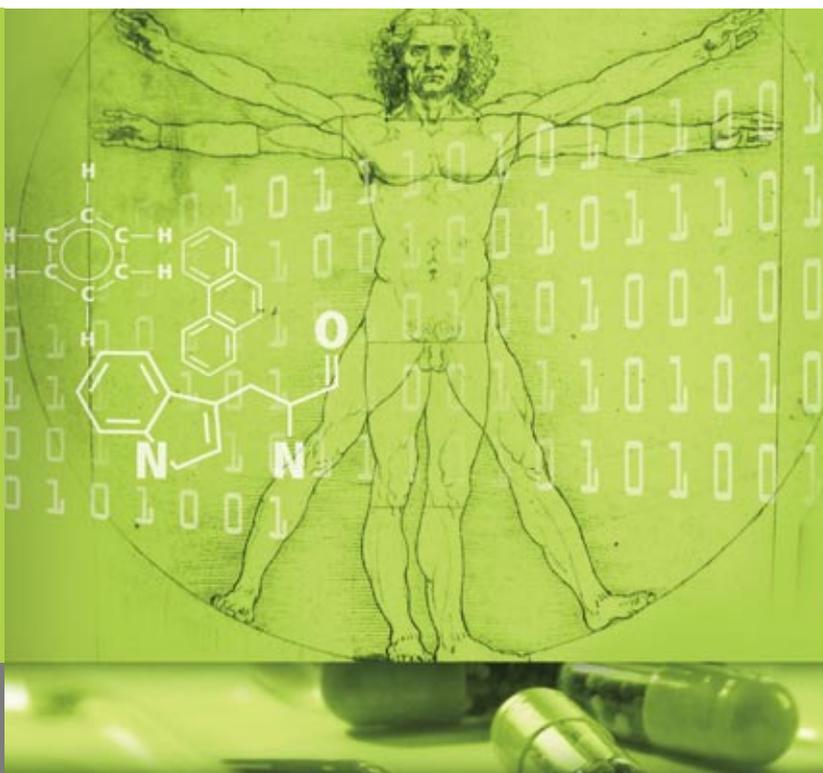


MEDICI-PK



Technology
in
Computing



A virtual laboratory
for innovation
in pharmacokinetic modeling

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MEDICI-PK – a virtual lab for innovation in drug modeling

The medical benefits of a drug do not only depend on its biological effect on the target protein, but also on its life cycle within the organism – from its absorption into the blood, distribution to tissue until its eventual breakdown or excretion by the liver.

Many *in vitro* data on physiochemical properties and specific ADME processes are already available and identifiable, even at early stages of the drug discovery process. These data can be used in physiologically based PK (PBPK) models to predict, analyse and optimize the PK of new drugs.

Pharmacokinetics (PK) is the study of the drug-organism interaction, i.e. the investigation of absorption, distribution, metabolism and excretion (ADME) processes.

MEDICI-PK is the software tool that makes complete, efficient and meaningful *in silico* modeling possible.

The simulation object presents a whole-body PK model, including all necessary information to describe a virtual patient and the drug dosing.

Overview of and access to the used parameters is evident.

the Modular design principle allows variability

The image shows two overlapping screenshots of the MEDICI-PK software interface. The top screenshot displays a 3D anatomical model of a human torso with various organs highlighted. A tree view on the right lists components like 'lung', 'Arterial_Blood', 'Venous_Blood', 'Topology', 'Modeling of Phases', 'Dosing', 'Plasma', 'VolumeTreatment', 'brain', 'heart', 'muscle', 'gut', 'spleen', 'skeleton', 'skin', 'kidney', 'liver', 'BC', 'Interstital', 'Binding mo', 'Transfer m', 'Metabolism', 'Tissue', and 'VolumeTreatment'. The bottom screenshot shows a 'Simulation' window with a table of parameters for 'propranolol' modeling.

No.	th...	Name	Value	Unit	Individual	Unit	Compound	Unit
1		H ₀			4.500e-01	n.a.		
2		f ₀ F (species index)					1.300e-01	n.a.
3		B ₀ P					8.000e-01	1
4		D ₀ last					1.000e-02	1/hr
5		logP _{ow}					3.200e-00	1
6		f ₀ veP			3.400e-01	value between...		
7		f ₀ hP			2.250e-03	value between...		
8		f ₀ veP			3.500e-03	value between...		
9		MAT					0.000e+00	(n.l.)
10		f ₀ ve					0.000e+00	(n.l.)
11		f ₀ ve					n.a.	(n.l.)

