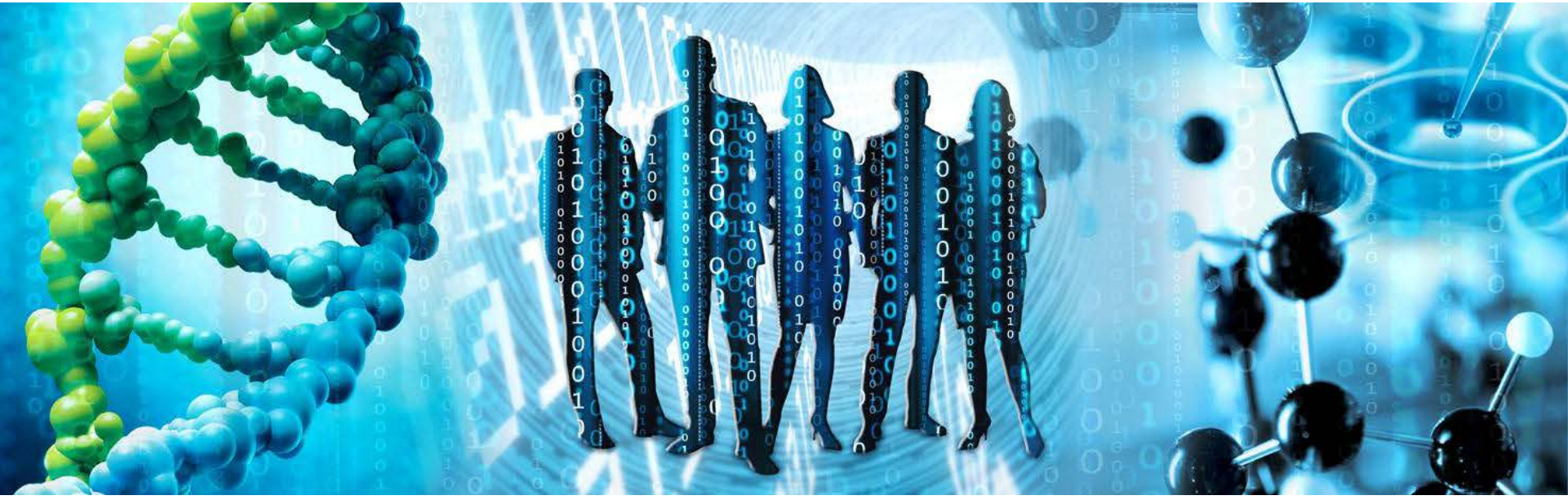
Science For A Better Life



PK-Sim

for Mechanistic Oral Absorption Modeling and Simulation and More

Thomas Eissing, FDA workshop, White Oak, May 19, 2016

Agenda

- Introduction: PBPK modeling with PK-Sim & MoBi
- Oral absorption and dissolution modeling
  - Concept
  - Examples
  - Implementation
- Summary

Agenda

- **Introduction: PBPK modeling with PK-Sim & MoBi**
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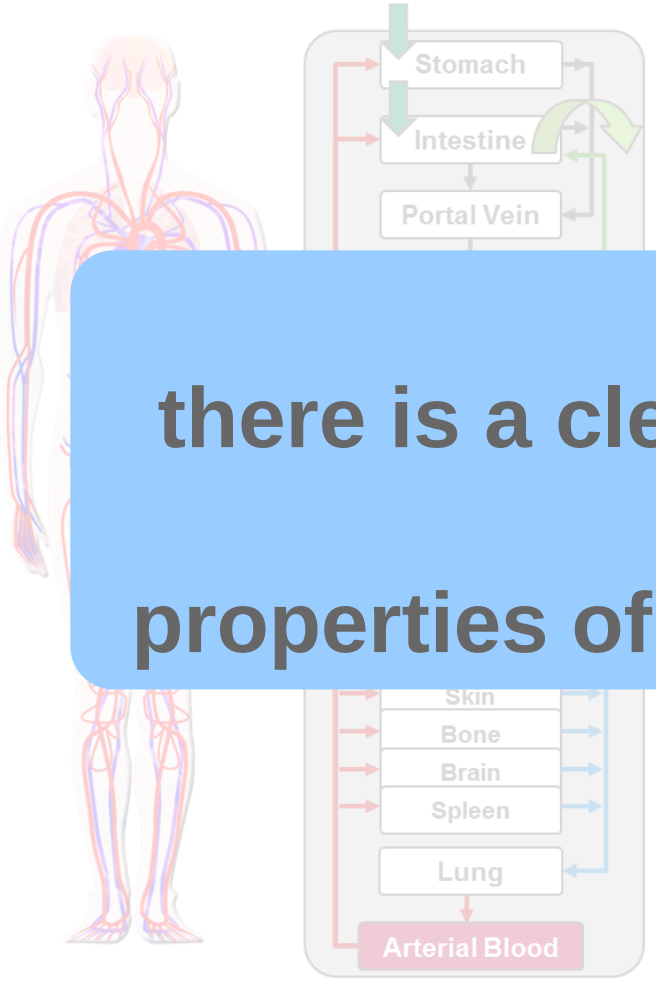
Physiology-based pharmacokinetic (PBPK) modelling with PK-Sim



Physiology-based pharmacokinetic (PBPK) models

- extensive data collections of prior biological and
- comprehensive representation of experimental data from different scales of biological organization

In PBPK,
there is a clear and explicit distinction between
properties of the organism and the drug

PK-Sim®

Platform Concept:

Integration of PK-Sim, MoBi and Interfaces Provide **Flexibility** and **Transparency**

Import & Export

Excel®

SBML*

SCAMP*

other

Software Tools

PK-Sim®

PBPK modeling & simulation

MoBi®

Biological modeling & simulation

Common Core

Simulation Kernel

MODEL
(XML-Formulation)

MoBi Toolboxes/ Interfaces for

MATLAB® (technical computing)

R (statistical computing)

*import functions to be updated to latest version

Eissing 2009

What is PBPK Modeling good for?
Translational Modeling

Integration & Translation of knowledge from different sources and preclinical and clinical stages to understand, treat and prevent diseases in different individuals and populations.

Physiologically-based Extrapolation

Interspecies scaling in preclinical development

Clinical development

scaling from „healthy volunteers“ to **special populations**, e.g.

- children or elderly
- obese individuals
- diseased individuals (renally/hepatically impaired, COPD, CF…)
- special genotypes
- **and combinations of the former!**

extrapolation to new experimental conditions e.g.

- dosing schedule change
- formulation change
- co-administration of other drugs
- surgical interventions (ventilation, cardio-pulmonary bypass…)
- charcoal block, bile-duct blockage & cannulation

Agenda

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- **Oral absorption and dissolution modeling**
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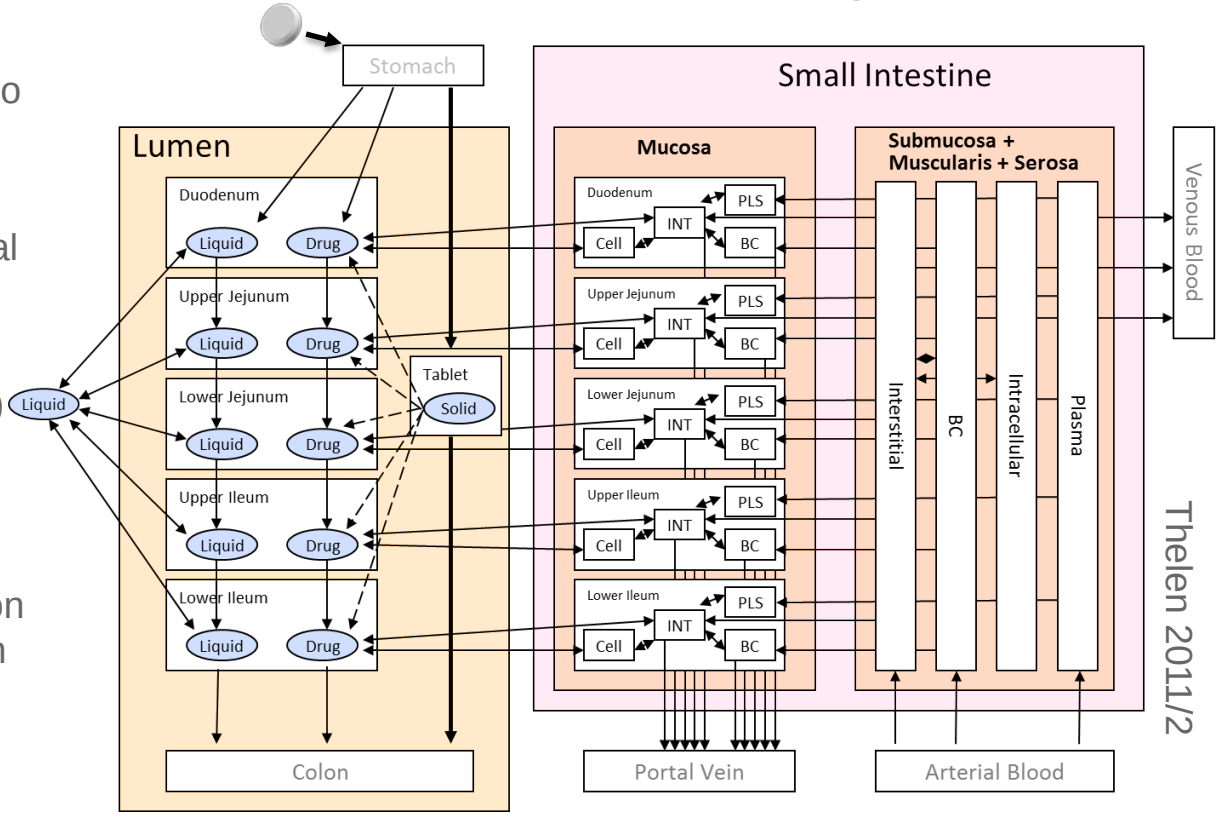
Simulation of Intestinal Absorption

Multi-compartment model for stomach, small and large intestine:

- 12 compartments representing the lumen of the GI tract from stomach to rectum; varying properties (dimensions, surface area, pH)
- Each segment contains physiological liquid volumes (Liquid) and drug in solution (DIS)
- Solid dosage form (SDF, e.g. Tablet) is transported along the GI tract independently
- Once released from SDF and dissolved according to the dissolution function, the drug is transferred from the SDF species to the DIS species
- 11 compartments representing the intestinal mucosa which is (subdivided into enterocytes, interstitial and vascular space)



… similar structure for large intestine

General Features & Dissolution Options

General features

- Separation of liberation, transit, and absorption
- Representation of food including caloric content to account for food effects
- Enterohepatic cycling and multiple applications can transit at any time
- Mucosal blood flow provides physiological absorption into the blood stream
- Active processes such as transporters (apical and basolateral) can be added

PK-Sim offers predefined options to model drug dissolution

- Weibull, Lint80, zero- and first order functions
- Table read-in and particle dissolution
- Customized solutions for dissolution and absorption can be implemented by a modelling expert

Model for Passive Absorption

Intestinal permeability is based on a modified semi-empirical equation:

