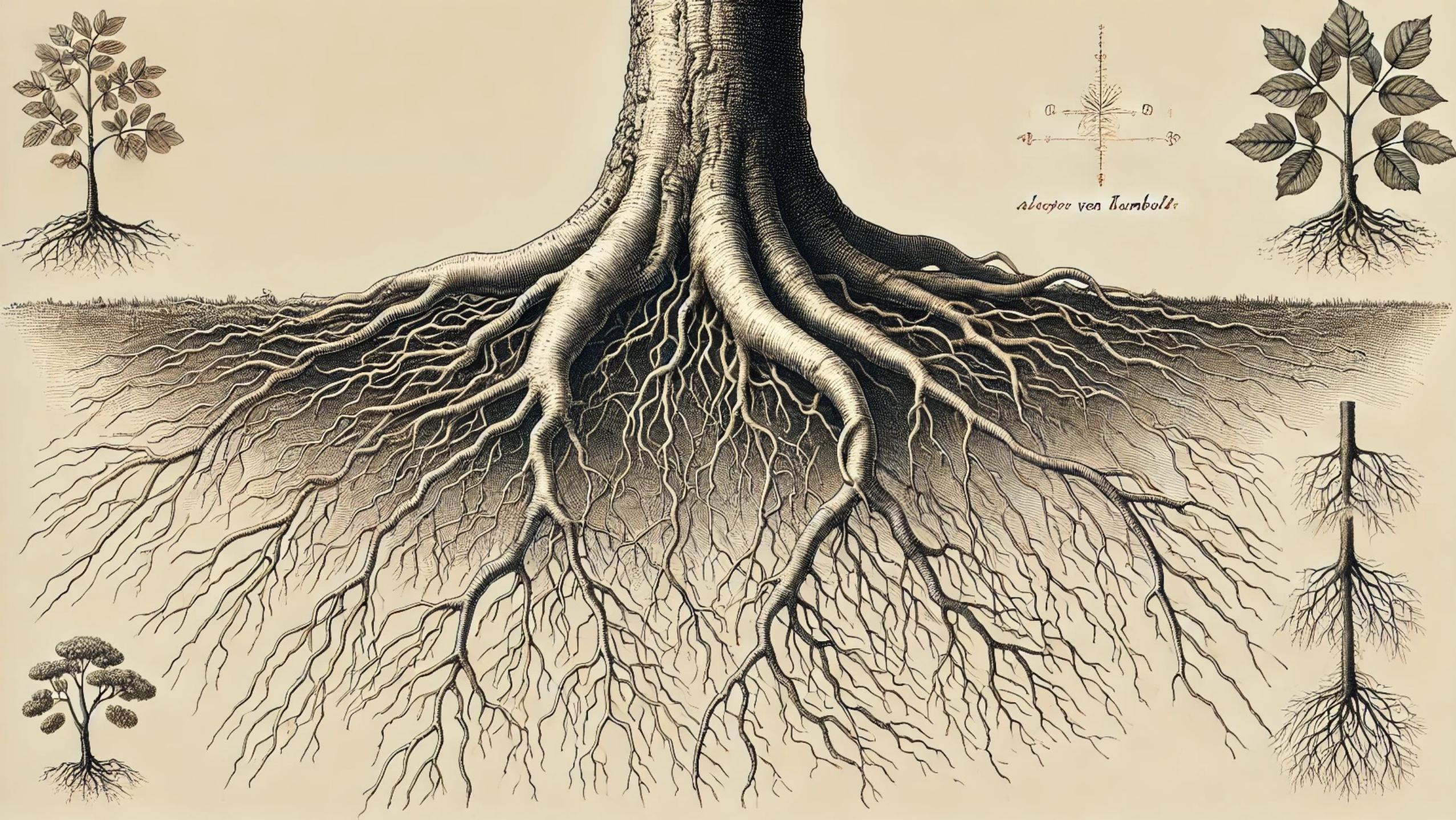


Roots & Leafs

Jörg Lippert
2024-10-07







afbeelding van Lambolle

An almost or not so random pick of deep roots

JOURNAL OF
PHARMACEUTICAL
SCIENCES

OCTOBER 1983
VOLUME 72 NUMBER 10

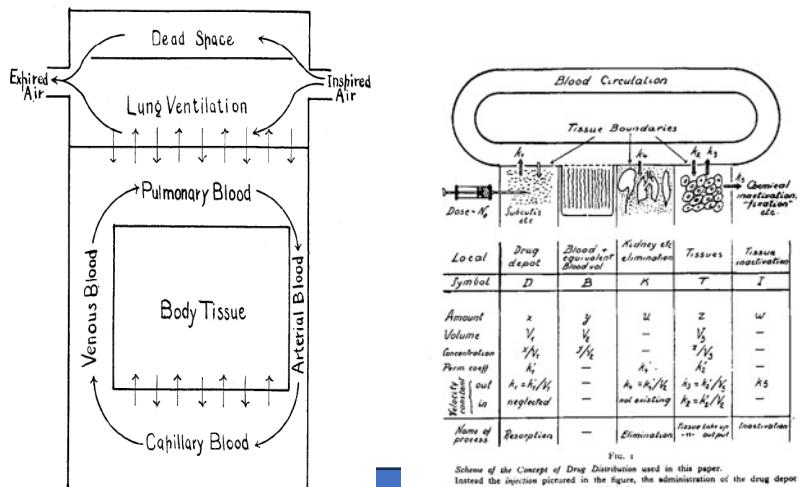
THE ABSORPTION, DISTRIBUTION, AND ELIMINATION OF ETHYL ETHER.

II. ANALYSIS OF THE MECHANISM OF ABSORPTION AND ELIMINATION OF SUCH A GAS OR VAPOR AS ETHYL ETHER.

By HOWARD W. HAGGARD.

(From the Laboratory of Applied Physiology, Yale University, New Haven.)

(Received for publication, March 1, 1924.)



Haggard 1924

Teorell 1937

Gerlowski & Jain 1983

LITERATURE SURVEY

Physiologically Based Pharmacokinetic Modeling: Principles and Applications

LEONARD E. GERLOWSKI and RAKESH K. JAIN *

Received March 25, 1982, from the Department of Chemical Engineering, Carnegie-Mellon University, Pittsburgh, PA 15213.

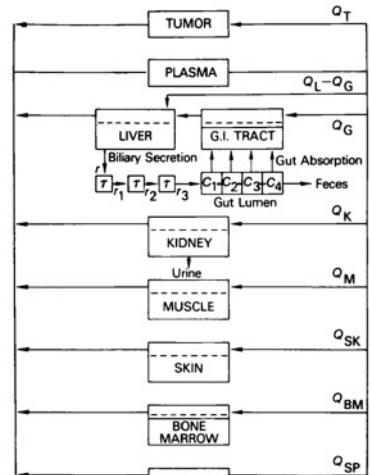


Figure 3—Location of the biliary and gut lumen compartments represented by well-mixed subcompartments connected in series.

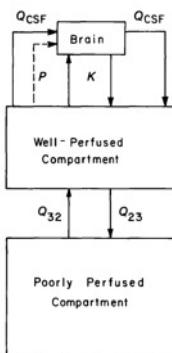


Figure 4—Location of the brain compartment (74). Reprinted from the Journal of Applied Physiology with permission, copyright 1980, American Physiological Society.

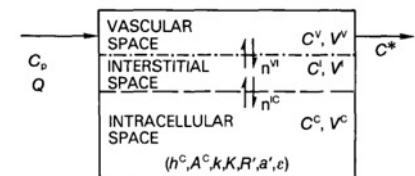
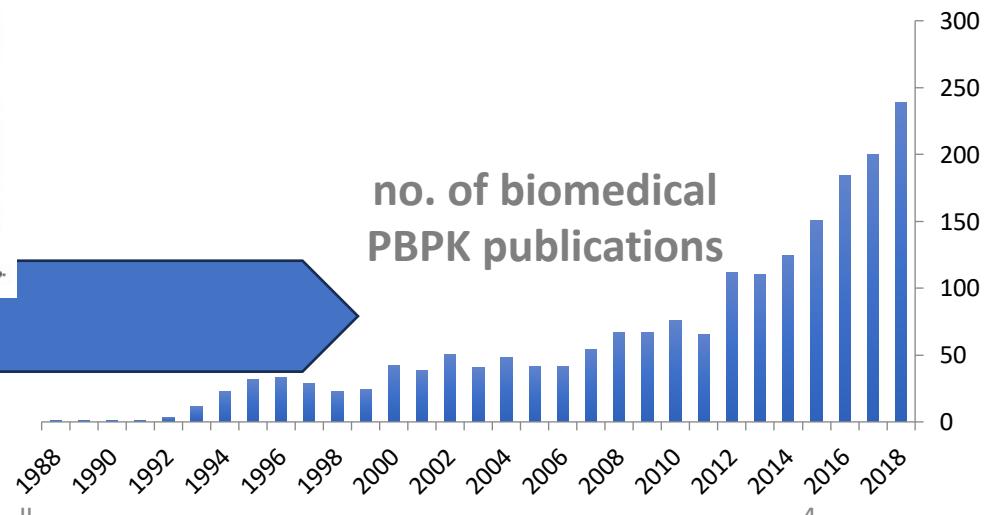


Figure 2—Schematic representation of the vascular, interstitial, and intracellular spaces of an organ. The flux of the substance occurs across the dashed lines, the arrows represent the direction of blood flow.

no. of biomedical
PBPK publications



An almost or not so random pick of deep roots



Search Wikipedia Search

Dona

Hodgkin–Huxley model

Contents hide

(Top)