- Creative
- Flexible
- Transparent

Virtual lab



PHARMACOKINETICS

MEDICI-PK is a modular, transparent, application-specific and user-friendly software tool that supports the process of PK and pharmacodynamic (PD) modeling in an open way.

A model basis includes the descriptions for the pharmaceutical processes. To support the user's creativity in modeling **MEDICI-PK** allows each customer to build his/her own model basis, tailored to his/her indications and knowledge.

Increasing knowledge enlarges this model basis, and simplified models may be exchanged by more complex descriptions.

Parameter definitions also lie in the hand of the user. He/she defines the parameters and their meaning in the model context.

The whole modeling remains completely transparent, all necessary parameters are accessible

– transparency is a prerequisite for confidence in the modeling process!

The modular design principle implemented in **MEDICI-PK** allows the complete definition of a virtual patient within a few clicks.

Comparative studies of different species, different individuals, different compounds and/or different models are easy and suggestive to perform.

Different types of individuals or species can be defined and be modeled within the same project.

The modular design principle:

- Define your organ/compartment basis
- Define your organ topologies
- Define your compound(s)
- Define your individual(s)
- Define your general and mixed parameters, depending on available compounds and individuals
- Create a FullBodyTemplate, basing on a topology and on model definitions
- Join these modules together in a simulation object

... and the virtual patient is completed

Individual description as database member containing all relevant modeling parameters.

Organ-dependent as well as organ-independent parameters are stored within each compound and individual.

Compound definition based on chemical data

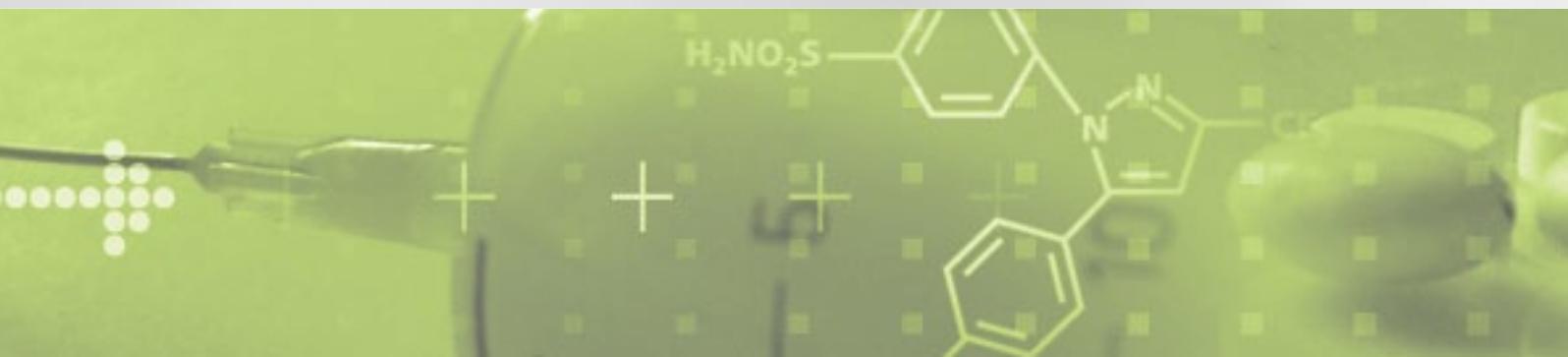
The screenshot displays the MEDICI-PK software interface with several overlapping windows. The 'Individual' window for '250g rat' shows a table of parameters:

No.	m...	Name	Actual value	Unit
1		Hct	4.5000e-01	
2		body weight	2.5000e-01	kg
3		f/rnP	1.4700e-03	value between 0 and 1
4		f/phP	8.3000e-04	value between 0 and 1
5		f/wP	9.6000e-01	value between 0 and 1

The 'Compound' window shows properties for 'ibuprofen' and 'discepan'. The 'Individual' window for 'human healthy volunteer' shows a table of parameters:

No.	m...	Name	Actual value	Unit
1		Hct	4.5000e-01	
2		albumin (plasma)	5.7270e-02	microM
3		f/rnP	1.5000e-03	value between 0 and 1
4		f/phP	2.2500e-03	value between 0 and 1
5		f/wP	5.4500e-01	value between 0 and 1
6		body weight	8.0000e+01	kg

Other windows include 'Import Model Requirements' and 'Init Desigs. Initialize Set SetComp Close'.