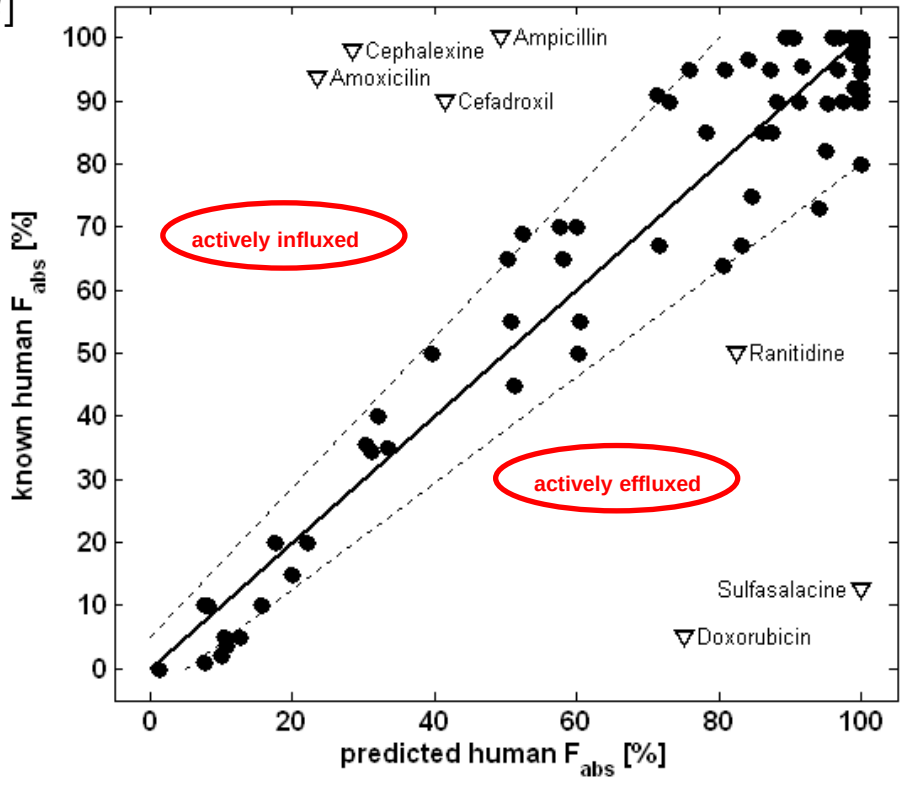
$$P_{\text{int}}(MW_{eff}, MA) = 265.796 * MW_{eff}^{-4.49968} * MA[cm/s]$$

(modified from D. Leahy et al. in *Novel Drug Delivery and Its Therapeutic Application* (1989))

Model for the intestinal permeability coefficient was build using a data set of 111 passively absorbed drugs with no solubility limitation at therapeutic doses.

An excellent fit was obtained (correlation coefficient: 0.970).

Seven outliers are known to be substrates to active transport



Thelen et al. **(2011)** *J Pharm Sci*. 100(12):5324-45.

Agenda

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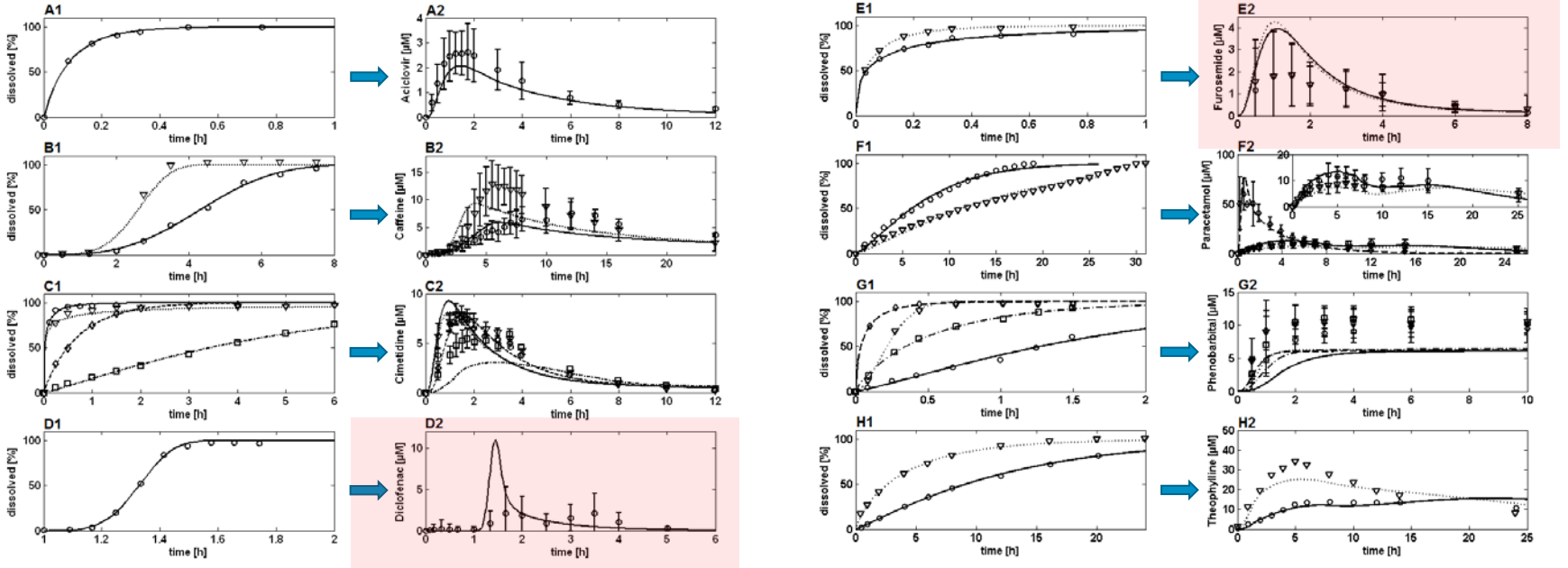
Integration of Dissolution Data

- Eight model drugs with different physicochemical properties
- Established models for IV and PO (solution) administration
- Integration of the dissolution kinetics of various dosage forms of the eight drugs by fitting the Weibull equation to *in vitro* dissolution data
- Extrapolation of plasma concentration time profiles from the *in vitro* data

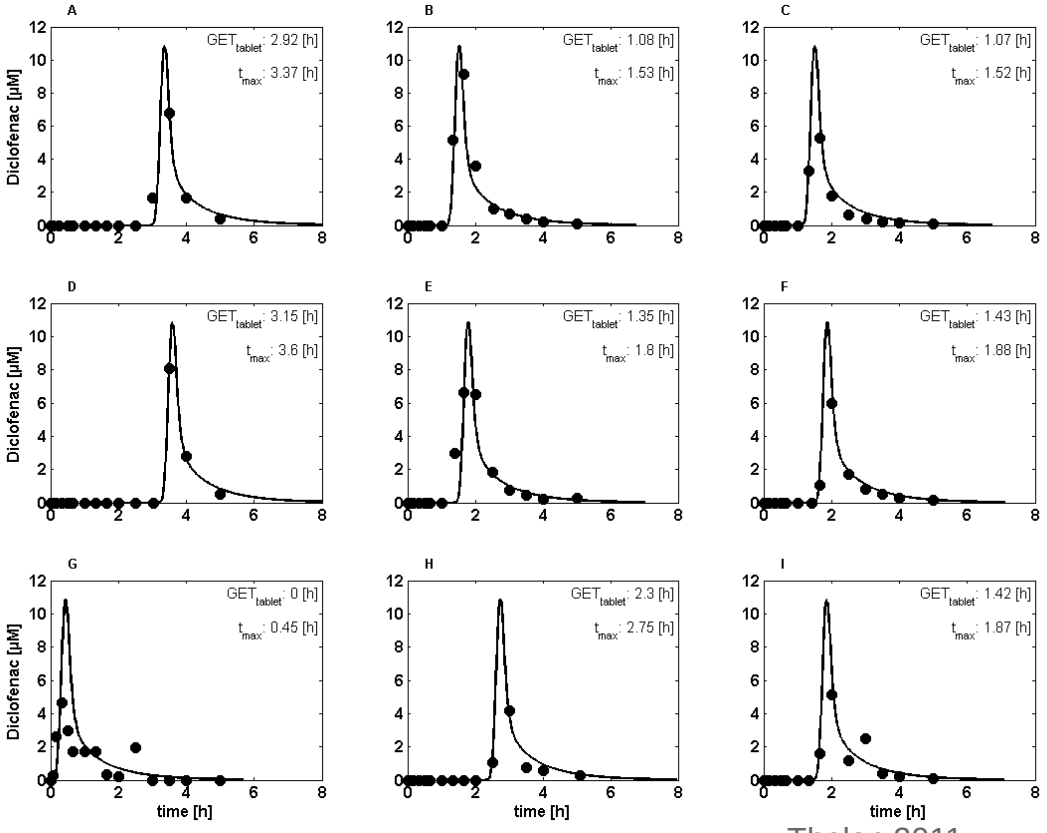


Thelen 2011

Analysis of individual data

Diclofenac:

- Poor prediction of mean plasma concentration time profile of Voltaren®50 enteric-coated (EC) tablets
- Individual plasma concentration time profiles of diclofenac EC tablets were simulated for GETs varying between 0 and 200 min. T_{lag} of the Weibull function was extended by the same factor
- Deviations between mean predicted and mean observed plasma concentrations were attributable to the large variability in GET of the EC tablets

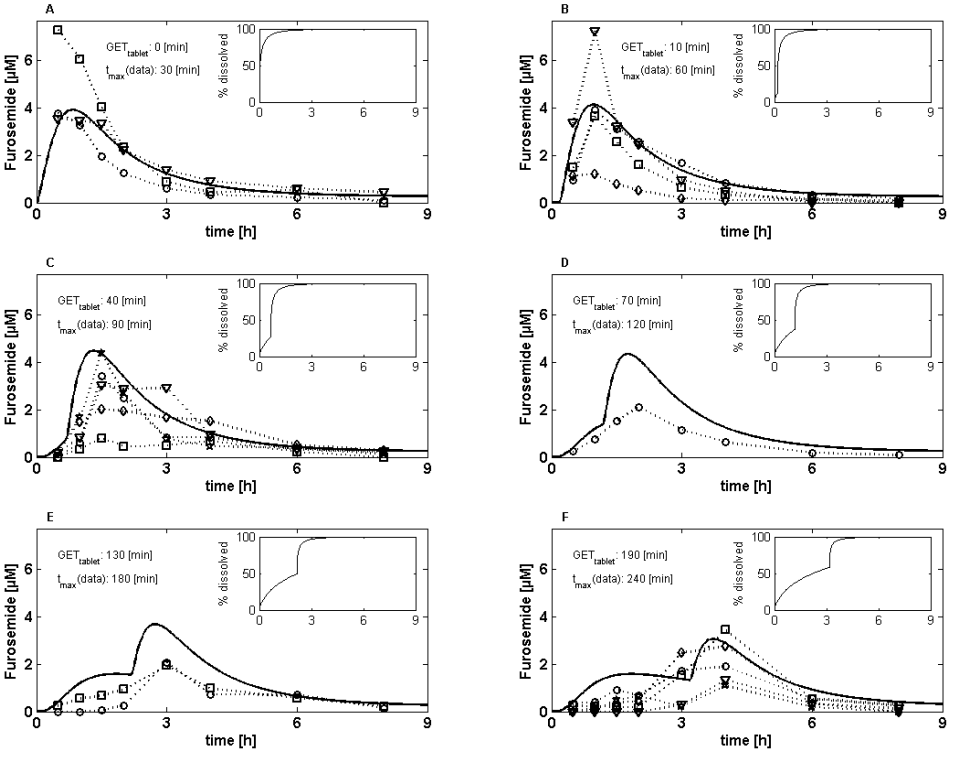


Thelen 2011

Analysis of individual data

Furosemide:

- Likewise, poor prediction of mean plasma concentration time profile of the acidic drug furosemide based on *in vitro* dissolution data obtained at pH 5.8
- Combination of dissolution profiles obtained at pH 2.6 (for t ≤ GET of non-disintegrated moiety) with those obtained at pH 5.8 (for t > GET of non-disintegrated moiety
- Meanwhile, dissolved furosemide leaves the stomach according to the emptying rate of the liquid
- Six scenarios were tested for lag times of 0, 10, 40, 70, 130, and 190 min in gastric emptying of the non-disintegrated moiety

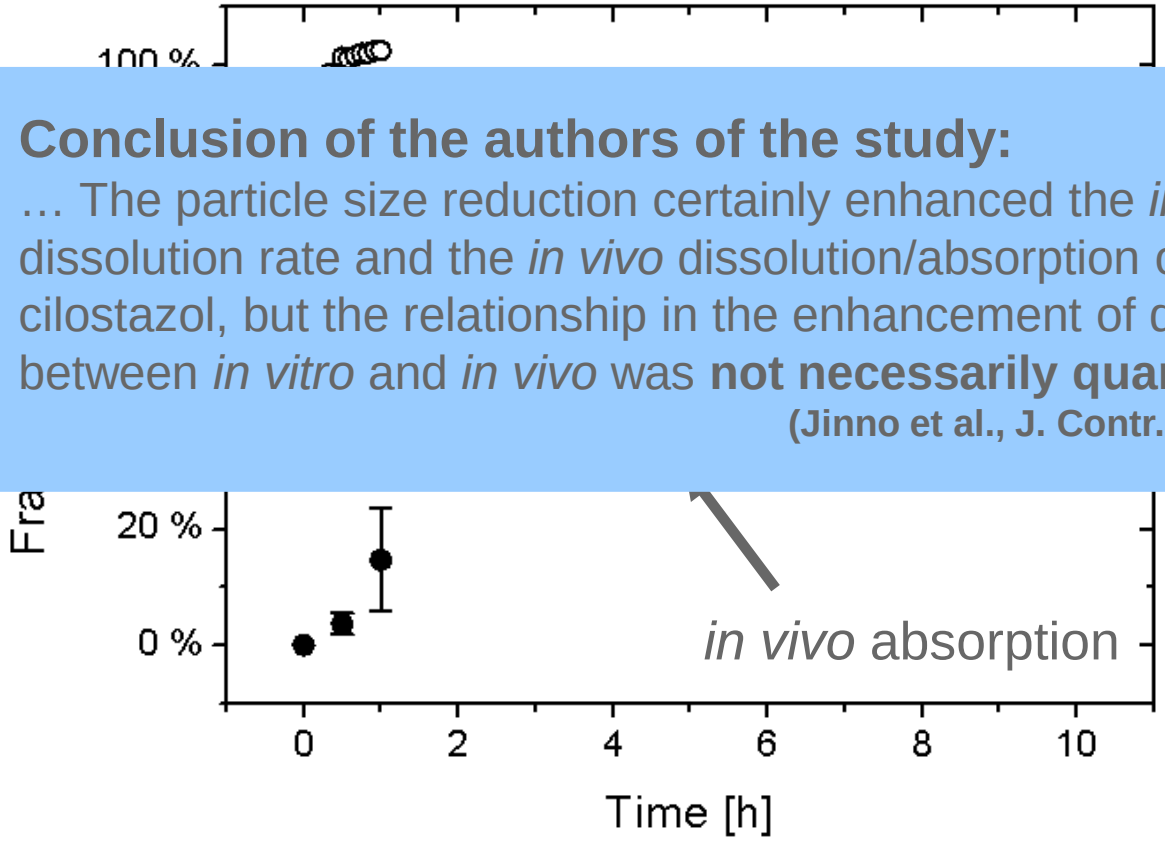


Thelen 2011

Cilostazol Kinetics in Dogs

Challenge to relate *in vitro* dissolution to *in vivo* absorption

Comparison of dissolution and absorption rates (jet-milled, fed)



Conclusion of the authors of the study:

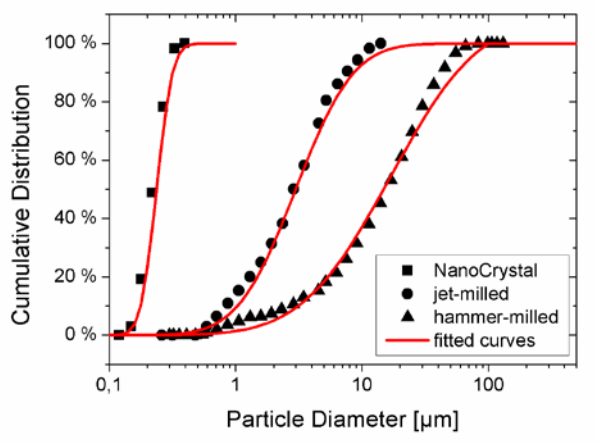
… The particle size reduction certainly enhanced the *in vitro* dissolution rate and the *in vivo* dissolution/absorption of cilostazol, but the relationship in the enhancement of dissolution between *in vitro* and *in vivo* was **not necessarily quantitative…**

(Jinno et al., J. Contr. Rel. 2006)

Cilostazol Kinetics in Dogs

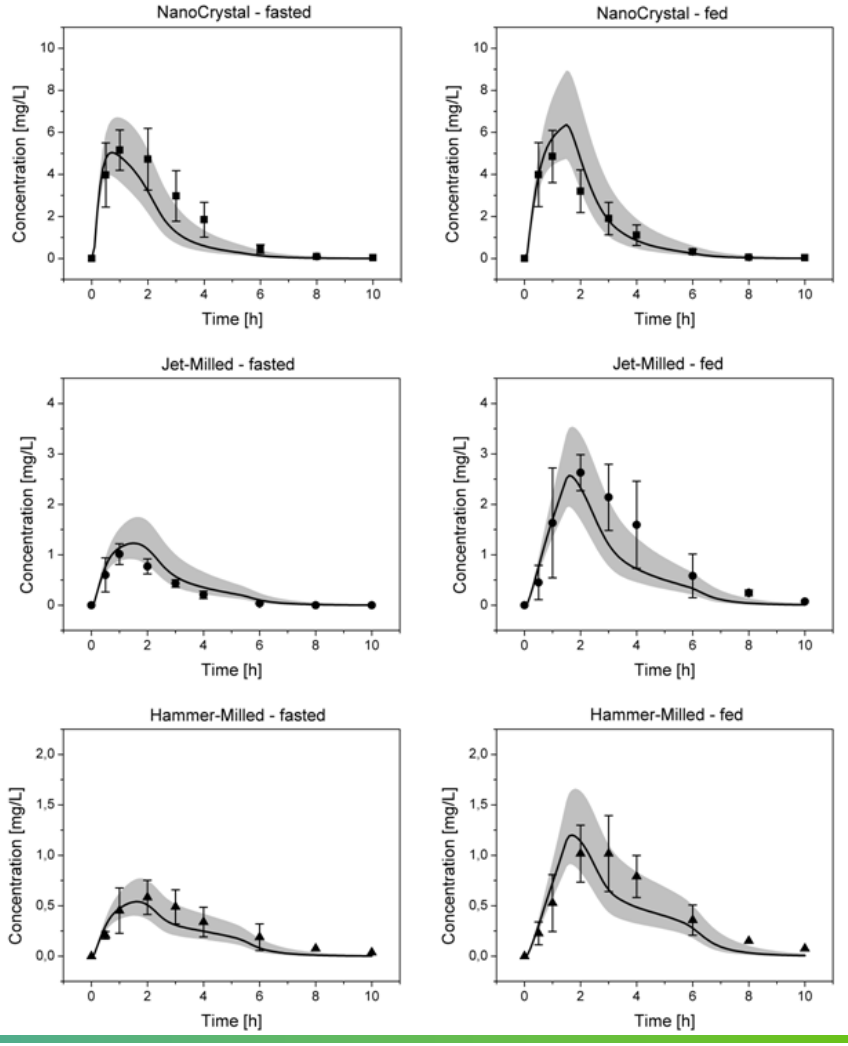
Model can bridge *in vitro* to *in vivo*

1. Fit *in vitro measured* particle-size distribution with log-normal distribution



2. Input distribution into software and predict *in vivo* absorption

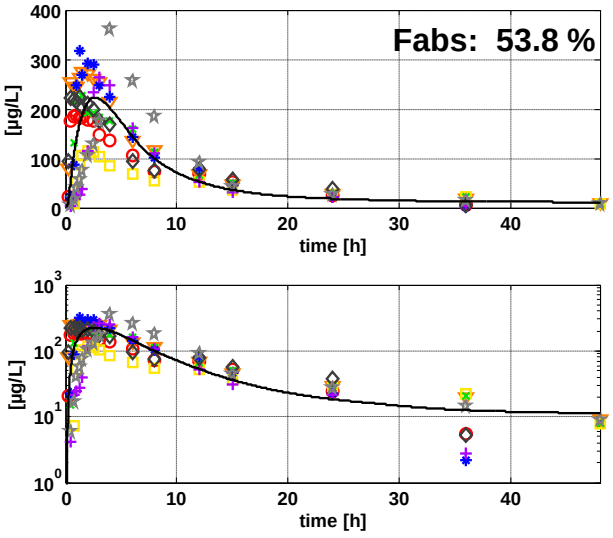
Rate and extent of absorption well predicted under fasted and fed conditions



