given topology combined with a selection of models for the basic processes (one for each physiological process) builds a description of the PBPK model.

In mathematical terms, a PBPK model constitutes a large 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. Instead, the requirements on user-friendliness and flexibility can be fulfilled by the use of sophisticated modular software concepts and structures and this has been done in MEDICI-PK.

During the development of the architecture of MEDICI-PK all parts of a PBPK model have been identified and examined in view of their connection. This has led to the orthogonal structure presented in Fig. 2. All structures principally defining the model equations but independent of concrete parameters are summarized as a so-called 'full body template'. 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, (iv) general parameters. For a selection of compounds a given full body template can be (automatically) transformed into a simulation scenario now making possible simulation studies

- with different parameter sets
- with variations of basic processes
- with different dosing strategies
- for different individuals
- for different compounds
- with additional systems biology balances.

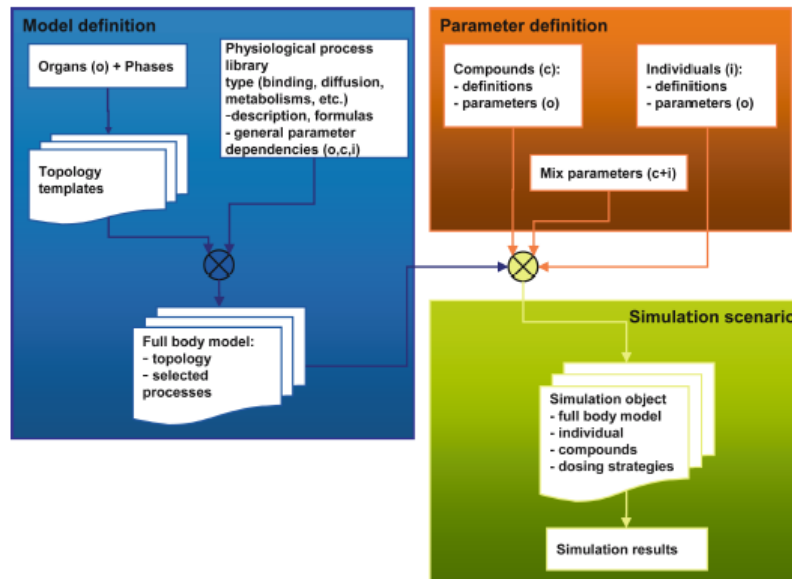


Figure 2: Schematic illustration of the orthogonal approach to software supported pharmacokinetic modeling [2]

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.

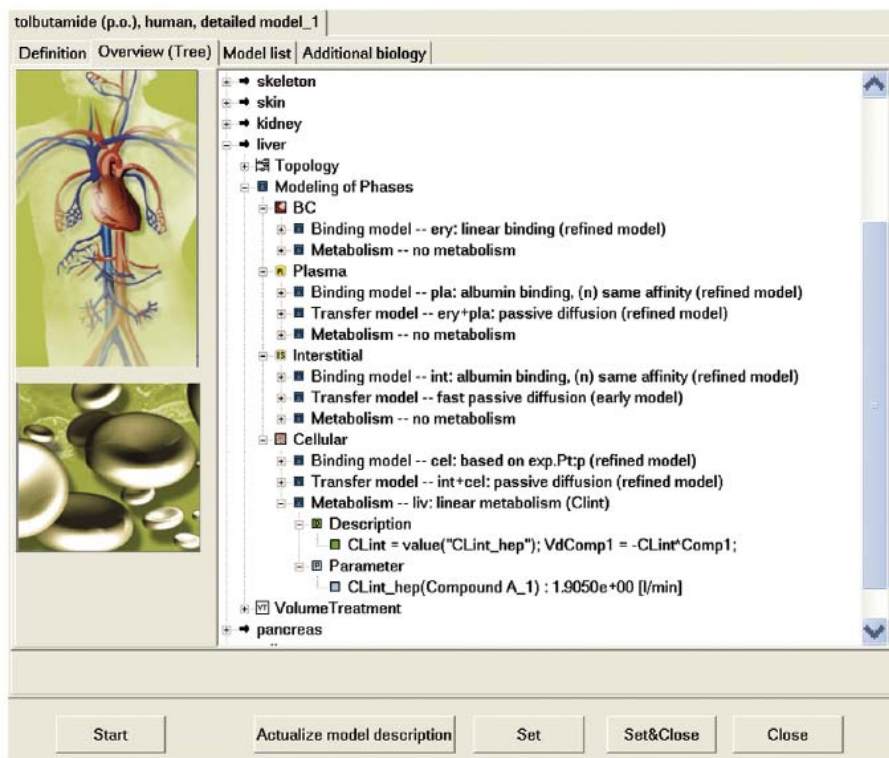


Figure 3: Tree view (among other overviews) of a MEDICI-PK simulation scenario

The development of MEDICI-PK was accompanied by several practical exercises with advanced students, in-house projects of companies and additional research activities. Actually it is used in a graduate research program. By that, from the beginning of the development, concept and architecture of the approach and its implementation were benchmarked. The feature matrix in Fig. 4 shows how the various design principles are realized in MEDICI-PK.

#### Important feature of the virtual laboratory MEDICI-PK

Property	Description	Realization in MEDICI-PK
User-friendliness	Assistance of the specific needs in physiologically based pharmacokinetic (PBPK) modeling.	Support of model building, hypothesis testing, user-defined output variables, data import from SBML, data export to Excel.
Application specificity	Software in terms of a PK-specific language.	Application-motivated design of underlying software structure; compounds, species, organs, dosing schemes, simulation objects as typical building blocks.
Modularity	Characterization of the overall PK model in terms of simple, independent modules that can be used in multiple contexts.	Extendable list of modules (physiological processes such as binding, transfer, metabolism, metabolic pathways, etc.) in a model basis. Definition of each full-body PK model in terms of the underlying physiological processes.
Orthogonal design and flexibility	Separation of model constituents that are independent of each other.	Independent definition of compound-specific data, species-specific physiological parameters and mathematical models to archive largest flexibility.
Openness	No limitation for adding new types of parameters, compounds, organs, species, physiological models, etc.	Easily extendable lists of parameters, compounds, organs, species, physiological models, dosing schemes, etc.
Transparency	No hidden calculations or parameters.	All parameters and models are directly assessable and editable.
Computational efficiency	Use of fast and accurate numerical techniques.	Integration of state-of-the-art numerical algorithms.

Figure 4: Design principles of Medici-PK [3]

Several different models and simulation studies have already been performed in MEDICI-PK in this way (e.g. a model for Cyclosporine A [5], a detailed model on the PK of tolbutamide and a generic PBPK model for early drug development [6]). Immediately, extensions of the existing models could be studied, for example incorporation of metabolites, comparison of different binding and tissue distribution models, drug–drug interaction studies, and comparison between different species (human, rat, and so on).

Based on our experience in other fields of chemistry and biology we see a high potential for in silico PK and PD approaches in the drug discovery and development process - if properly realized. Since even automatic parameter identification tools have been added to Medici-PK, new modeling ideas can directly be compared to experimental results.

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