



INNOVATION

ENGINEERING

OPTIMIZATION

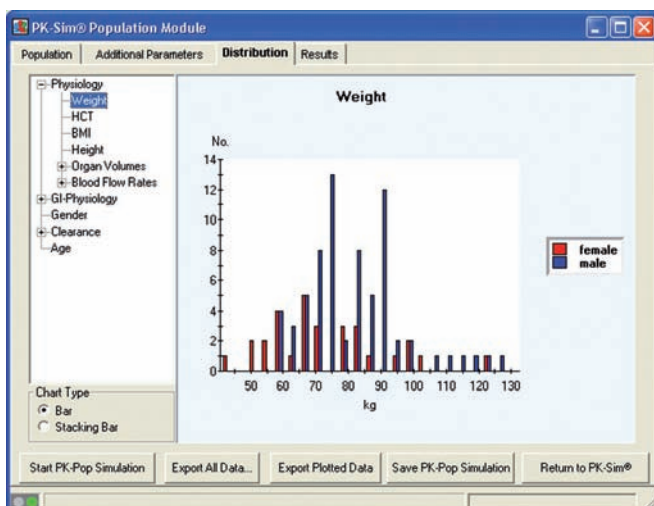
The Comprehensive Software Tool for Whole-Body Physiologically Based Pharmacokinetic Modeling

Whole-body physiologically-based pharmacokinetic (PBPK) simulation is a technique that has been in use for many years to investigate the fate of xenobiotics, particularly drugs, in the human body. Our software package PK-Sim[®] has proven its excellence in analyzing and predicting the absorption, distribution, metabolism and excretion (ADME) properties of individual mean subjects. However, in particular during clinical trials of later phases with a large number of subjects the focus of interest is not on one mean individual but on the variability of drug response in a whole population. A prominent issue in clinical trials is the occurrence of subpopulations with a specific drug response behavior. Not only anatomical differences must be taken into account but also enzymatic polymorphisms. Especially the strong age dependence of clearance makes children a major subpopulation with a sophisticated drug response. Due to the explicit consideration of anatomical and physiological properties in PBPK models, they are perfectly suited for the simulation and pre-evaluation of pharmacokinetic variability occurring in clinical trials.

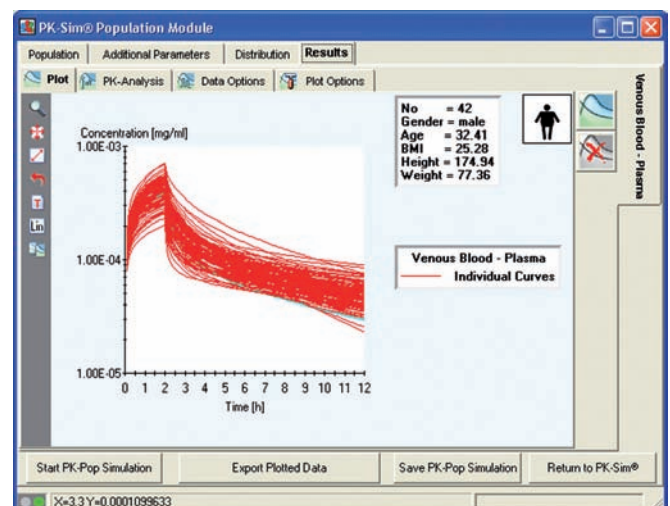
PK-Sim[®] Clinical: This package is an extension of PK-Sim[®] especially designed to simulate the pharmacokinetics of a trial population comprising individuals with a certain deviation from the norm. To explicitly include infant populations PK-Sim[®] Clinical offers the possibility to adapt renal and hepatic clearances to infant physiology. Your benefit includes an understanding of how the variability in anatomy, physiology, age, and gender relates to deviations from the normal drug response. In addition, you may assess the range of drug response which is to be expected and make predictions of infant pharmacokinetics.

Population-PK Module

Built-in databases comprise the heart of the Population-PK Module. They contain information about the age and gender dependence of mean values and variability of the relevant anatomical parameters such as body size, organ volumes and blood flow (e.g. from the US NHANES III study). The anatomical parameters of virtual individuals are randomly chosen from these empirical parameter distributions.