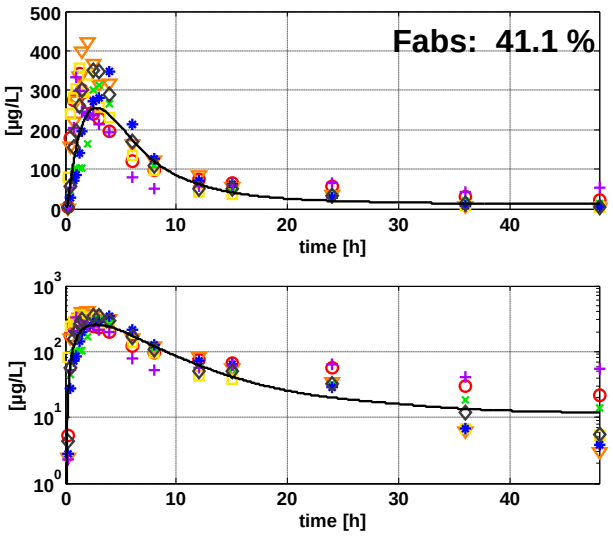
Willmann 2010

Drug X – PO, IR tablet, fasted

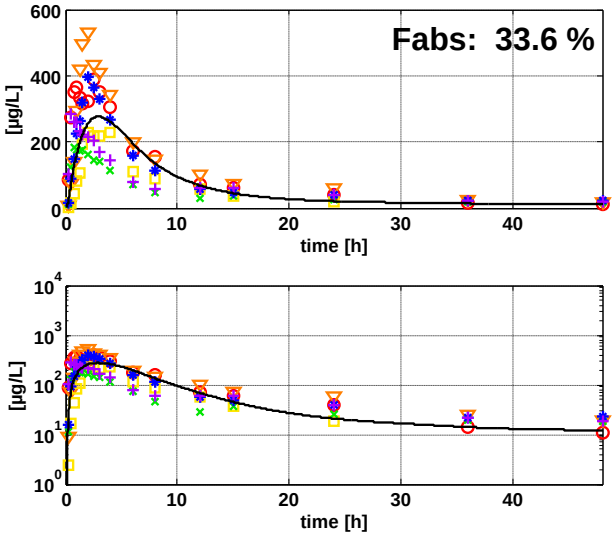
40 mg



60 mg



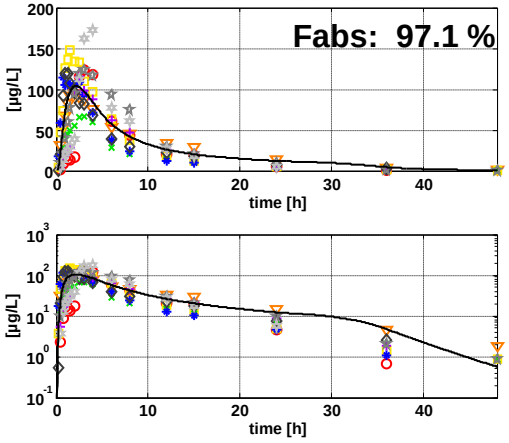
80 mg



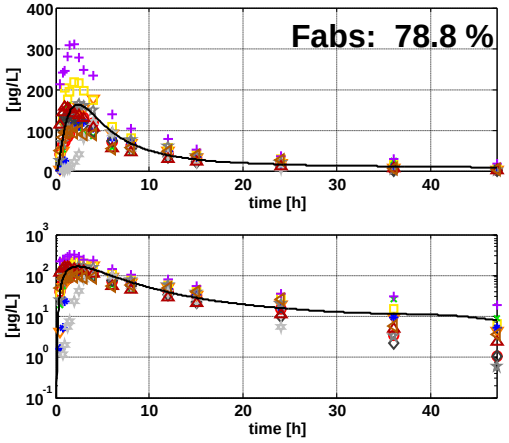
Good description of the solution and IR tablet administered in the fasted state at various dose levels !

Drug X – PO, IR tablet, food effects

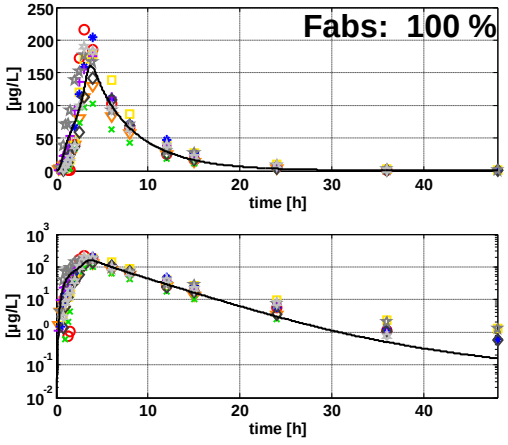
10 mg, fasted state



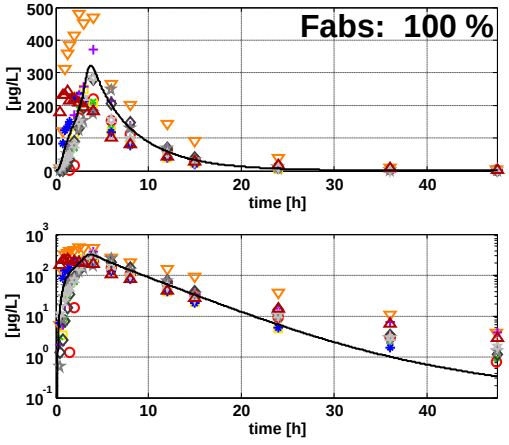
20 mg, fasted state



10 mg, fed state



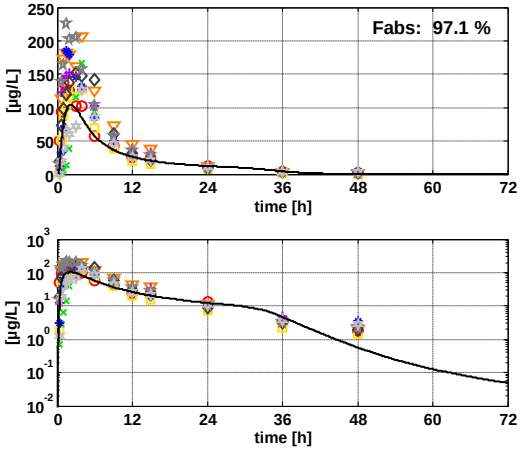
20 mg, fed state



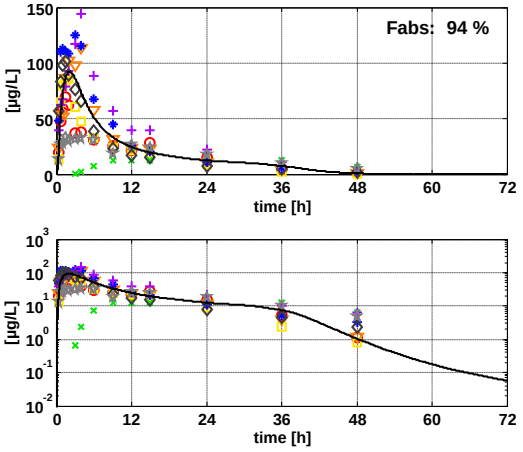
Good description of the influence of food on the absorption of IR tablets !

Drug X – Absorption Site Study

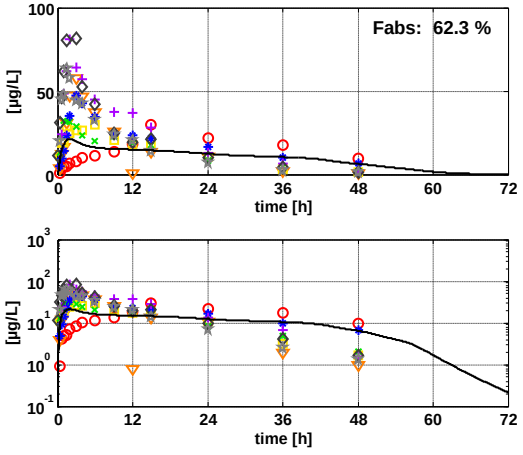
IR tablet orally



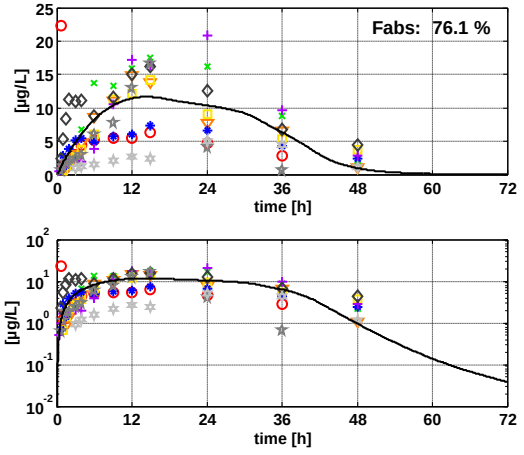
10 mg granules to proximal SI (UJ)



10 mg granules to distal SI (LI)



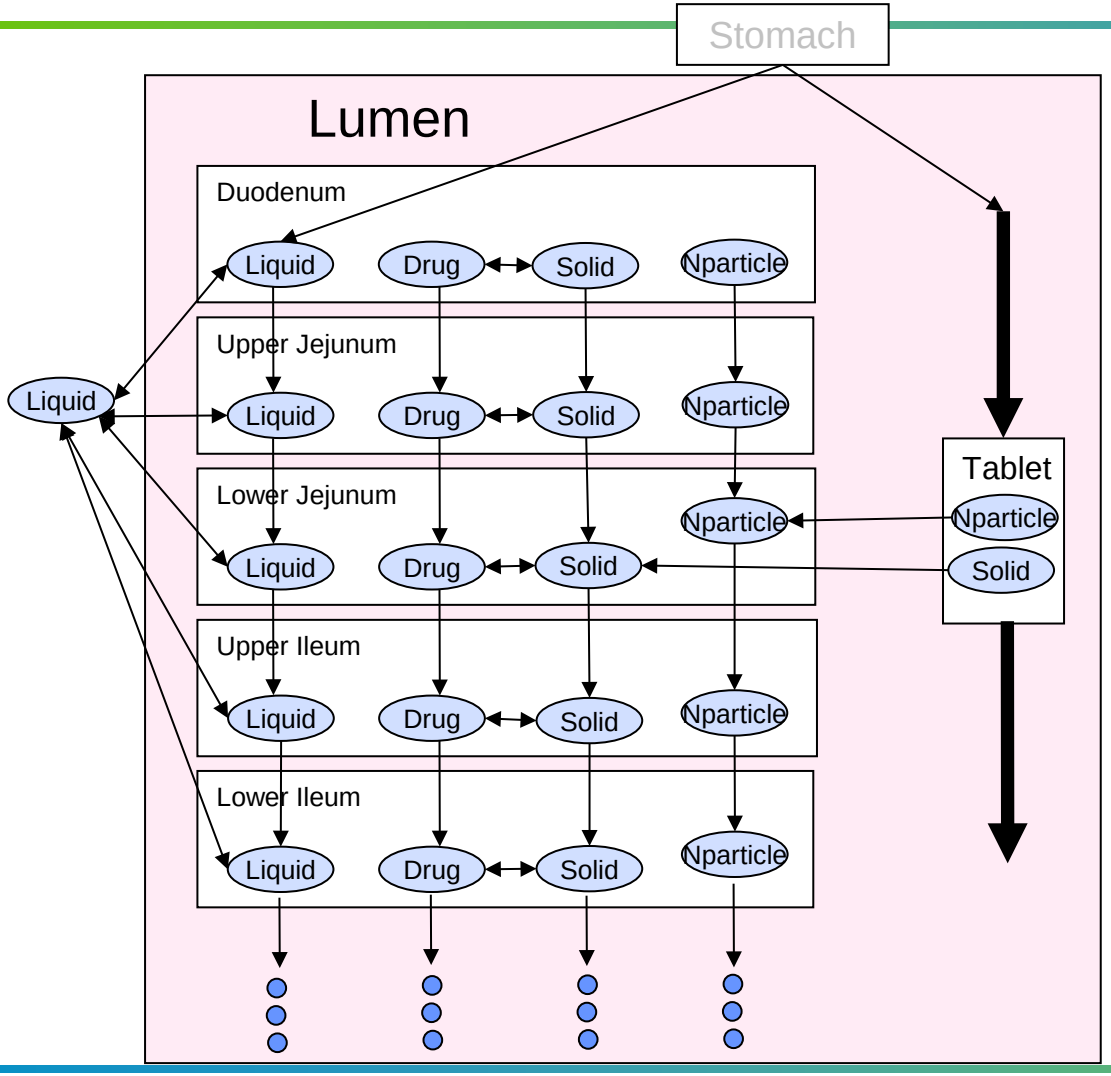
10 mg granules to colon ascendens

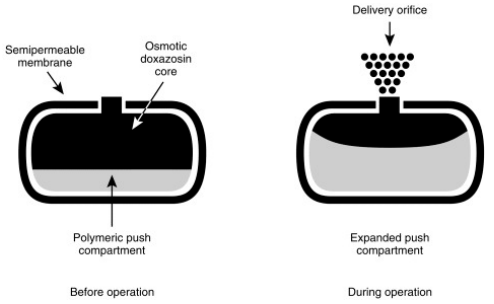


Good description of the regional absorption along the GI tract !