Basic components

Ionic current characterization

Voltage-gated ion channels

Leak channels

Pumps and exchangers

Mathematical properties

Center manifold

Bifurcations

Improvements and alternative models

See also

References

Further reading

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15 languages ▼

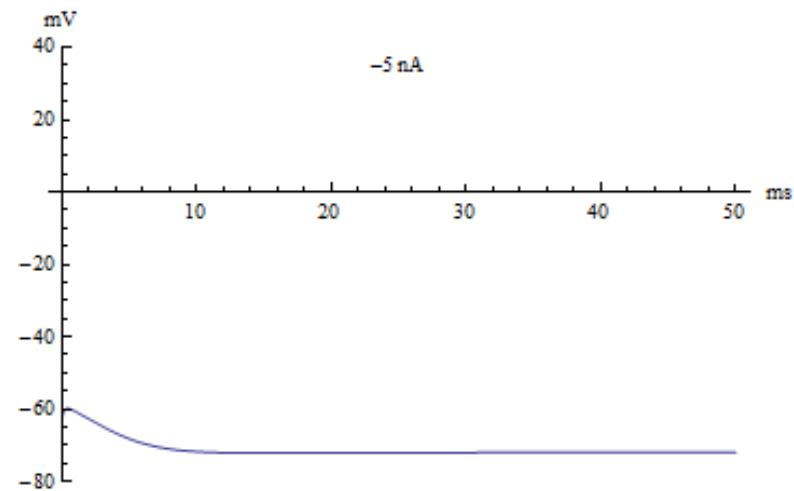
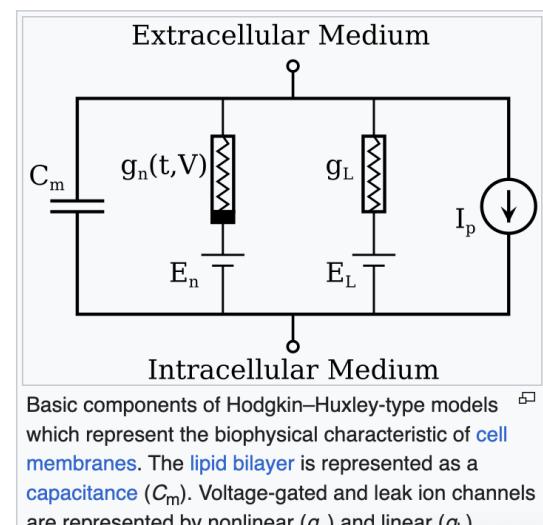
From Wikipedia, the free encyclopedia

The **Hodgkin–Huxley model**, or **conductance-based model**, is a mathematical model that describes how action potentials in neurons are initiated and propagated. It is a set of nonlinear differential equations that approximates the electrical engineering characteristics of excitable cells such as neurons and muscle cells. It is a continuous-time dynamical system.

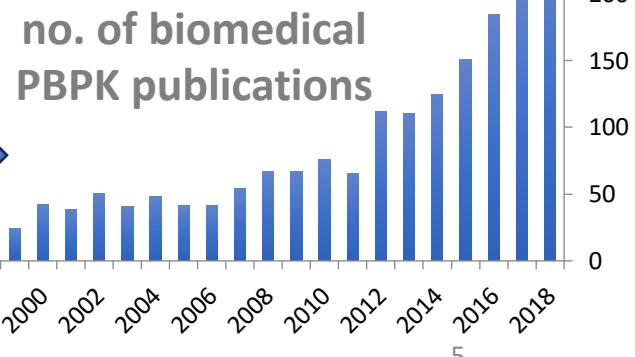
Alan Hodgkin and Andrew Huxley described the model in 1952 to explain the ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon.^[1] They received the 1963 Nobel Prize in Physiology or Medicine for this work.

Basic components [edit]

The typical Hodgkin–Huxley model treats each component of an



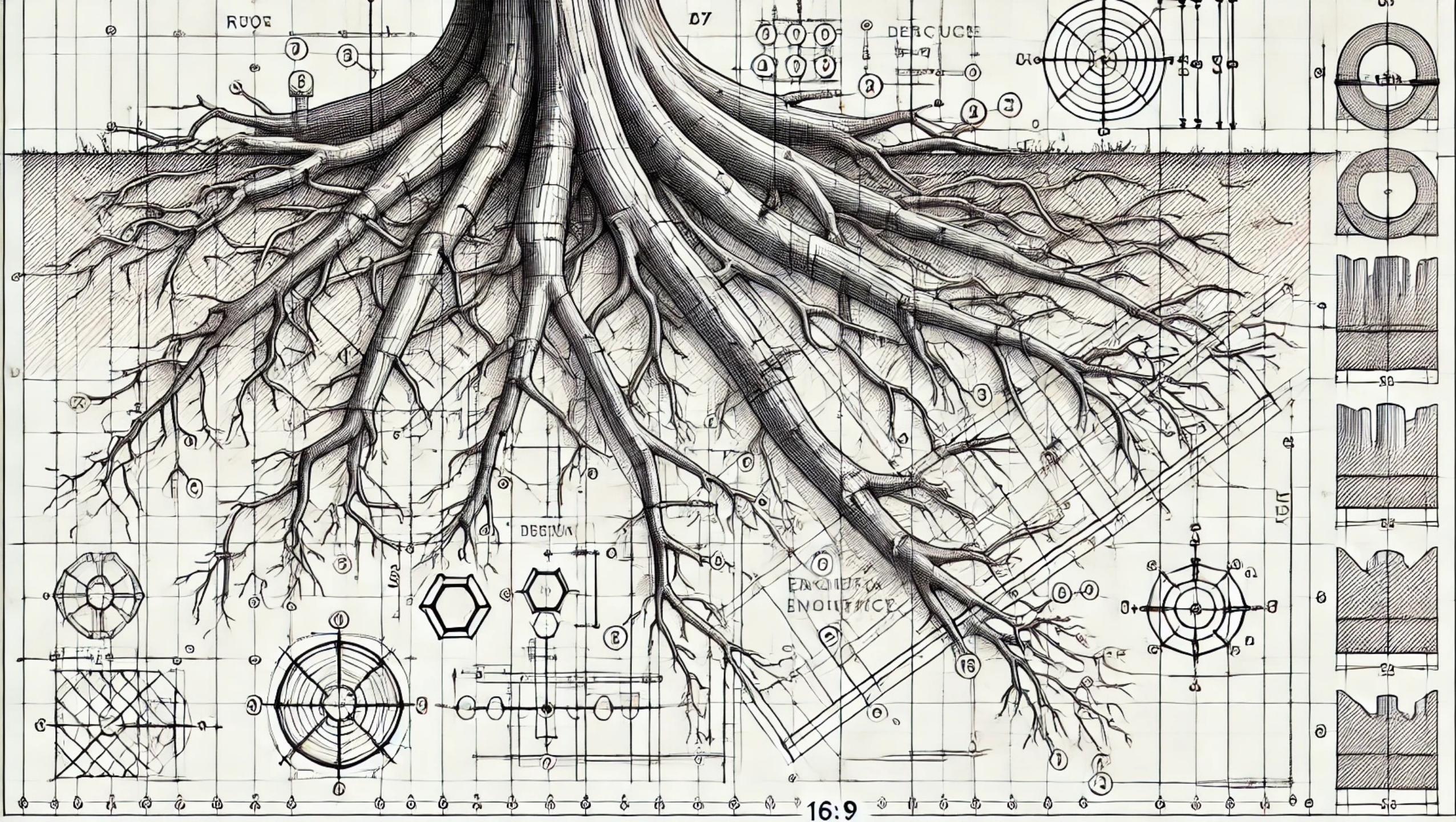
[Alexander J. White](#) - Own work



Haggard 1924

Teorell 1937

Gerlowski & Jain 1983



(Re)engineering roots...

May 2002 – demand identified

Sachbearbeiter: Dr. W. Schmitt
Telefon: (02173-38) 4546
Dateiname:
Geb.: 6240
Telex: (02173-38) 4869
Werk: Monheim
Zentrale Forschung
ZF-PY-MW/Biophysik

Besprechungsprotokoll

Thema:

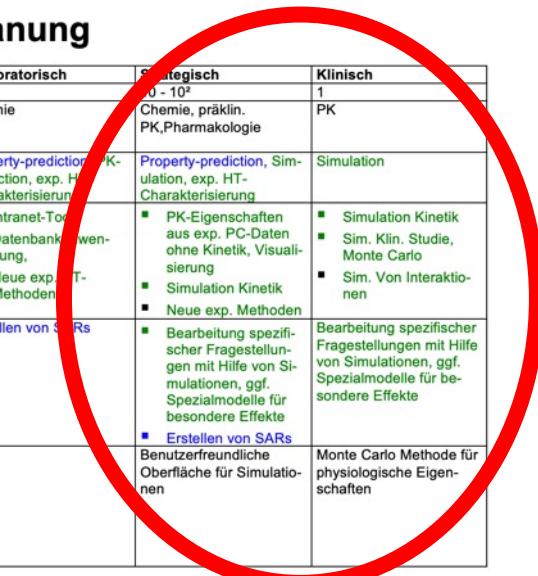
Zusammenarbeit Biophysik und Math. Verfahrenstechnik-M&M auf dem Gebiet ADME

am: 2002-05-17

Teilnehmer: Bieringer (zeitweise), Lippert, Ohrenberg, Schmitt, Schuppert, Willmann