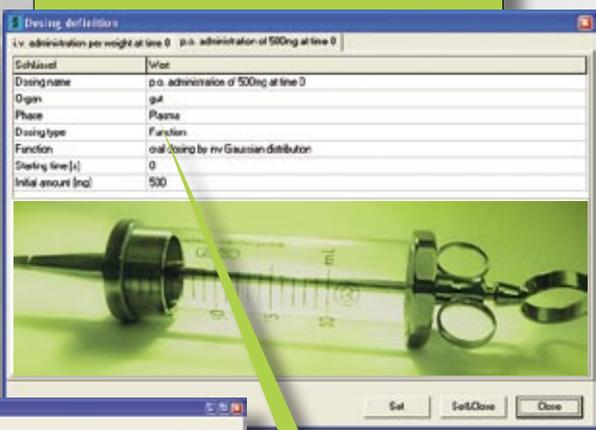
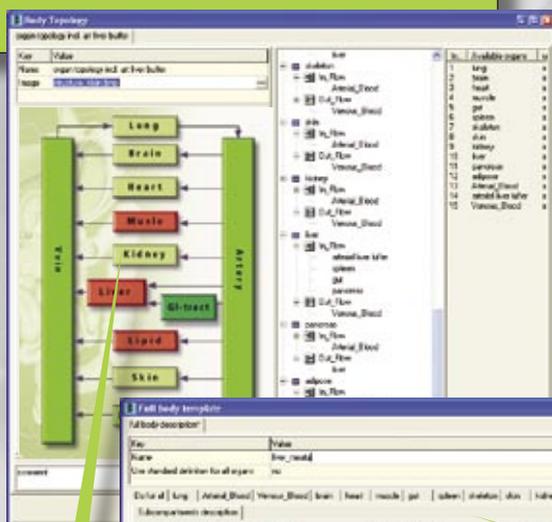
Powerful but easy-to-use and suggestive **MEDICI-PK** offers a wide range of abilities:

- Each organ includes four main compartments by default: blood cell, plasma, interstitial and cellular tissue. Together with the user defined organ topology a detailed representation of an organism is guaranteed.
- An extendable set of different species (e.g. human, mouse, dog, ...) and an arbitrary number of individuals are configurable. Therefore comparative studies of different beings are possible.
- The time-dependent evolution of the concentration of a user-given number of compounds can be simultaneously calculated, allowing the modeling of real metabolism/interactions taking place in any of the compartments.
- Each physiological effect can be pictured by the user, no predefined models restrict modeling phantasy.
- Integration of systems biology models (SBML) into MEDICI-PK allows the extension of compound interactions by full cell biology systems.

The use of state-of-the-art scientific numerical algorithms and comfortable output like online concentrations graphs and diverse derived data as well as Excel interface support the perception and understanding.

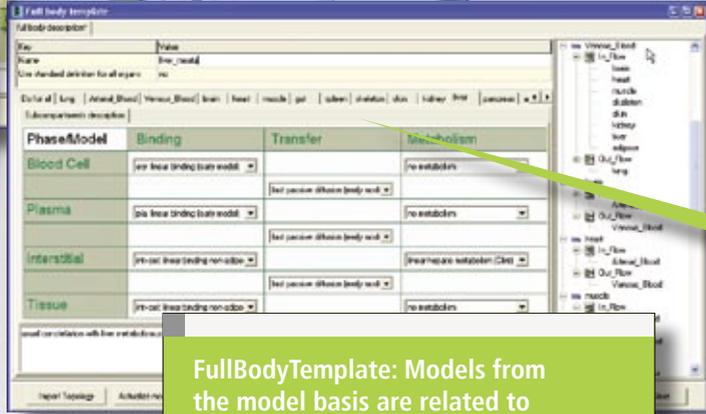
Topologies may be created by means of the available organs – easy handling by drag & drop.

Dosing is possible wherever needed: select organ and compartment.



Bolus injection as well as more general applications of drugs are possible.

User-defined images can be loaded to visualize the defined topology.



FullBodyTemplate: Models from the model basis are related to compartments in selected organs determined by a user-defined topology.

Four main compartments are defined by default for each organ. The list can easily be enlarged within the software concept.

in silico modeling

- Variable
- Modular
- Exact



Advantage of *in silico* modeling

Modeling and simulation help to understand large complex processes, in particular processes with strongly coupled influences and time-dependent interactions as they occur in pharmacokinetics.

In silico predictions have the decisive advantage that much less investment in technology, resources and time is needed compared to

in vivo experiments. Results obtained by **MEDICI-PK** prevent misleading paths and make promising directions evident. So, the earlier *in silico* studies are made during the drug development process - the better.

The vision and the benefit

The combination of *in vitro* experiments and *in silico* modeling will dramatically increase the insight into pharmacokinetic processes.