Drug X – GITS

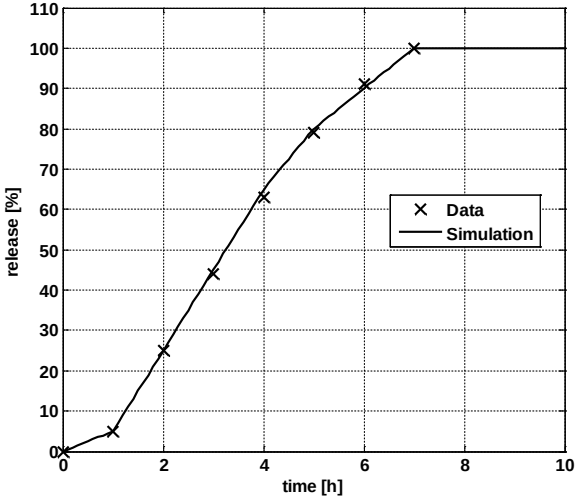
controlled-release gastrointestinal therapeutic system formulation





Chung 1999

GITS release profile

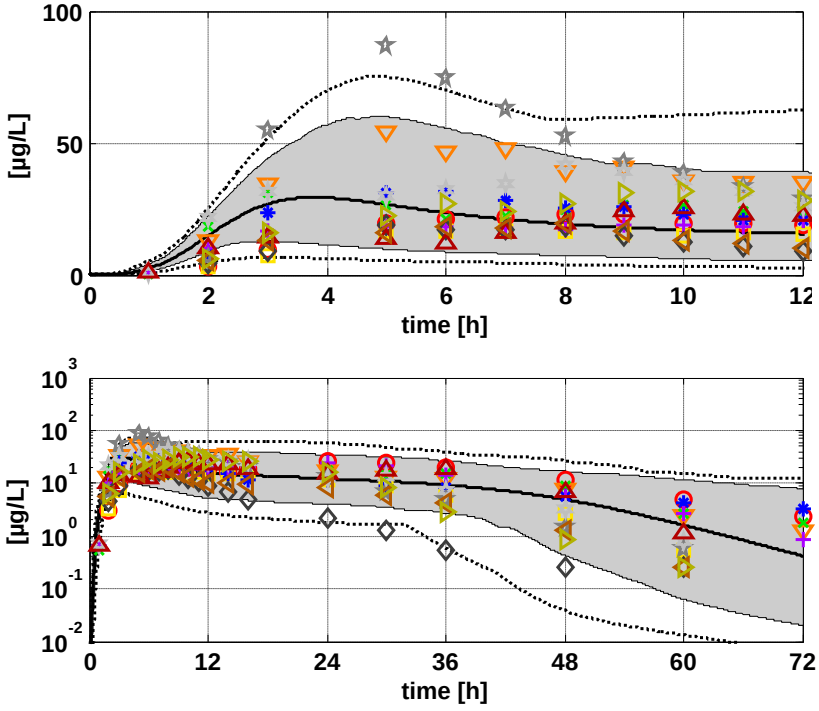


LagTime tablet:

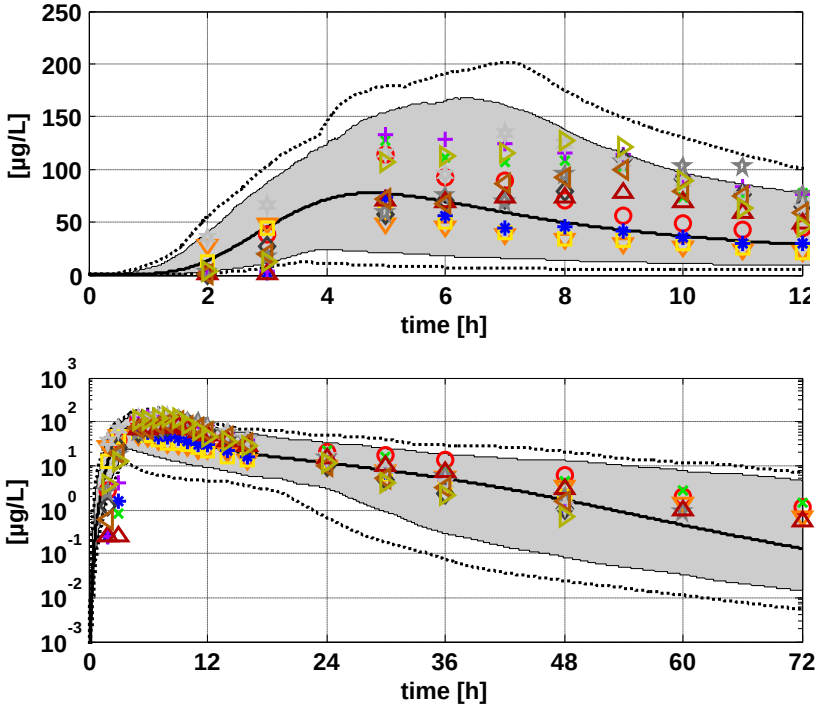
- fasted 30 min
- fed 120 min

Drug X – GITS population predictions

GITS fasted



GITS fed



Good description of the GITS formulation !

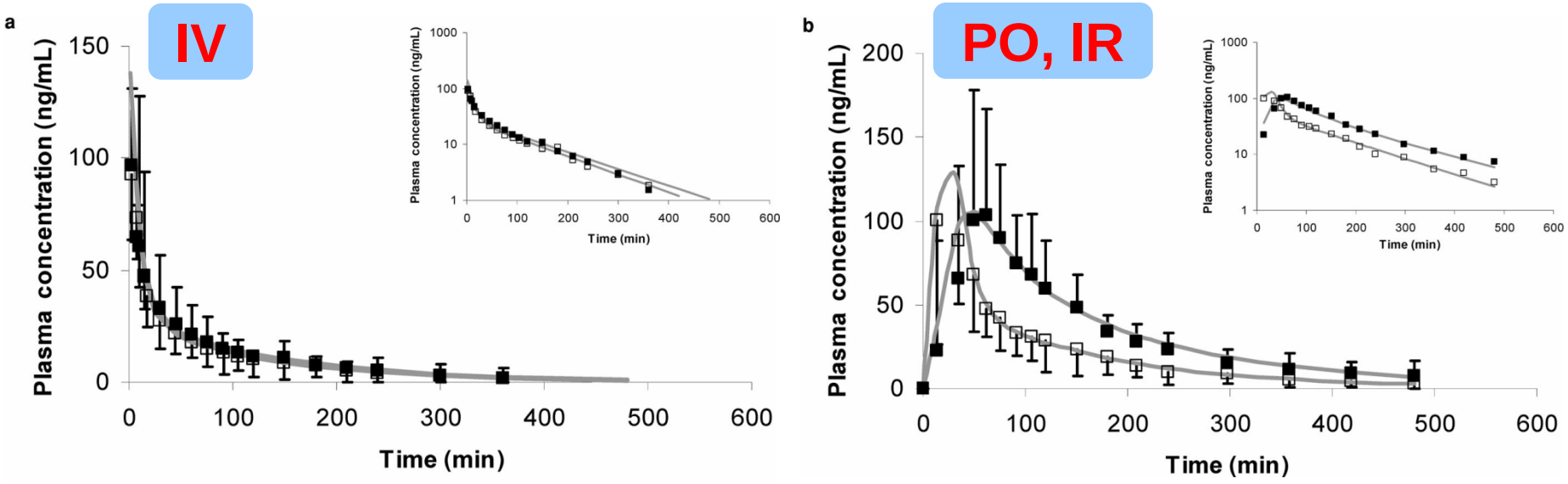
Utilizing *In Vitro* and PBPK Tools to Link ADME Characteristics to Plasma Profiles: Case Example Nifedipine Immediate Release Formulation

CHRISTIAN WAGNER,[1] KIRSTIN THELEN,[2] STEFAN WILLMANN,[2] ARZU SELEN,[3] JENNIFER B. DRESSMAN[1]

[1]Institute of Pharmaceutical Technology, Goethe University, 60438 Frankfurt am Main, Germany

[2]Technology Package Computational Systems Biology, Bayer Technology Services GmbH, 51368 Leverkusen, Germany

[3]Office of New Drug Quality Assessment/OPS/CDER, United States Food and Drug Administration, Silver Spring, Maryland 20993



Nifedipine dissolution and influence of grapefruit juice well described

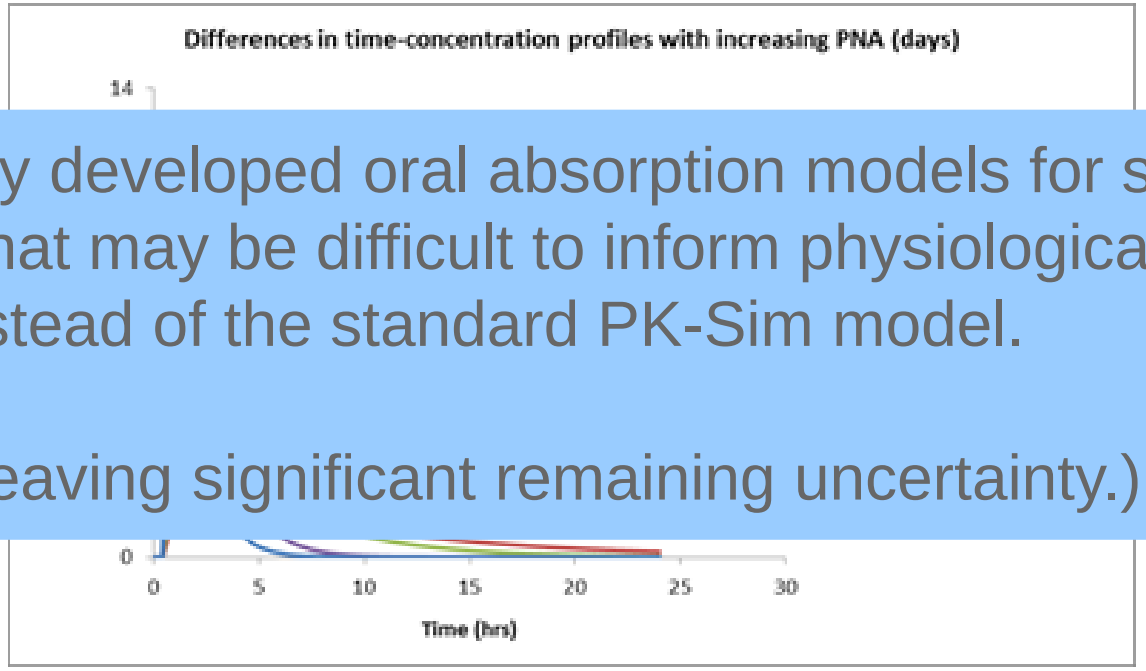
Figure 4. Comparison between the *in vivo* (■: with grapefruit juice; □: without grapefruit juice) and the simulated (pale gray lines) nifedipine plasma profiles. (a) Administration of 2.5 mg nifedipine intravenously. (b) Administration of one Adalat® 10 mg IR soft gelatine capsule orally. The *in vivo* data[12] is presented as mean ± SD. The inserts display the same plot on a semilogarithmic scale.