Portfolioplanung

Stadium	Substanzbibliothek	Screening	Exploratorisch	Strategisch	Klinisch
# Substanzen	$10^3 - 10^6$	10^3	10^2	$10^0 - 10^2$	1
Ansprechpartner in Teilkonzernen	Kombichem, Chemie, HTS, Substanz-Einkauf, Comput. Chemistry	HTS, Chemie, Comput. Chemistry	Chemie	Chemie, präklin. PK,Pharmakologie	PK
Methoden	Property-prediction	Property-prediction, PK-prediction, evtl. exp. HT-Charakterisierung	Property-prediction, PK-prediction, exp. HT-Charakterisierung	Property-prediction, Simulation, exp. HT-Charakterisierung	Simulation
Produktvorschlag	System zur Vorhersage von Eigenschaften und Klassifizierung nach Regeln (verbesserte Lipinski-rules)	<ul style="list-style-type: none"> ■ Module für Datenbankanwendungen (PILO, PIX) ■ Neue exp. HT-Methoden 	<ul style="list-style-type: none"> ■ Intranet-Tour ■ Datenbankanwendung, ■ Neue exp. HT-Methoden 	<ul style="list-style-type: none"> ■ PK-Eigenschaften aus exp. PC-Daten ohne Kinetik, Visualisierung ■ Simulation Kinetik ■ Sim. Klin. Studie, Monte Carlo ■ Simulation Kinetik ■ Sim. Von Interaktionen 	
Consulting	Optimierung und Versuchsplanung für HTS	Optimierung und Versuchsplanung für HTS	Erstellen von SARS		<ul style="list-style-type: none"> ■ Bearbeitung spezifischer Fragestellungen mit Hilfe von Simulationen, ggf. Spezialmodelle für besondere Effekte ■ Erstellen von SARS
Was fehlt?	<ul style="list-style-type: none"> ■ Metabolisierungs-raten ■ Löslichkeiten ■ pKa-Werte ■ Modelle für den aktiven Transport 	<ul style="list-style-type: none"> ■ Metabolisierungs-raten ■ Löslichkeiten ■ pKa-Werte ■ Modelle für den aktiven Transport 		Benutzerfreundliche Oberfläche für Simulationen	Monte Carlo Methode für physiologische Eigenschaften



Jul 2002 – GUI design aligned

INTERN

Dr. J. Lippert
Telefon: 5 48 13
Fax: 6 48 01
Geb. K 9
Leverkusen
ZT-TE 2.3
Zentrale Technik
Mathematische Verfahrenstechnik



Leverkusen, 2002-07-05

Protokoll: Anforderungsprofil PK-SIM

Datum: 2002-07-03, 9:30 – 12:00 Uhr,
Teilnehmer: Lippert, Loosen, Schmitt, Willmann

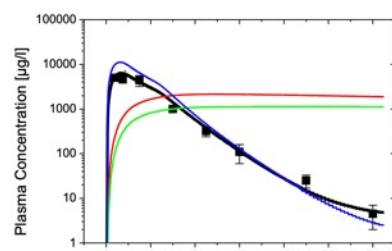
ANHANG: Entwurf für Bildschirmmaske

COMPOUND	XYZ	
Name	XYZ	
LogMA =	2.5	
LogHSA =	-4.5	
Mol. Weight =	400	
Hepatic CL =	150 ml/min	
Renal CL =	250 ml/min	
Acid	○	
Base	○	
pK =	6.7	

START

PHYSIOLOGY	Partition Coeff.		Permeabilities	
	RESET	Factor	RESET	Factor
Organ Intestine	PC Tuning	2.0	PA Tuning	2.0
Lung	2.6	●	7.4	●
Liver	2.3	●	5.4	●
Kidney	1.2	●	1.2	●
Brain	1.3	●	1.5	●
Skin	1.0	●	2.4	●
Bone	2.1	●	3.6	●
Muscle	2.2	●	5.6	●
Heart	2.3	●	4.3	●
	2.1	●	2.1	●

ORGAN
○ Plasma
○ Lung
○ Liver
○ Bile
○ Kidney
○ Brain
○ Skin
○ Bone
○ Muscle
○ Heart
○ Fat
○ ...
○ LIN ○ LOG



(Re)engineering roots...

Jul 2002 – GUI design aligned

INTERN

Bayer

Dr. J. Lippert Telefon: 5 48 13 Geb. K 9
Telefax: 6 48 01 Leverkusen

ZT-TE 2.3
Zentrale Technik
Mathematische Verfahrenstechnik

Leverkusen, 2002-07-05

Protokoll: Anforderungsprofil PK-SIM

Datum: 2002-07-03, 9:30 – 12:00 Uhr,
Teilnehmer: Lippert, Loosen, Schmitt, Willmann

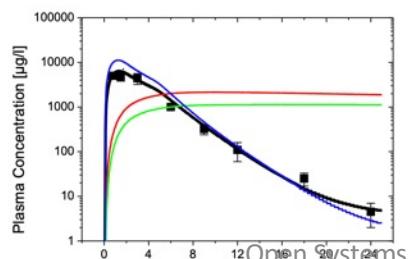
ANHANG: Entwurf für Bildschirmmaske

COMPOUND		SPECIES		APPLICATION	
Name	XYZ	<input checked="" type="radio"/> human	<input type="radio"/> intravenous	Applied dose =	1.0 mg/kg
LogMA =	2.5	<input type="radio"/> dog	<input type="radio"/> oral	Solubility =	50.0 mg/L
LogHSA =	-4.5	<input type="radio"/> rat	<input type="radio"/> subcutan	Simulation Time	1440 min.
Mol. Weight =	400	<input type="radio"/> mouse	<input type="radio"/> dermal		
Hepatic CL =	150 ml/min	<input type="radio"/> user defined	<input type="radio"/> respiratory	<input type="radio"/> multiple dosing	dosing intervall
Renal CL =	250 ml/min				
<input checked="" type="radio"/> Acid <input type="radio"/> Base	pK = 6.7				

START

	Partition Coeff.		Permeabilities	
	RESET	Factor	RESET	Factor
Organ	PC	Tuning	PA	Tuning
Intestine	2.6	•	7.4	•
Lung	2.3	•	5.4	•
Liver	1.2	•	1.2	•
Kidney	1.3	•	1.5	•
Brain	1.0	•	2.4	•
Skin	2.1	•	3.6	•
Bone	2.2	•	5.6	•
Muscle	2.3	•	4.3	•
Heart	2.1	•	2.1	•

ORGAN	
<input type="radio"/> Plasma	<input type="radio"/> Lung
<input type="radio"/> Liver	<input type="radio"/> Bile
<input type="radio"/> Kidney	<input type="radio"/> Brain
<input type="radio"/> Skin	<input type="radio"/> Bone
<input type="radio"/> Muscle	<input type="radio"/> Heart
<input type="radio"/> Fat	<input type="radio"/> ...
<input type="radio"/> LIN	<input type="radio"/> LOG



Jul 2002 – object classes specified

PK-Sim: Klassenhierarchie

Dokumentation	ZT-TE-MVT-VTSW
Abteilung	
Version	1.0.0
Änderungsdatum	19.07.2002
Status	freigegeben am 19.07.2002
Papierablage	im Büro
Ablage	C:\SW-Dev\Projects\PK-Sim\Dokumentation\PK-Sim Klassen 2.doc

- **Simulation** Beinhaltet, **Project**
alle für Simulation notwendigen Angaben: Patient, Wirkstoff, Anwendungsart (des Wirkstoffes), ...
Oberste Klasse in der Hierarchie. Enthält u.a. eine Liste (Collection) der Simulationsläufe, eine Liste von Stoffdaten, ...
- **Eigenschaften:**
 - Name
 - Description
 - Patient As Species
 - Medicine As Compound
 - ApplicationType As Application
 - ControlledRelease As ControlledRelease (?? hier oder in Application?)
 - SimulationTime (Parameter t_max in der Maske Application)
 - TimeStep ???
- **Methoden:**
 - ResultsAvailable As Boolean
 - Simulationsergebnisse bereits zur Verfügung?
- **Calculate** Startet
Simulation
- **GetValues(Optional Time() as Double, Optional OrganNames() as Double) As Double()**
Liefert 2d-Array von Simulationsergebnissen – komplett oder nur für angegebene Zeitpunkte und / oder Organe.
- **Load(Optional FileName As String, Optional DBName As String) As Boolean**
- **SaveAs(Optional FileName As String, Optional DBName As String) As Boolean**
- **Save As Boolean**
Falls aus Datei/DB geladen, werden die alten Daten mit den neuen überschrieben.
- **LoadCompounds(DBName As String) As Boolean**
Laden von Stoffdaten aus (Access-)DB.

(Re)engineering roots...