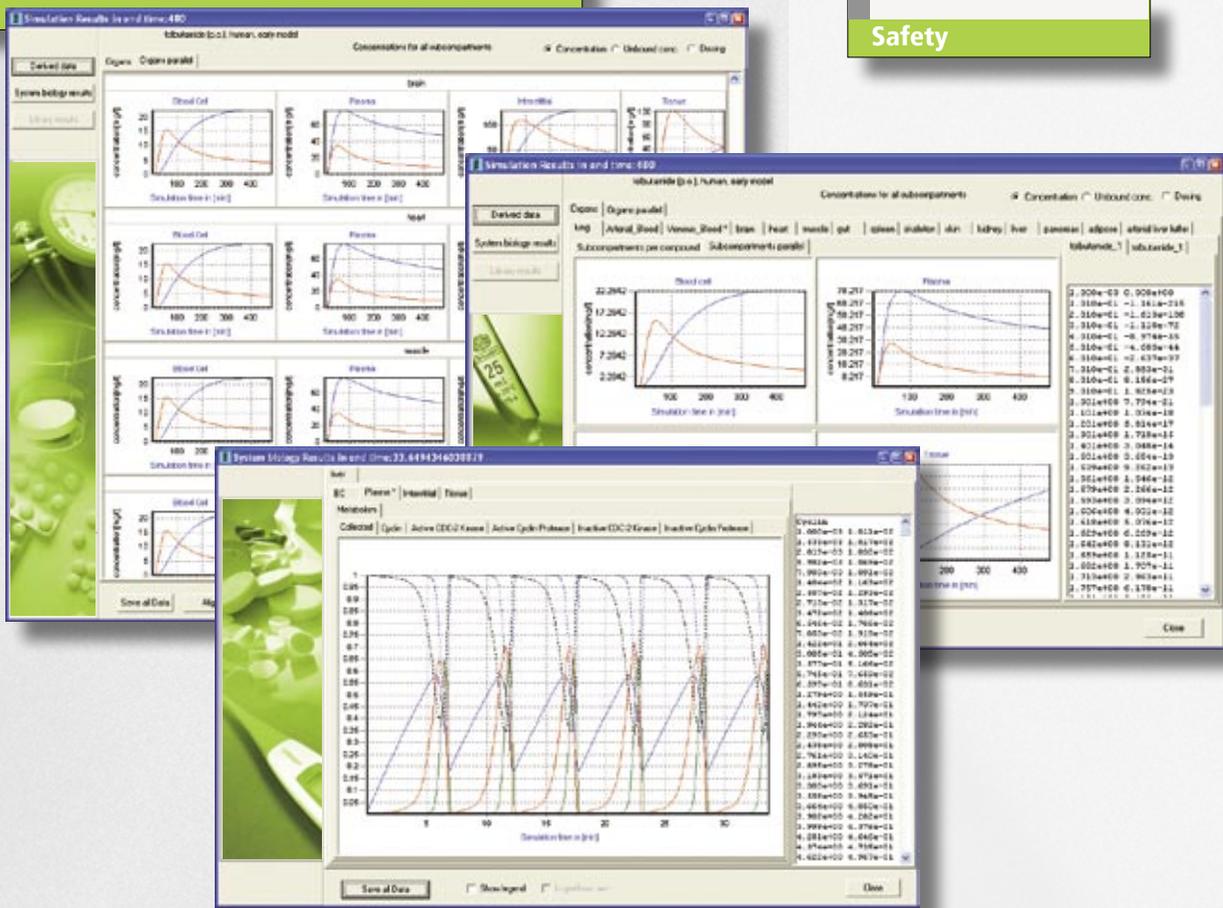
Research on target identification, lead generation and optimization, candidate selection and preclinical development are vertically integrated. They are accompanied by an *in silico* modeling process that integrates the knowledge gained in each of these steps into a diseases-specific whole body model.

MEDICI-PK opens the door to efficient and free modeling, aiming at increasing knowledge and predictivity.

Concentration-time-curves, mass balance and AUC are presented, any user-defined output is available.

Efficacy

Safety



Understanding

Integration

Prediction

Virtual patient

PHARMACOKINETICS

CiT has well established know-how in modeling and simulation software. Our software packages

Predici[®], **Presto-Kinetics[®]**,
Parsival[®] and **RioNet[®]**

are used world-wide and have set landmarks in each of the respective fields chemical kinetics, chemical engineering and bio chemistry.

MEDICI-PK[®] enlarges this list of successful simulation software packages.

MEDICI-PK[®] has been developed in close cooperation with
Dr. W. Huisinga, Junior Research Group „Computational Physiology“,
Freie Universität Berlin and
DFG Research Center MATHEON “Mathematics for key technologies”, Berlin.

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