Wagner 2013

Influence of PNA on Indomethacin Exposure after Oral Administration in Preterm Neonates

Maturation function from Anderson et al. is integrated with the Pop-PK model from Al Za'abi et al.

$$T_{abs}\,(\text{neonate}) = T_{abs}\,(\text{child}) \times \left(1 + \beta_{abs} \times e^{(-\text{PNAGE in days})} \times \frac{\ln(2)}{T_{formulation}}\right)$$



Alternatively developed oral absorption models for specific purposes that may be difficult to inform physiologically can be used instead of the standard PK-Sim model.

(Example leaving significant remaining uncertainty.)

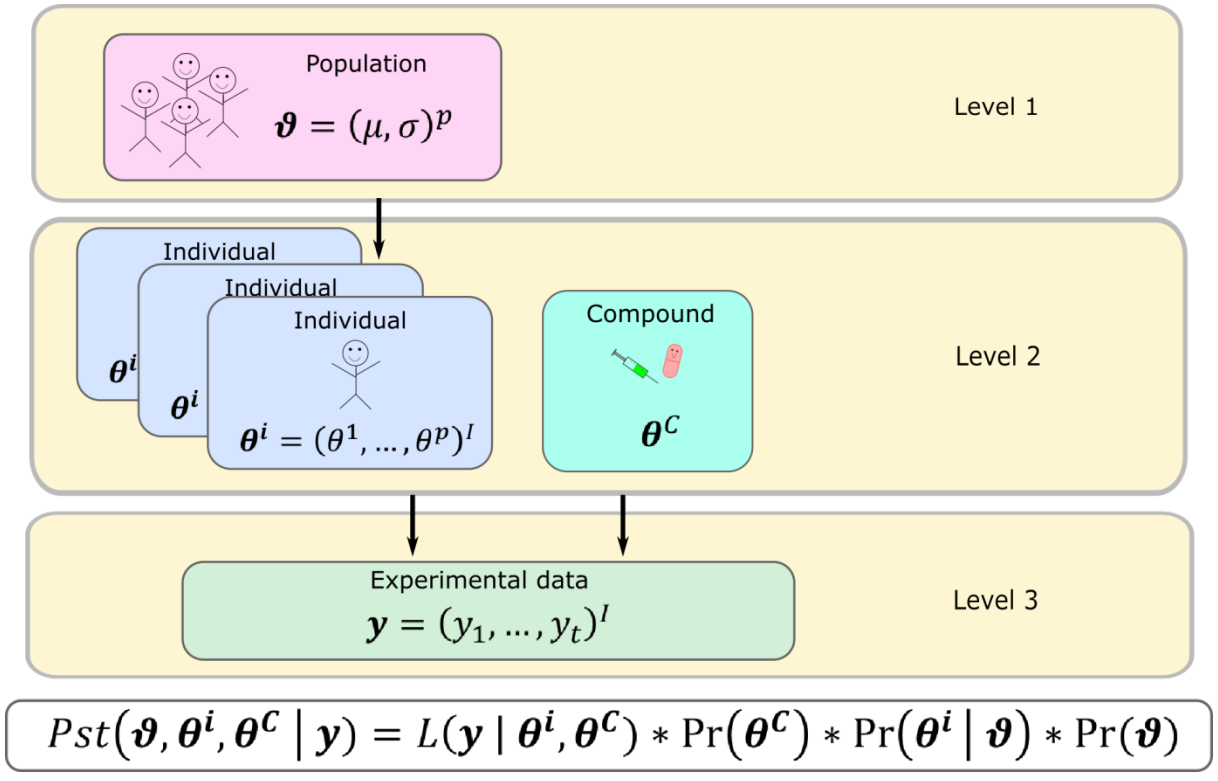
Somani 2015

Simulated time-concentration profiles for a pre-term neonate (At PCA 28.42 and PNAGE 0.5, 1 and 2) given 2 ml of 0.2 mg/ml of indomethacin suspension. The oral absorption maturation function described in Anderson et al. was integrated with the model structure (one compartment model) and CL, V parameter estimates from the pop pk study of indomethacin to very premature neonates with patent ductus arteriosus from Al Za'abi, M. et al..

Anderson, B. et al. Acetaminophen developmental pharmacokinetics in premature neonates and infants. Anesthesiology 96, 1336-45 (2002).

The New Frontier: Population PBPK

Method

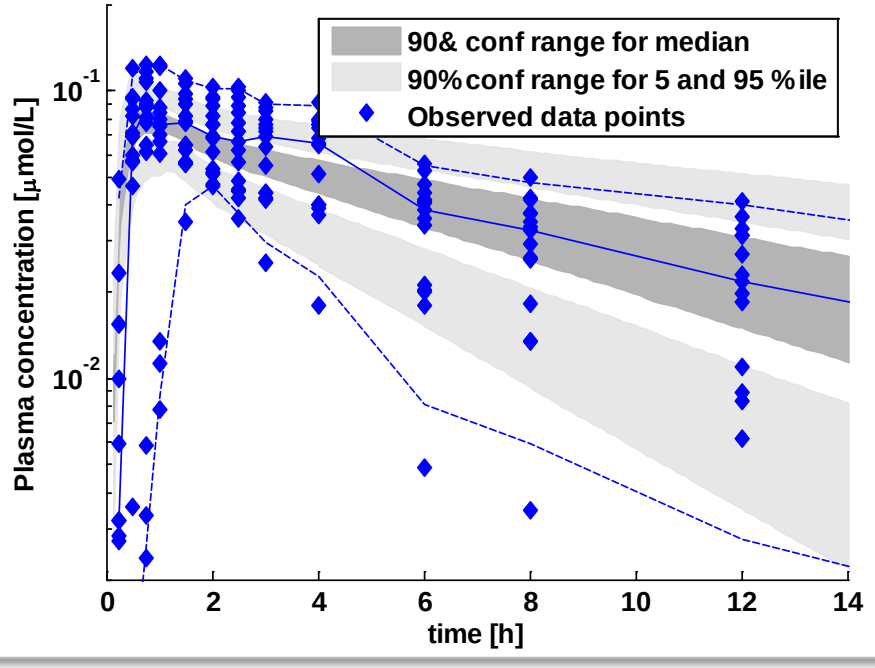


- Hierarchical Bayesian statistical model
- Prior knowledge from PK-Sim data base, literature and in vitro experiments
- Sampling of posterior distribution using Markov Chain Monte Carlo (MCMC) based on the PK-Sim whole body model

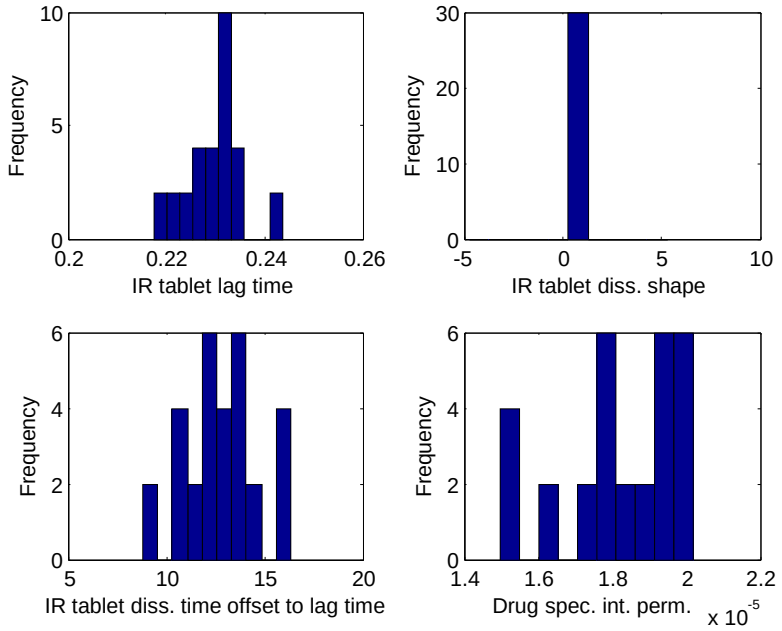
Population PBPK

Absorption parameters from popPBPK

Visual predictive check



Selected parameter distributions



- popPBPK on clinical data of bioavailability study
- Access to variabilities and uncertainties of PBPK parameters given model structure, data and prior knowledge
- Combined IV and PO (crossover) data set is very informative for absorption parameters

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MODEL
(XML-Formulation)