Jul 2002 – GUI design aligned

PK-Sim: Klassenhierarchie

Dokumentation

Abteilung ZT-TE-MVT-VTSW

Version 1.0.0

Änderungsdatum 19.07.2002

Status freigegeben am 19.07.2002

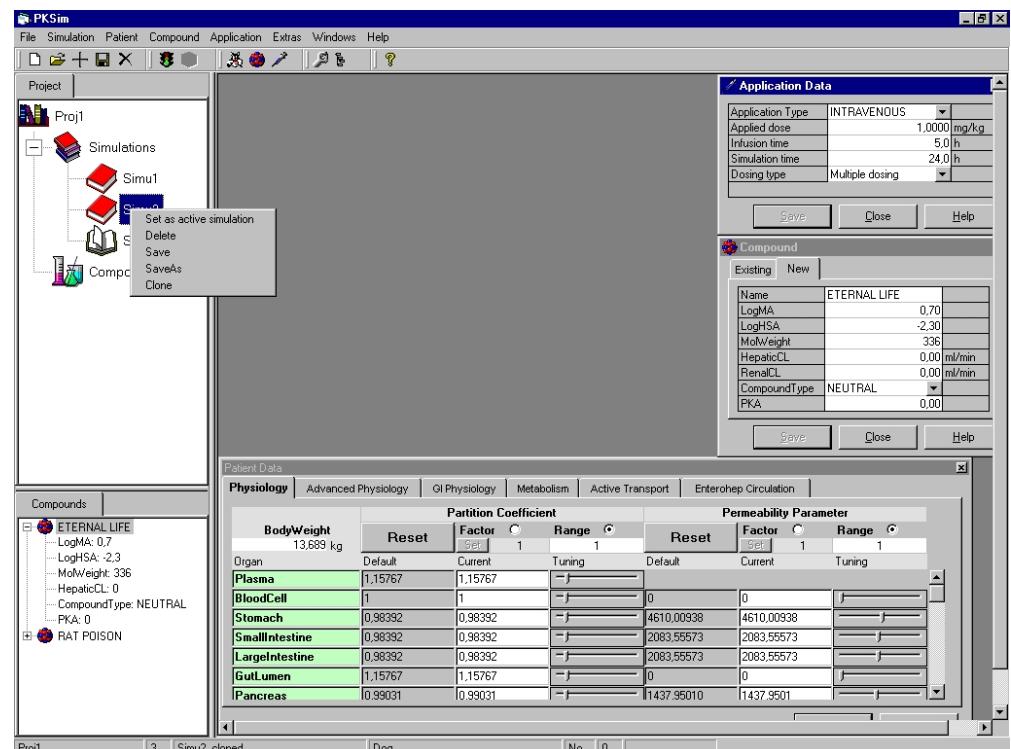
Papierablage im Büro

Ablage C:\SW-Dev\Projects\PK-Sim\Dokumentation\PK-Sim
Klassen 2.doc

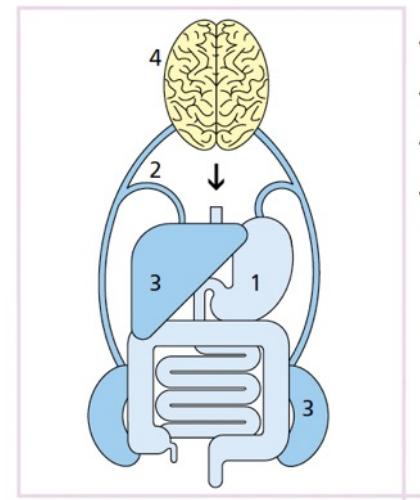
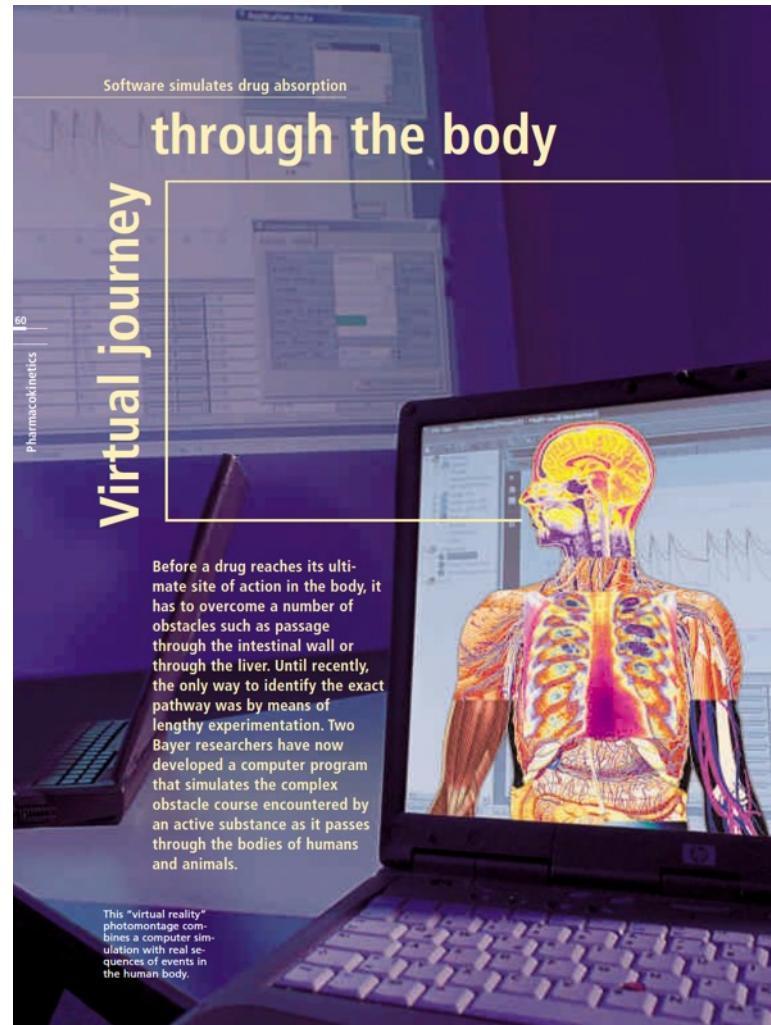
Simulation Beinhaltet Project
alle für Simulation notwendigen Angaben: Patient, Wirkstoff, Anwendungart (des Wirkstoffes), ...

- Eigenschaften:
 - Name
 - Description
 - Patient As Species
 - Medicine As Compound
 - ApplicationType As Application
 - ControlledRelease As ControlledRelease (?? hier oder in Application?)
 - SimulationTime Simulationsdauer (Parameter t_max in der Maske Application)
 - TimeStep ???
- ResultsAvailable As Boolean Stehen Simulationsergebnisse bereits zur Verfügung?
- Methoden:
 - Calculate Simulation Startet
 - GetValues(Optional Time() as Double, Optional OrganNames() as Double) As Double()
Liefert 2d-Array von Simulationsergebnissen – komplett oder nur für angegebene Zeitpunkte und / oder Organe.
 - Load(Optional FileName As String, Optional DBName As String) As Boolean
 - SaveAs(Optional FileName As String, Optional DBName As String) As Boolean
 - Save As Boolean Falls aus Datei/DB geladen, werden die alten Daten mit den neuen überschrieben.
 - LoadCompounds(DBName As String) As Boolean Laden von Stoffdaten aus (Access-)DB.