Population-PK Module: Graphical display of body weight distribution



Population-PK Module: Simulated concentration time profiles



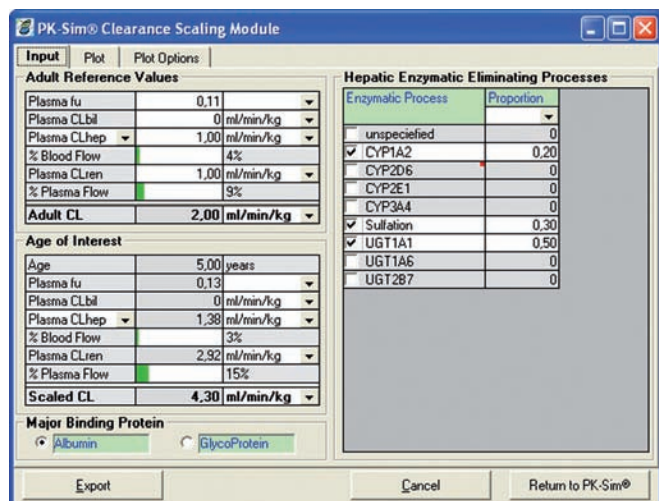
For the explicit consideration of special subpopulations, such as obese people, a virtual population can be shifted by the definition of an underlying mean individual.

Another source for deviations in drug response originates from enzyme polymorphisms in trial subjects. After the explicit introduction of metabolism enzymes like CYP3A4, this phenomenon can be realized by defining a distribution for the enzyme-related parameters. This feature allows the inclusion of subjects displaying well-defined pathologies like renal or hepatic impairment into the population simulation.

Clearance Scaling Module

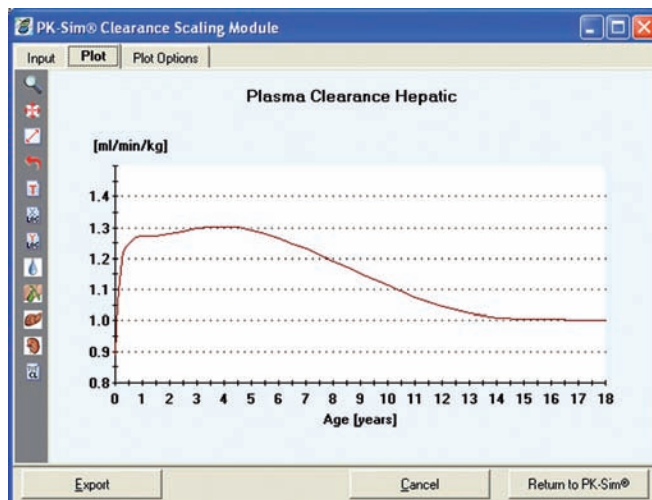
To simulate pharmacokinetic profiles in children, age dependent infant anatomy is included in the mean individuals of the database. However, the strong age dependence of infant drug response partly arises from the ontogeny of enzymes, plasma proteins and renal function.

The Clearance Scaling Module of PK-Sim® Clinical explicitly models infant clearance pathways and automatically scales the clearance to infant ages based on the specification of the adult clearances and the contributions of the eliminating processes involved. Renal clearance is calculated from age depending allometric formulas for renal function parameters. Hepatic clearance is calculated from the adult intrinsic clearances for the different enzymes, which are scaled to infant enzyme activity and liver weight. Infant biliary excretion is scaled allometrically to liver weight. The full age-dependencies of clearance, from newborns to adults, for a given compound can be displayed.



Clearance Scaling Module: Input Window

To conclude, the Population-PK and Clearance Scaling Modules of PK-Sim® Clinical are indispensable tools for risk assessment, study design and decision making in the clinic.



Clearance Scaling Module: Plot of age-dependent clearance

Additional Key Features to PK-Sim® Pre-Clinical

- Definition of trial populations by ethnicity, age, gender and body size
- Scaling of anatomical parameters to body size
- Random interindividual variability predefined or user defined
- Minimum, mean and maximum concentration curves, concentration density plots
- Median and percentile curves
- Statistics of pharmacokinetic parameters
- Distribution plots for pharmacokinetic parameters

System Requirements

- OS: Vista®, Windows XP®, Windows 2000®
- Processor: Pentium III, 500 MHz (1 GHz recommended for PK-PD and/or PK-Pop Module)
- Memory: 512 MB RAM (1024 MB recommended for PK-PD and/or PK-Pop Module)
- Disk Space: 100 MB (additional 120 MB required for PK-Pop examples)

Integrated Solutions and Services

Products	<ul style="list-style-type: none"> • PK-Sim® • MoBi® • MoBi® Toolboxes for MATLAB® and R
Services	<p>Drug Discovery Support</p> <ul style="list-style-type: none"> • Target Identification & Validation • Biomarker Analysis • Proof-of-Mechanism <p>Drug Development Support</p> <ul style="list-style-type: none"> • Species Extrapolation • Extrapolation to Special Populations • Proof-of-Concept • Bioequivalence Studies

For further information on our software tools and services visit our website www.systems-biology.com.

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