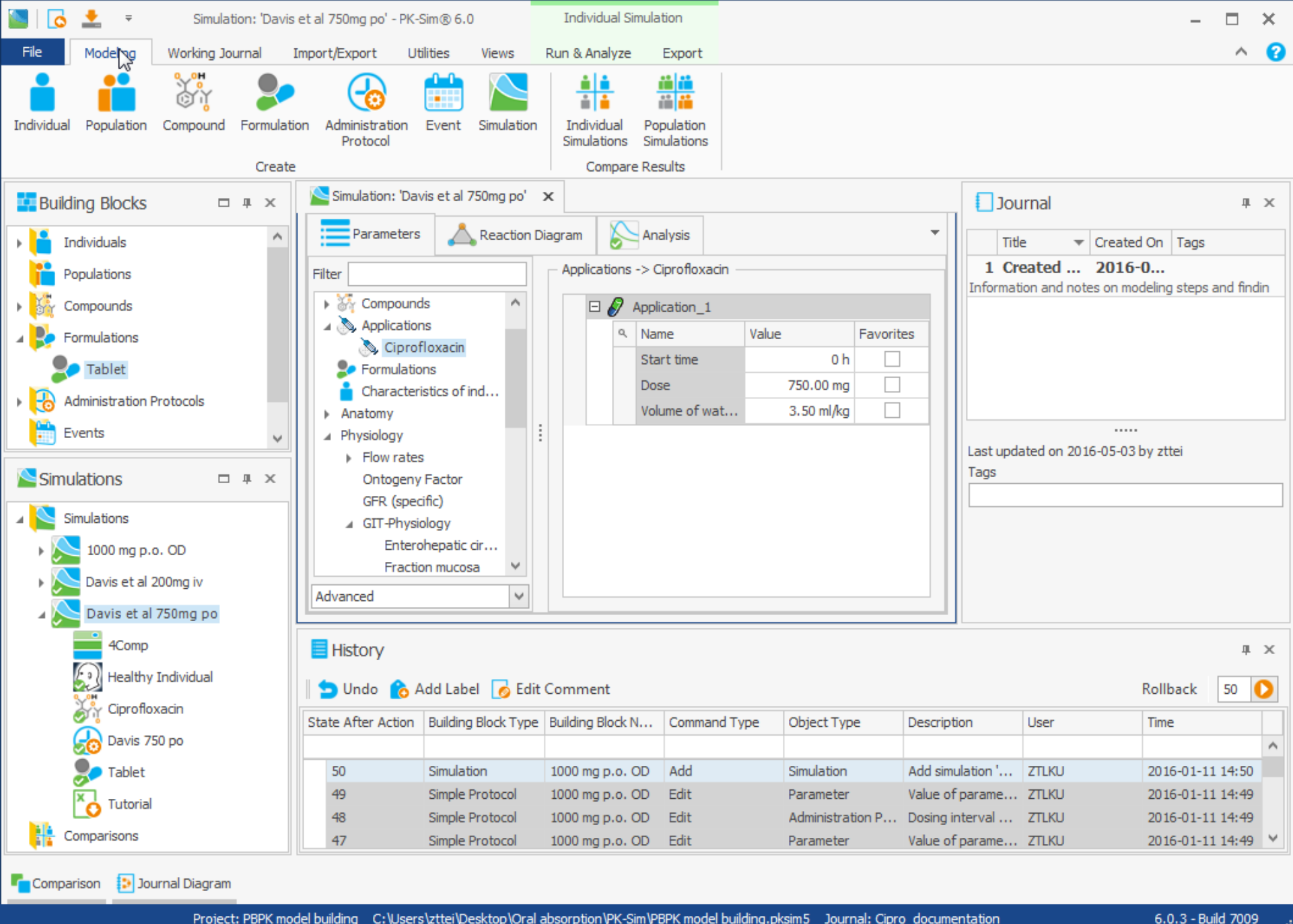
MoBi Toolboxes/ Interfaces for

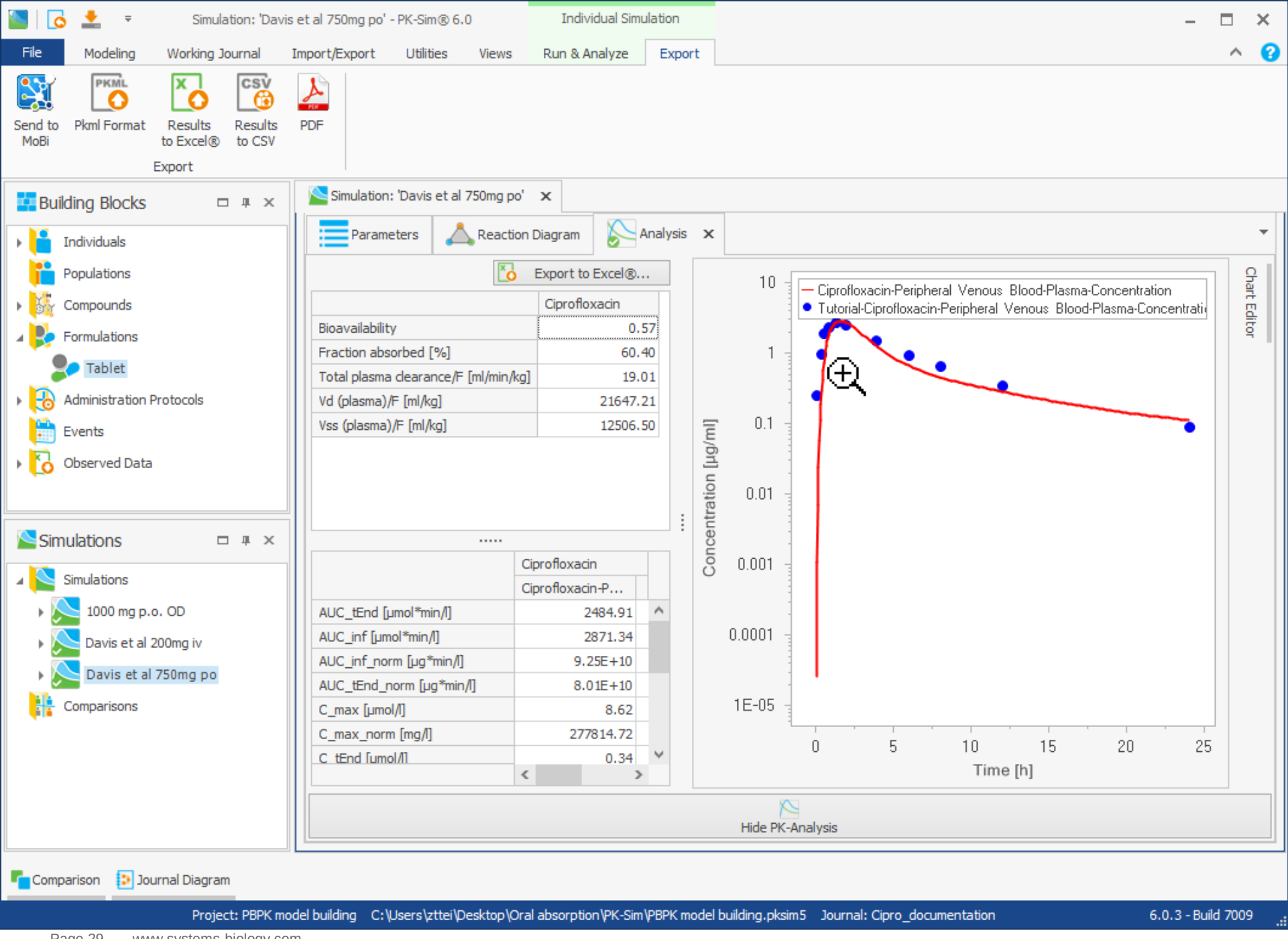
MATLAB® (technical computing)

R (statistical computing)