Mar 2003 – PK-Sim 1.0 released



...and we tried to spread the word



Key issues in pharmacokinetics

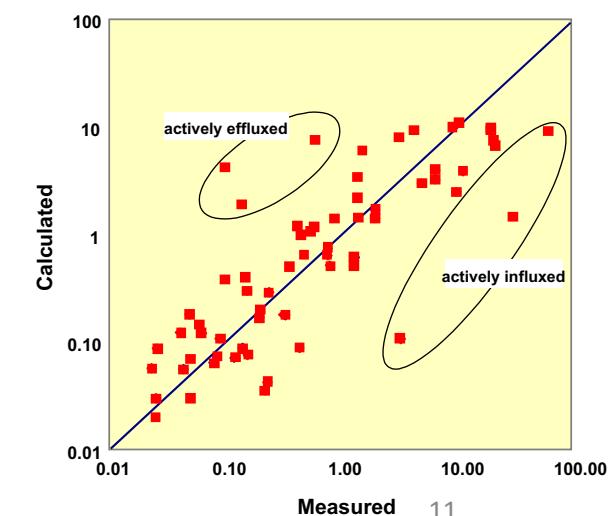
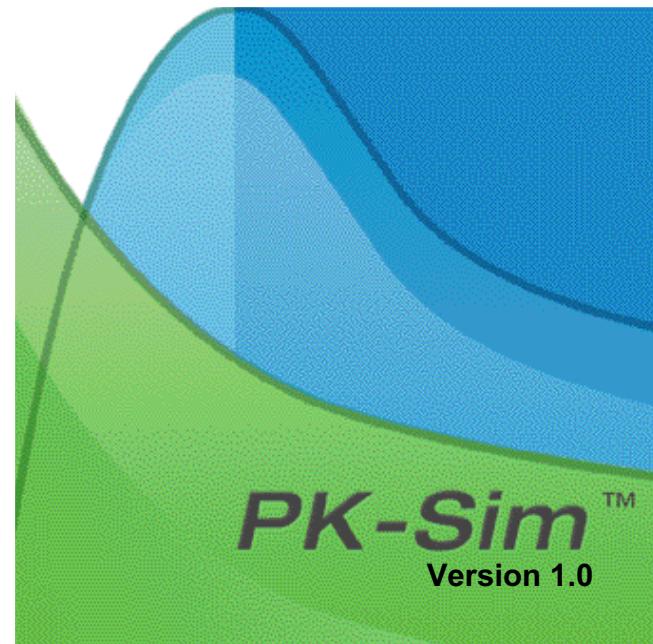
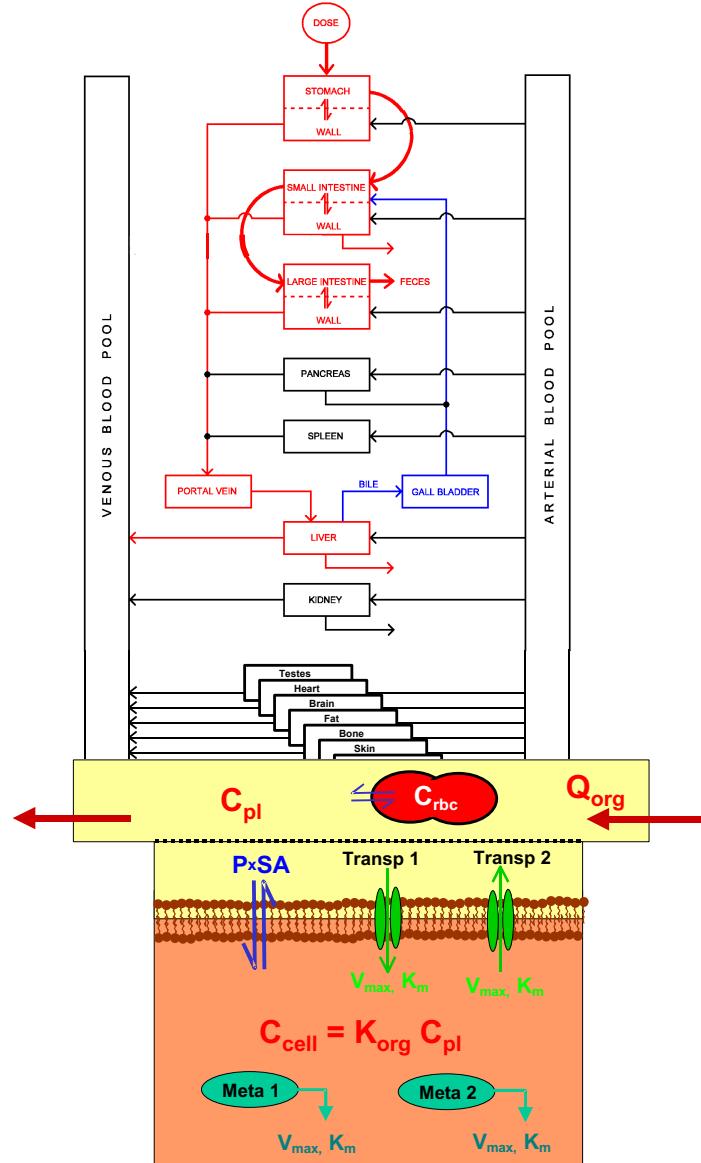
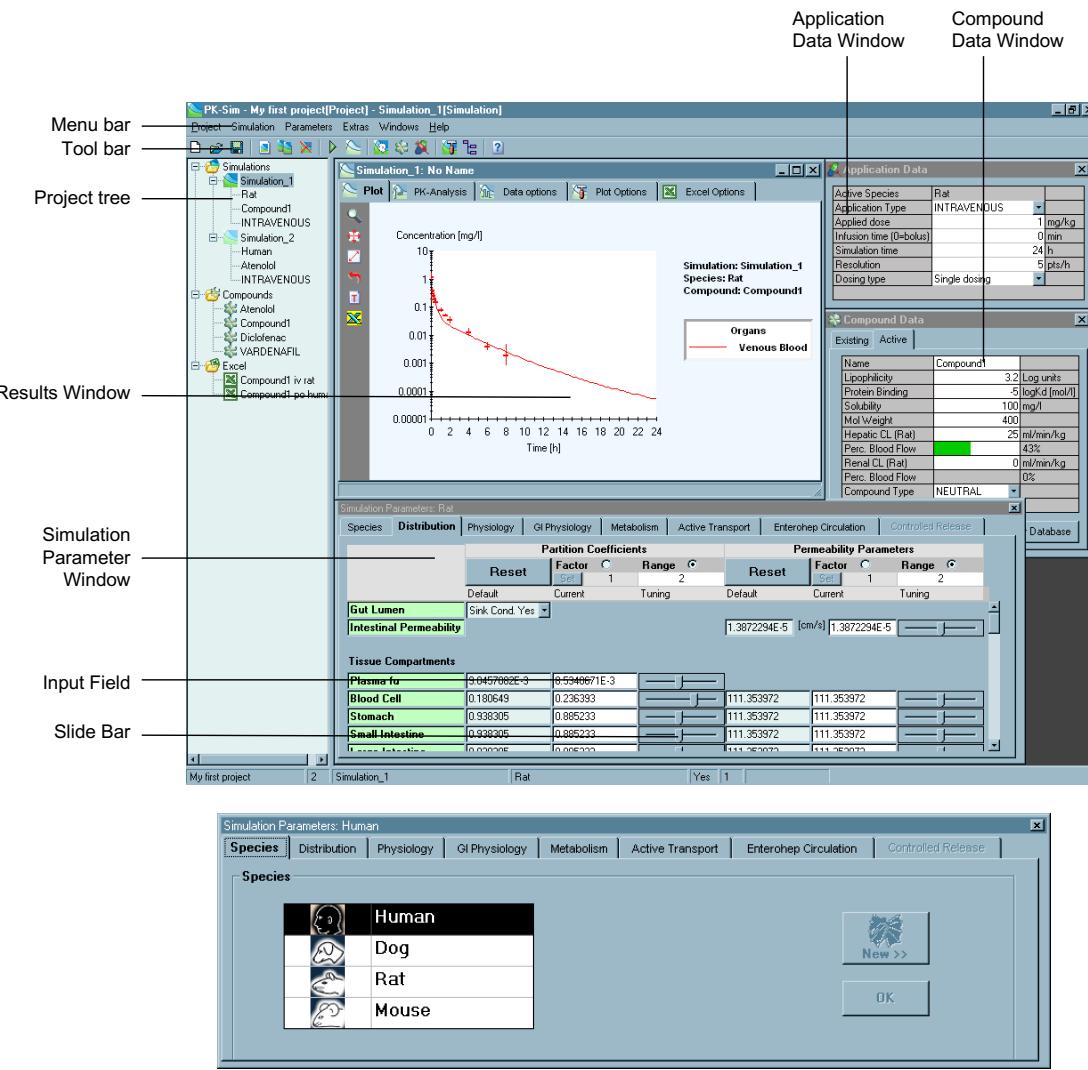
- How much of the compound is absorbed and from where?
- How much remains in the bloodstream and for how long?
- How much is metabolized or excreted and when does this happen?
- How much reaches the target site and how quickly?

The pattern of distribution of a compound in the body can be worked out with the PK-Sim® software. This involves computer simulation of the properties of the body's most important organs: gastrointestinal tract (1), bloodstream (2), liver and kidneys (3) and brain (4).



The "body detectives", Walter Schmitt (right) and Stefan Willmann, track medicines on their virtual journey through the body.

PK-Sim 1.0



The primary interest: understanding & predicting pharmacokinetics

Active Liver Transport: Importance of Permeation Barrier

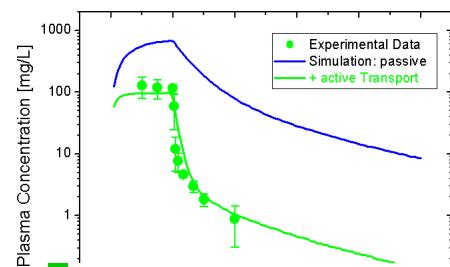
Example: Compound X (Di-carboxylic acid: Substrate for Transporters ?)

Compound Data:
 LogMA: 3.26
 Plasma fu: 0.2 %
 MolWeight: 590
 blood-flow limited CL

Plasma concentration time curve assuming passive distribution deviates from experiment.

Inclusion of an active transport process in the liver yields an almost exact match.

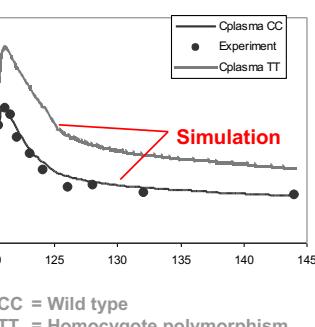
iv infusion (2h) of 0.5 mg/kg to rats:



MDR 1 Polymorphism

Influence on Digoxin pharmacokinetics

Plasma concentrations



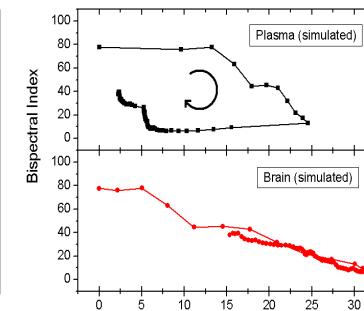
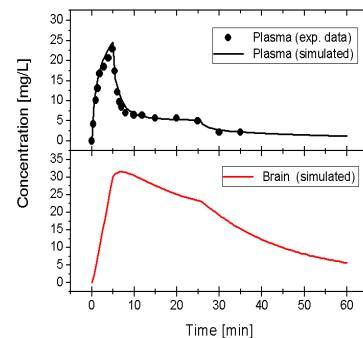
Polymorphism	Expression level (%)	Cmax in Plasma <i>in vivo</i> ($\mu\text{g/l}$)	Cmax in Plasma <i>in silico</i> ($\mu\text{g/l}$)
CC	100	1.7	1.7
TT	49	2.2	2.4

Conclusion

Influence of polymorphism-induced expression levels of active transporters can be predicted with considerable accuracy!

Pharmacodynamics of Propofol

Reduction of hysteresis by choice of appropriate concentration



Inter-individual Variation and Influence of Release Rate

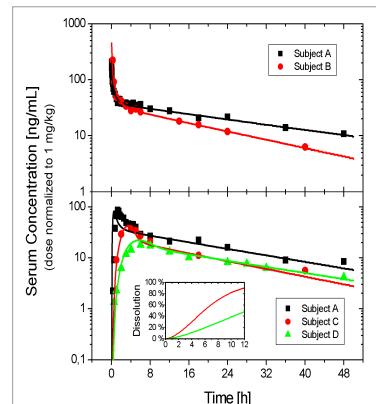
Example: Haloperidol

Dose-normalized serum concentrations in different subjects after single i.v. or p.o. administration

⇒ Inter-subject variability explained by individual variations in protein binding (f_u between 2.0 and 4.6%) and intrinsic clearance (between 0.11 and 0.15 L/h/kg)

⇒ IR as well as different CR formulations can be modeled.