*import functions to be updated to latest version

Eissing 2009


Simulation: 'Davis et al 750mg po' - PK-Sim® 6.0
Individual Simulation
File
Modeling
Working Journal
Import/Export
Utilities
Views
Run & Analyze
Export
Individual
Population
Compound
Formulation
Administration Protocol
Event
Simulation
Create
Individual Simulations
Population Simulations
Compare Results
Building Blocks
Individuals
Populations
Compounds
Formulations
Tablet
Administration Protocols
Events
Simulations
Simulations
1000 mg p.o. OD
Davis et al 200mg iv
Davis et al 750mg po
4Comp
Healthy Individual
Ciprofloxacin
Davis 750 po
Tablet
Tutorial
Comparisons
Simulation: 'Davis et al 750mg po'
Parameters
Reaction Diagram
Analysis
Filter
Compounds
Applications
Ciprofloxacin
Formulations
Characteristics of ind...
Anatomy
Physiology
Flow rates
Ontogeny Factor
GFR (specific)
GIT-Physiology
Enterohepatic cir...
Fraction mucosa
Advanced
Applications -> Ciprofloxacin
Application_1
Name
Value
Favorites
Start time
0 h
Dose
750.00 mg
Volume of wat...
3.50 ml/kg
Journal
Title
Created On
Tags
1 Created ...
2016-0...
Information and notes on modeling steps and findin
Last updated on 2016-05-03 by zttei
Tags
History
Undo
Add Label
Edit Comment
Rollback
50
State After Action
Building Block Type
Building Block N...
Command Type
Object Type
Description
User
Time
50
Simulation
1000 mg p.o. OD
Add
Simulation
Add simulation '...
ZTLKU
2016-01-11 14:50
49
Simple Protocol
1000 mg p.o. OD
Edit
Parameter
Value of parame...
ZTLKU
2016-01-11 14:49
48
Simple Protocol
1000 mg p.o. OD
Edit
Administration P...
Dosing interval ...
ZTLKU
2016-01-11 14:49
47
Simple Protocol
1000 mg p.o. OD
Edit
Parameter
Value of parame...
ZTLKU
2016-01-11 14:49
Comparison
Journal Diagram
Project: PBPK model building
C:\Users\zttei\Desktop\Oral absorption\PK-Sim\PBPK model building.pksim5
Journal: Cipro_documentation
6.0.3 - Build 7009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Results to CSV
PDF
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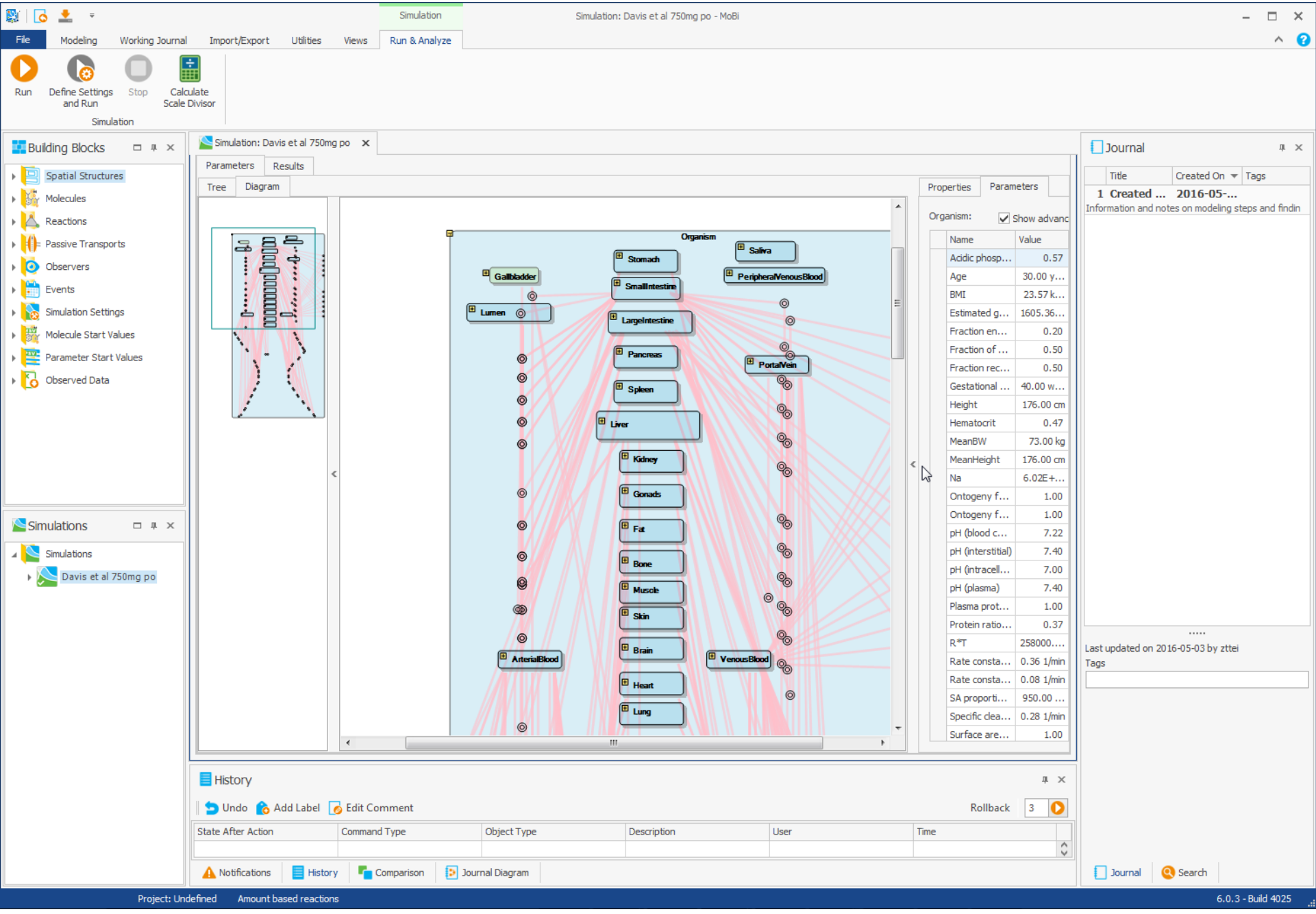
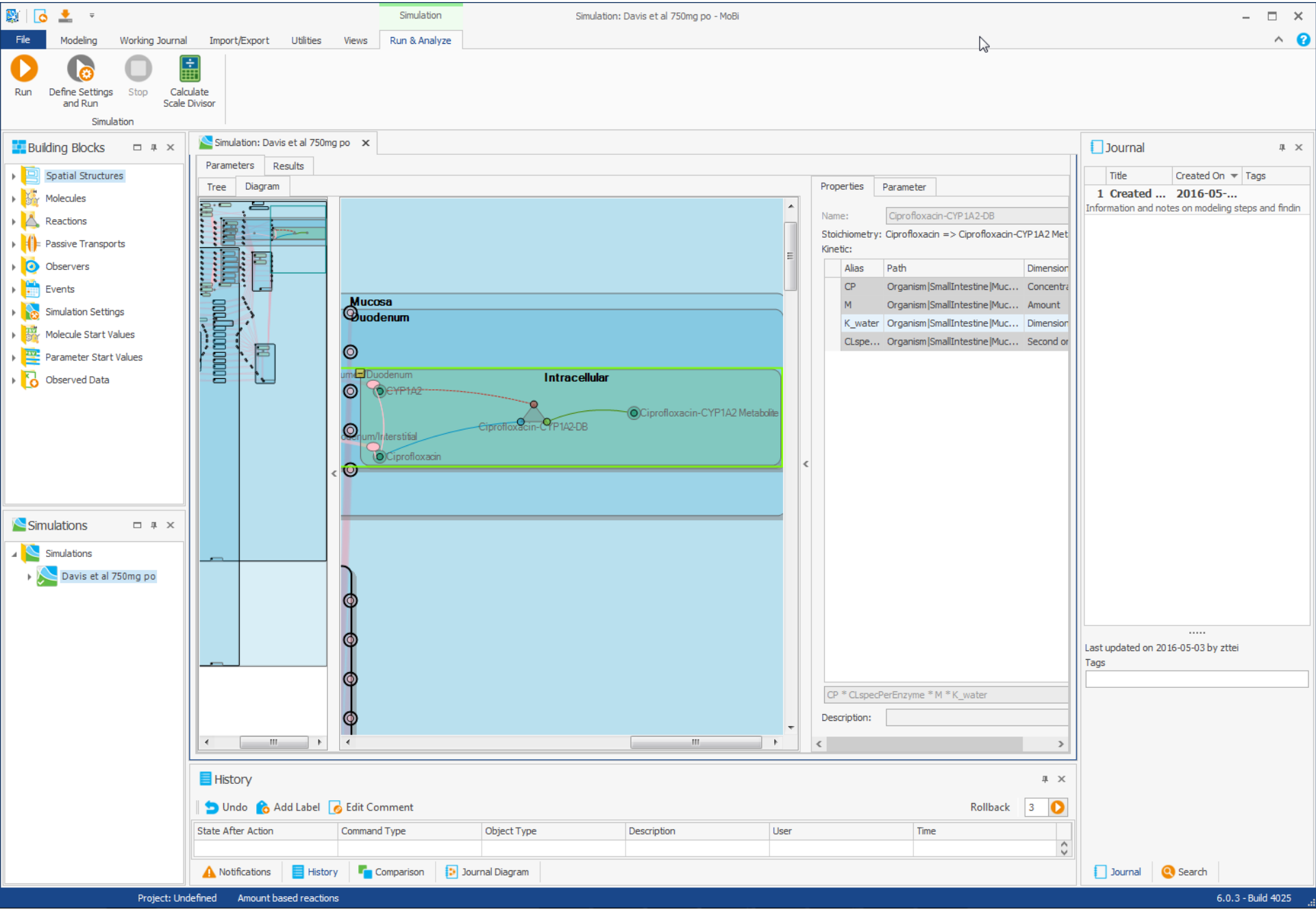
Compounds
Formulations
Tablet
Administration Protocols
Events
Observed Data
Simulations
Simulations
1000 mg p.o. OD
Davis et al 200mg iv
Davis et al 750mg po
Comparisons
Simulation: 'Davis et al 750mg po'
Parameters
Reaction Diagram
Analysis
Export to Excel®...
Ciprofloxacin
Bioavailability 0.57
Fraction absorbed [%] 60.40
Total plasma clearance/F [ml/min/kg] 19.01
Vd (plasma)/F [ml/kg] 21647.21
Vss (plasma)/F [ml/kg] 12506.50
Ciprofloxacin
Ciprofloxacin-P...
AUC_tEnd [µmol*min/l] 2484.91
AUC_inf [µmol*min/l] 2871.34
AUC_inf_norm [µg*min/l] 9.25E+10
AUC_tEnd_norm [µg*min/l] 8.01E+10
C_max [µmol/l] 8.62
C_max_norm [mg/l] 277814.72
C_tEnd [µmol/l] 0.34
Ciprofloxacin-Peripheral Venous Blood-Plasma-Concentration
Tutorial-Ciprofloxacin-Peripheral Venous Blood-Plasma-Concentrati
Concentration [µg/ml]
10
1
0.1
0.01
0.001
0.0001
1E-05
0
5
10
15
20
25
Time [h]
Chart Editor
Hide PK-Analysis
Comparison
Journal Diagram
Project: PBPK model building
C:\Users\zttei\Desktop\Oral absorption\PK-Sim\PBPK model building.pksim5
Journal: Cipro_documentation
6.0.3 - Build 7009


Simulation
Simulation: Davis et al 750mg po - MoBi
File
Modeling
Working Journal
Import/Export
Utilities
Views
Run & Analyze
Run
Define Settings and Run
Stop
Calculate Scale Divisor
Simulation
Building Blocks
Spatial Structures
Molecules
Reactions
Passive Transports
Observers
Events
Simulation Settings
Molecule Start Values
Parameter Start Values
Observed Data
Simulations
Simulations
Davis et al 750mg po
Simulation: Davis et al 750mg po
Parameters
Results
Tree
Diagram
Organism
Stomach
Saliva
Gallbladder
PeripheralVenousBlood
SmallIntestine
Lumen
LargeIntestine
Pancreas
PortalVein
Spleen
Liver
Kidney
Gonads
Fat
Bone
Muscle
Skin
Brain
ArterialBlood
VenousBlood
Heart
Lung
Properties
Parameters
Organism:
Show advanc
Name
Value
Acidic phosp... 0.57
Age 30.00 y...
BMI 23.57 k...
Estimated g... 1605.36...
Fraction en... 0.20
Fraction of ... 0.50
Fraction rec... 0.50
Gestational ... 40.00 w...
Height 176.00 cm
Hematocrit 0.47
MeanBW 73.00 kg
MeanHeight 176.00 cm
Na 6.02E+...
Ontogeny f... 1.00
Ontogeny f... 1.00
pH (blood c... 7.22
pH (interstitial) 7.40
pH (intracell... 7.00
pH (plasma) 7.40
Plasma prot... 1.00
Protein ratio... 0.37
R*T 258000....
Rate consta... 0.36 1/min
Rate consta... 0.08 1/min
SA proporti... 950.00 ...
Specific clea... 0.28 1/min
Surface are... 1.00
Journal
Title
Created On
Tags
1 Created ... 2016-05-...
Information and notes on modeling steps and findin
Last updated on 2016-05-03 by zttei
Tags
History
Undo
Add Label
Edit Comment
Rollback
3
State After Action
Command Type
Object Type
Description
User
Time
Notifications
History
Comparison
Journal Diagram
Journal
Search
Project: Undefined
Amount based reactions
6.0.3 - Build 4025


Simulation
Simulation: Davis et al 750mg po - MoBi
File
Modeling
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Run
Define Settings and Run
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Calculate Scale Divisor
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Simulation Settings
Molecule Start Values
Parameter Start Values
Observed Data
Simulations
Simulations
Davis et al 750mg po
Simulation: Davis et al 750mg po
Parameters
Results
Tree
Diagram
Mucosa
Duodenum
Intracellular
CYP1A2
Ciprofloxacin-CYP1A2 Metabolite
Ciprofloxacin-CYP1A2-DB
Ciprofloxacin
Properties
Parameter
Name:
Ciprofloxacin-CYP1A2-DB
Stoichiometry:
Ciprofloxacin => Ciprofloxacin-CYP1A2 Met
Kinetic:
Alias
Path
Dimension
CP
M
K_water
CLspe...
Organism|SmallIntestine|Muc...
Concentra
Amount
Dimensior
Second or
CP * CLspecPerEnzyme * M * K_water
Description:
Journal
Title
Created On
Tags
1 Created ...
2016-05-...
Information and notes on modeling steps and findin
Last updated on 2016-05-03 by zttei
Tags
History
Undo
Add Label
Edit Comment
Rollback
3
State After Action
Command Type
Object Type
Description
User
Time
Notifications
History
Comparison
Journal Diagram
Journal
Search
Project: Undefined
Amount based reactions
6.0.3 - Build 4025

Agenda

- Introduction: PBPK modeling with PK-Sim & MoBi
- Oral absorption and dissolution modeling
  - Concept
  - Examples
  - Implementation
- **Summary**

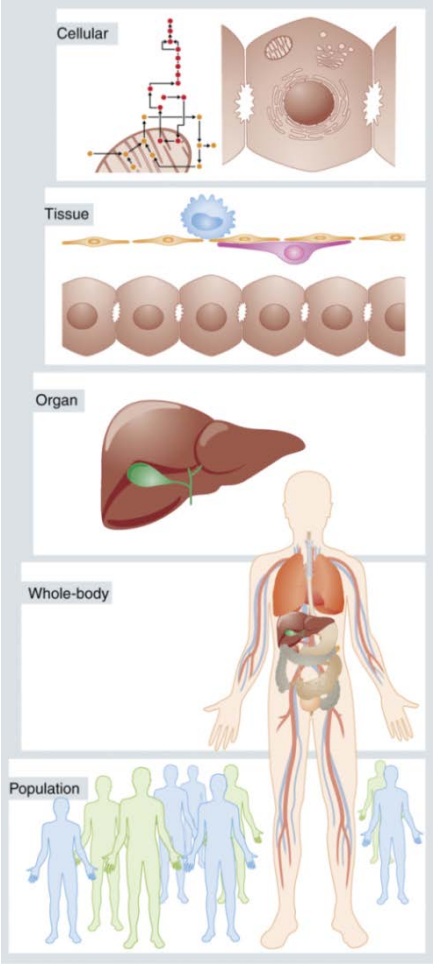
Summary & Conclusion

Summary

- Examples shown for how to model different formulations and their oral absorption in PK-Sim/MoBi to better understand PK

Conclusion

- PK-Sim is a PBPK tool with a focus on **flexibility** and **transparency**, together with MoBi leaving a lot of room for problem specific solutions …



Kuepfer 2010

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Thank you!