Experimental data taken from:
 Midha et al., *J. Pharm. Sci.* 78 (1989),
 Holley et al., *Clin. Pharmacol. Ther.* 33 (1983),
 Forsmann et al., *Curr. Therap. Res.* 20 (1976)



Consecutive versions of PK-Sim introduced

- **Databases for ethnic groups in different geographic regions**
- Dedicated pediatric population database representing anatomical and physiological characteristics of children
- **Population simulation module allowing automated scaling to special populations**
- **Alternative application routes**
- Predefined DDI scenarios
- **Prediction models for large molecules (peptides, mAbs, therapeutic proteins)**
- **Vascular endothelial barrier, endosomal clearance, FcRn recycling, and lymph circulation**
- **Library of predefined PD models**
- **More species (minipig, cat, mongrel/beagle, monkey, cattle...)**
- **Protein expression databases**
- ...

CARL VON LINNÉ

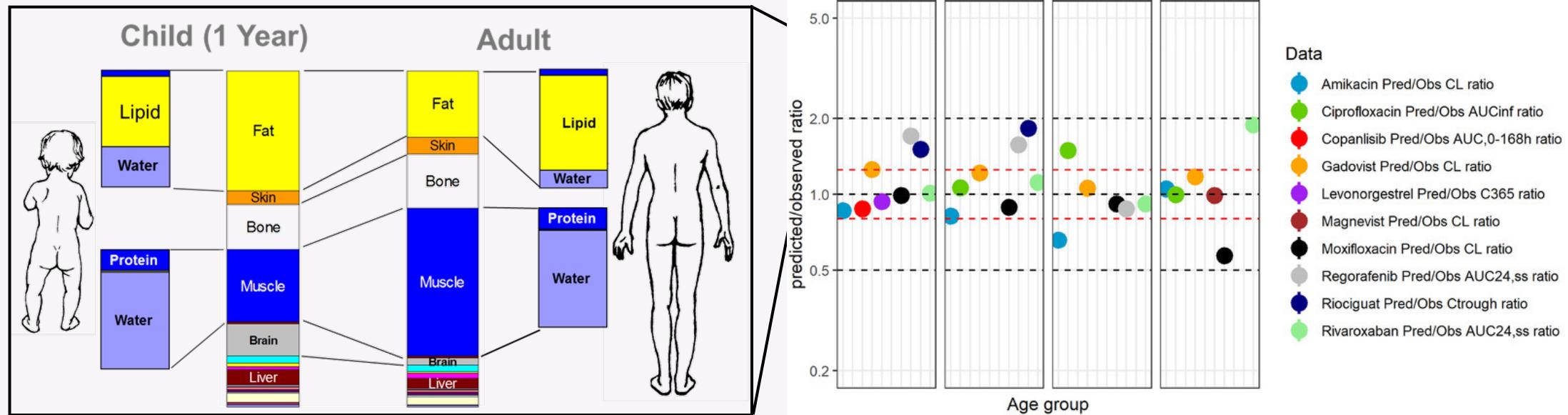
CARL VON LINNÉ

VON



Together with DDI prediction, pediatric extrapolation has generated significant value

Inclusion of physiological/anatomical information vs. age



Willmann et al., Clin. Pharmacokinet. (2013)

Ince et al. J Clin Pharmacol. 2021
Jun; 61(Suppl 1): S70–S82.

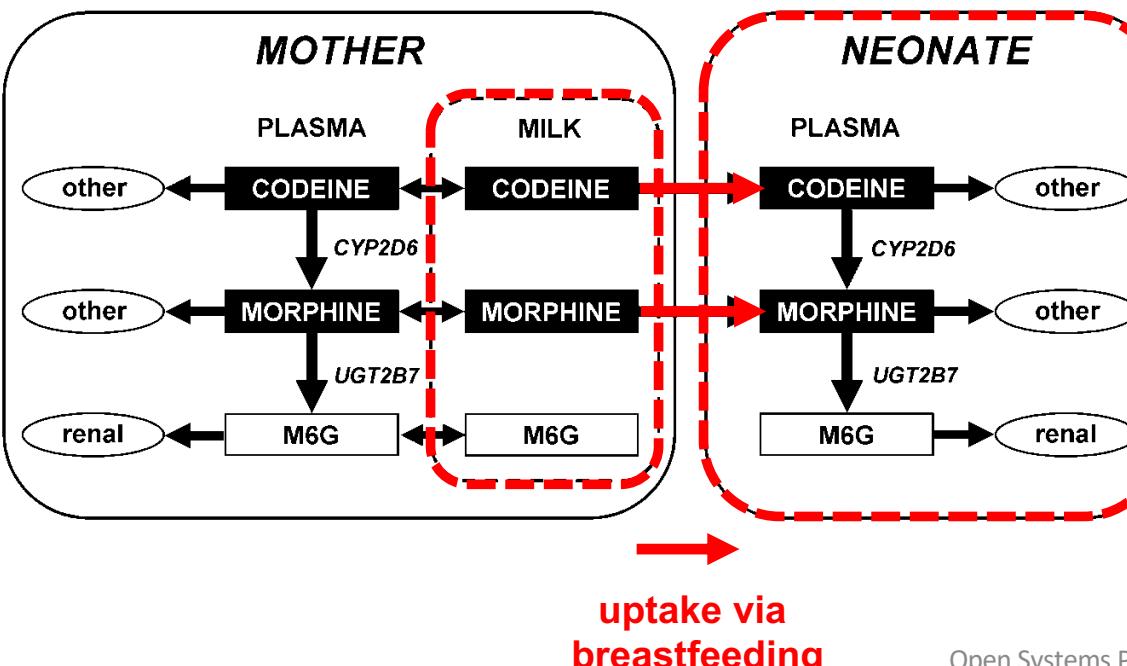
The technology development was sometimes facilitated by "exotic" applications

ARTICLES

Risk to the Breast-Fed Neonate From Codeine Treatment to the Mother: A Quantitative Mechanistic Modeling Study

¹Competence Center Systems Biology, Bayer Technology Services GmbH, Leverkusen, Germany; ²School of Pharmacy, University of Waterloo, Waterloo, Ontario, Canada; ³Clinical Pharmacokinetics, Bayer HealthCare AG, Wuppertal, Germany. Correspondence: S Willmann (stefan.willmann@bayertechnology.com)

Received 30 April 2009; accepted 19 June 2009; advance online publication 26 August 2009. doi:10.1038/clpt.2009.151



nature publishing group

NATIONAL REVIEW
of MEDICINE
ESSENTIAL NEWS FOR CANADA'S PHYSICIANS

JUNE 15, 2007 | VOLUME 4 NO. 11

PATIENTS & PRACTICE

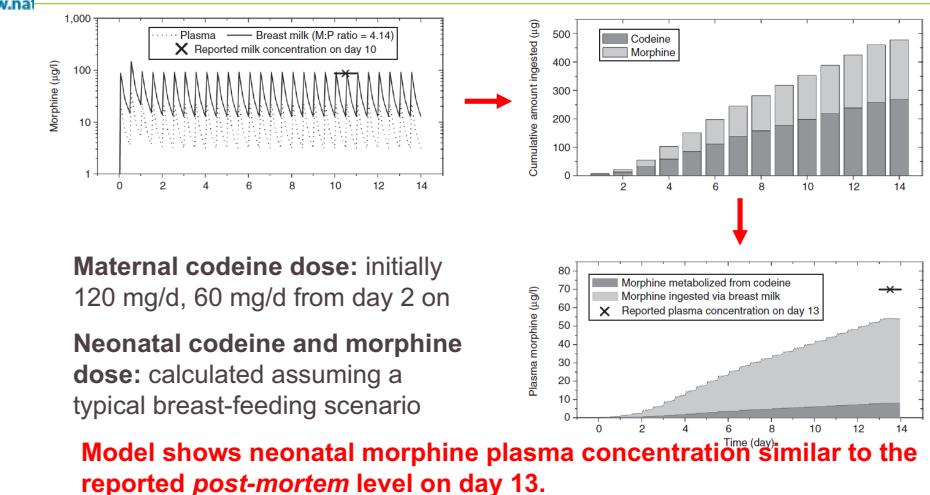
Codeine linked to breastfeeding danger



suit follow Toronto
ing death

ER

The Toronto case – coupled PBPK models
can be applied to simulate arbitrary scenario



Asian and African babies are at
greater risk of rapidly metabolizing
codeine

even-day mark, and at 11 days was

Page 16 • PBPK in Drug Development • M-CERSI Workshop • May 2014

Bayer HealthCare

The regulatory impact is sometimes high...

FDA U.S. FOOD & DRUG ADMINISTRATION Q Search

← Home / Drugs / News & Events for Human Drugs / FDA approves drug to treat, help prevent types of blood clots in certain pediatric populations

FDA approves drug to treat, help prevent types of blood clots in certain pediatric populations

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[Q&A with FDA Podcast](#)

[CDER Conversations](#)

[From Our Perspective](#)

[Spotlight on CDER](#)

Action

FDA has approved [Xarelto \(rivaroxaban\)](#) as tablets and an oral suspension to treat venous thromboembolism (VTE), or blood clots that form in the veins, and reduce the risk of VTE recurring in pediatric patients from birth to younger than 18 years who have received at least five days of injectable or intravenous treatment for blood clots.

Today, FDA has also approved Xarelto to prevent blood clots in pediatric patients **two years and older** with congenital (present from birth) heart disease after the Fontan procedure, a type of open-heart surgery.

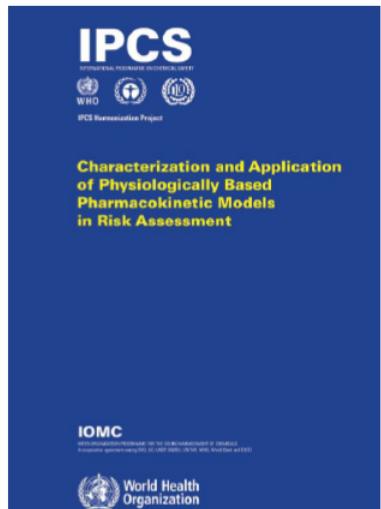
Content current as of:
12/20/2021

Regulated Product(s)
Drugs



...which explains policy development

2010



2012

nature publishing group

Clin Pharmacol Ther, 2012

Best Practice in the Use of Physiologically Based Pharmacokinetic Modeling and Simulation to Address Clinical Pharmacology Regulatory Questions

P Zhao¹, M Rowland^{2,3} and S-M Huang⁴

Physiologically based pharmacokinetic (PBPK) models are increasingly used by drug developers to evaluate the effect of patient factors on drug exposure. Between June 2008 and December 2011, the Office of Clinical Pharmacology at the US Food and Drug Administration (FDA) received 25 submissions containing PBPK analyses. This report summarizes the essential content of a PBPK analysis needed in a regulatory submission for the purpose of addressing clinical pharmacology questions.

2014

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 26 June 2014
2 EMA/CHMP/211243/2014
3 Committee for Medicinal Products for Human Use (CHMP)

4 Concept paper on qualification and reporting of physiologically-based pharmacokinetic (PBPK) modelling and analyses

Agreed by Pharmacokinetics Working Party 13 June 2014
Adopted by CHMP for release for consultation 26 June 2014
Start of public consultation 27 June 2014
End of consultation (deadline for comments) 30 September 2014

Comments should be provided using this template. The completed comments form should be sent to pkmr@ema.europa.eu

Keywords: Pharmacokinetics, PBPK, Interactions, Physiologically based, Modelling, Simulation

2016

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 21 July 2016
2 EMA/CHMP/458101/2016
3 Committee for Medicinal Products for Human Use (CHMP)

4 Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft agreed by Modelling and Simulation Working Group April 2016
Draft agreed by Pharmacokinetic Working Party May 2016
Adopted by CHMP for release for consultation 21 July 2016
Start of public consultation 29 July 2016
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Keywords: pharmacokinetics, modelling, simulation, qualification, predictive performance

2016

Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only. Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register or the date announcing the availability of the draft guidance. Submit electronic comments to CDER-OPCPD@fda.hhs.gov. Written comments may also be submitted to the Division of Dockets Management (DFA-101), Food and Drug Administration, 5630 Fishers Lane, Rm. 1014, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact CDER Office of Clinical Pharmacology, at 301-796-5000 or OPCD@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 2016
Clinical Pharmacology

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf>

2015

Citation: CPT Pharmacometrics Syst Pharmacol. (2015) 4, 226–230. doi:10.1002/cpt.43
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PERSPECTIVE

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

C Wagner¹, P Zhao^{1*}, Y Pan², V Hsu¹, J Grillo¹, SM Huang¹ and V Sinha^{1*}

2015

Citation: CPT Pharmacometrics Syst Pharmacol. (2015) 4, 221–225. doi:10.1002/cpt.43
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PERSPECTIVE

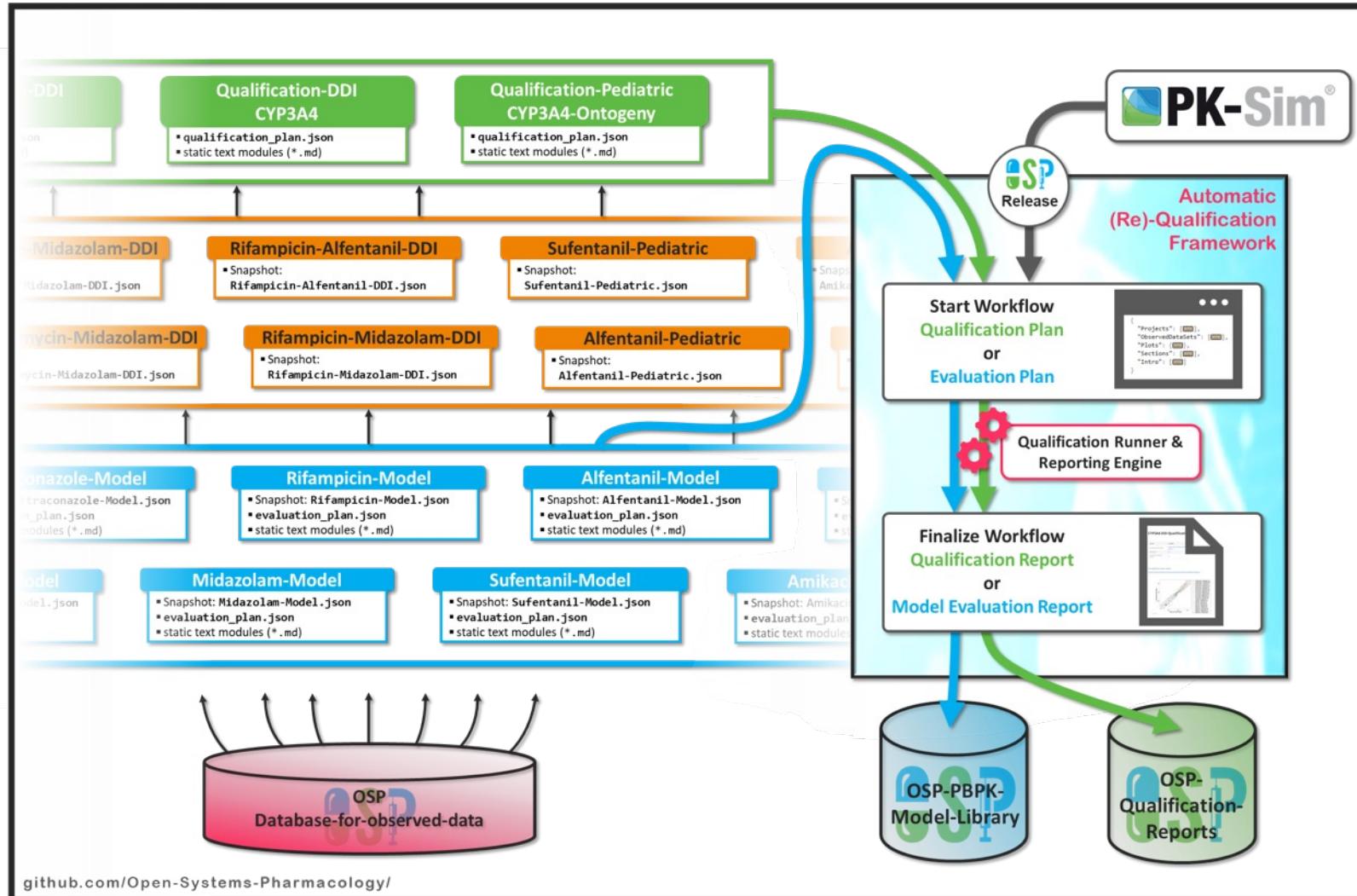
Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation

T Shepard^{1*}, G Scott², S Cole¹, A Nordmark³ and F Bouzoum⁴

<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM550577.pdf>

exemplary only

OSP has a built-in technical (re)qualification framework



from Frechen et al. CPT
Pharmacometrics Syst
Pharmacol . 2021..

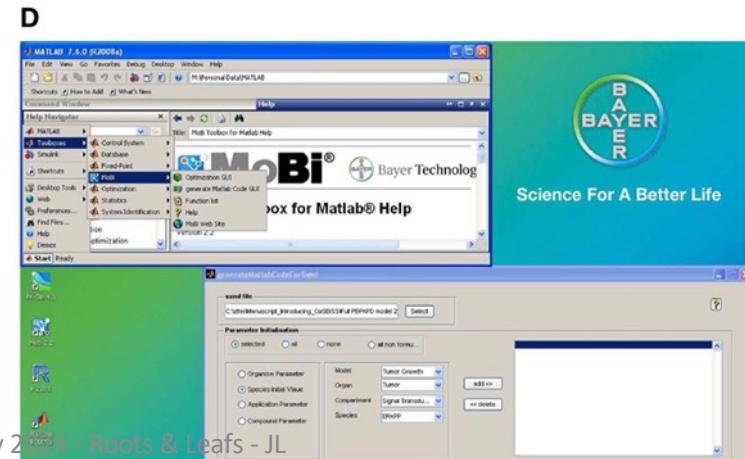
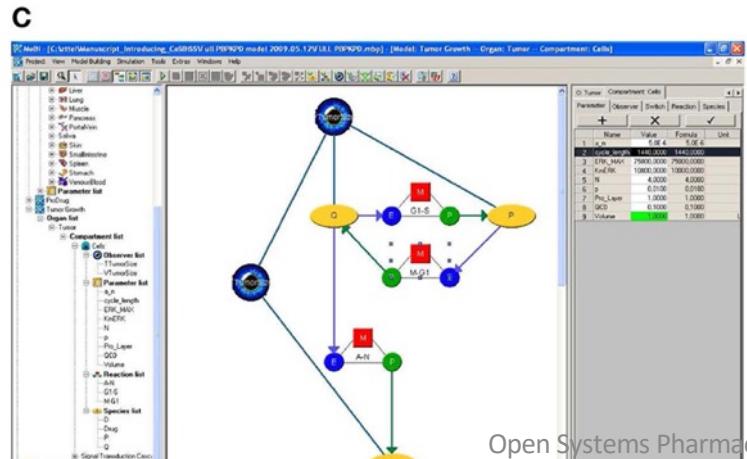
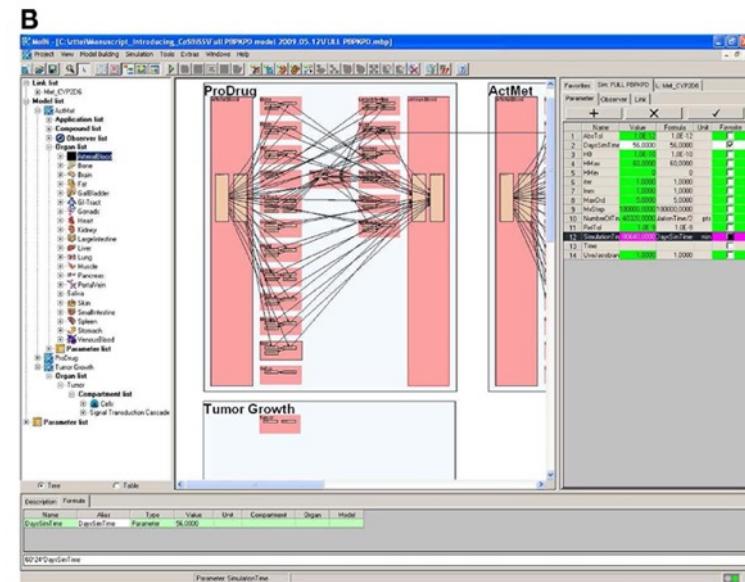
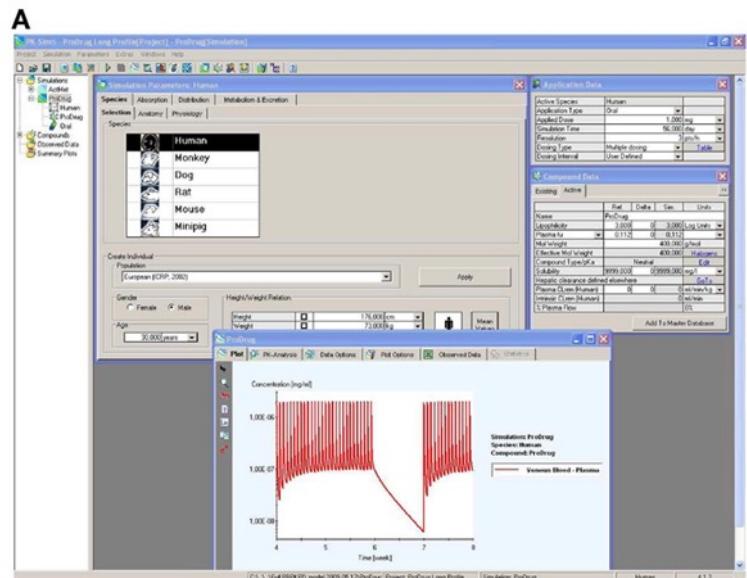
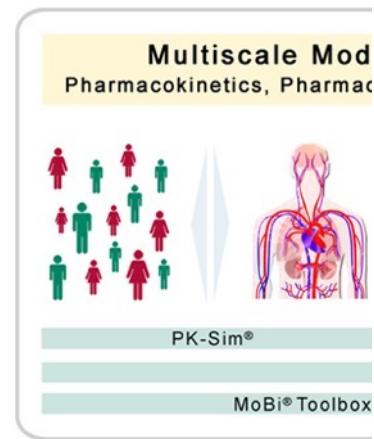
MoBi was designed to extend whole-body PBPK to fully flexible multiscale (patho)biology & pharmacology modeling

METHODS article

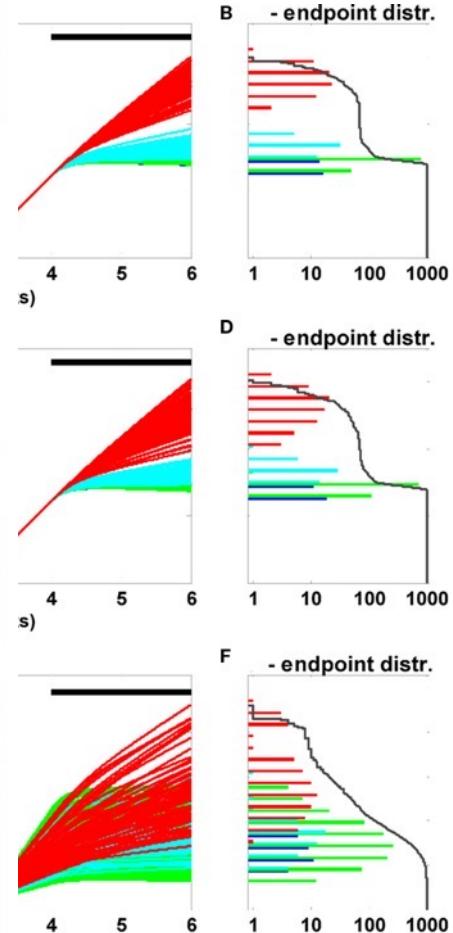
Front. Physiol., 24 February 2011 | <https://doi.org/10.3389/fphys.2011.00011>

A computation platform for multiscale simulation: integrating physiology, disease and reaction networks

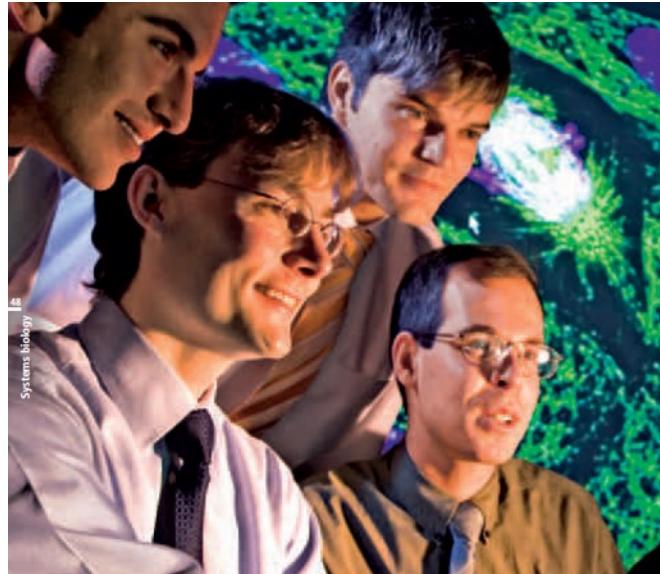
Thomas Eissing, Lars Kuepfer, Christian Goerlitz, Juergen Jaeger, Roland Sevestre, Hans-Ulrich Siegmund, Wolfgang Wendl, Stefan Willmann and Joe



Raf-Inhibitor Trial



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Systems biology

Simulation of living systems in virtual spaces

Cells growing in the computer

The functions of biological systems are usually attributed to individual biochemical mechanisms. A new discipline known as systems biology, on the other hand, takes a different approach, by simulating natural processes in all their complexity and constant interaction. Bayer scientists are currently developing a "virtual cell" which in the future could be of use not only in pharmaceutical research, but also in routine clinical practice.

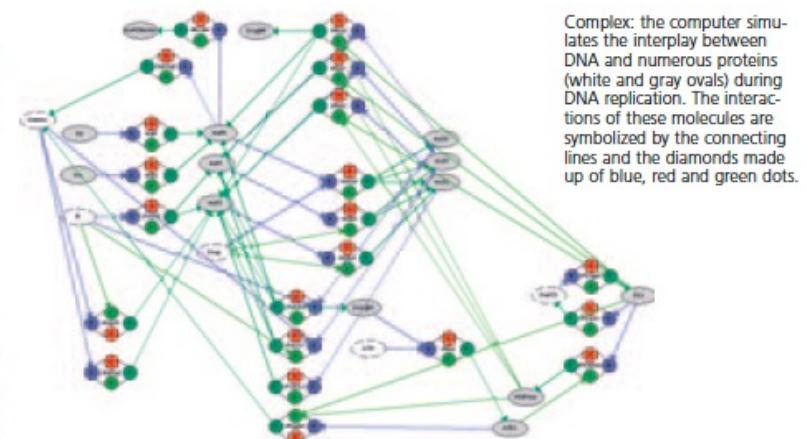
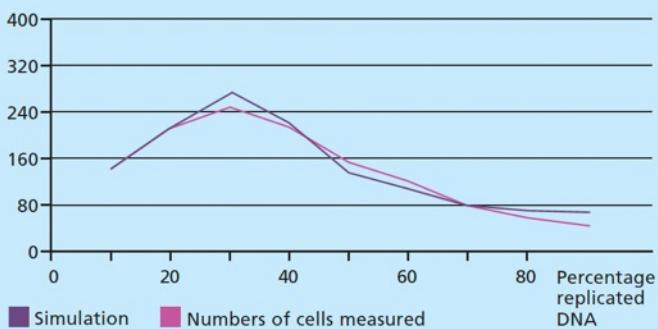


Systems biologists:
(from left)
Michael Sevestre,
Dr. Jörg Lüpert,
Volker Wöhrel,
Juri Solodenko,
and Dr. Katrin
Coboken with the
"virtual cell".

An experiment confirms the simulation

The effects of certain chemotherapeutic agents on cancer cells can be simulated very well using Bayer computer software. Nucleoside analogs like gemcitabine are drug products which inhibit DNA replication in the cells, so that the tumor cells which divide particularly enthusiastically are doomed.

Number of cells

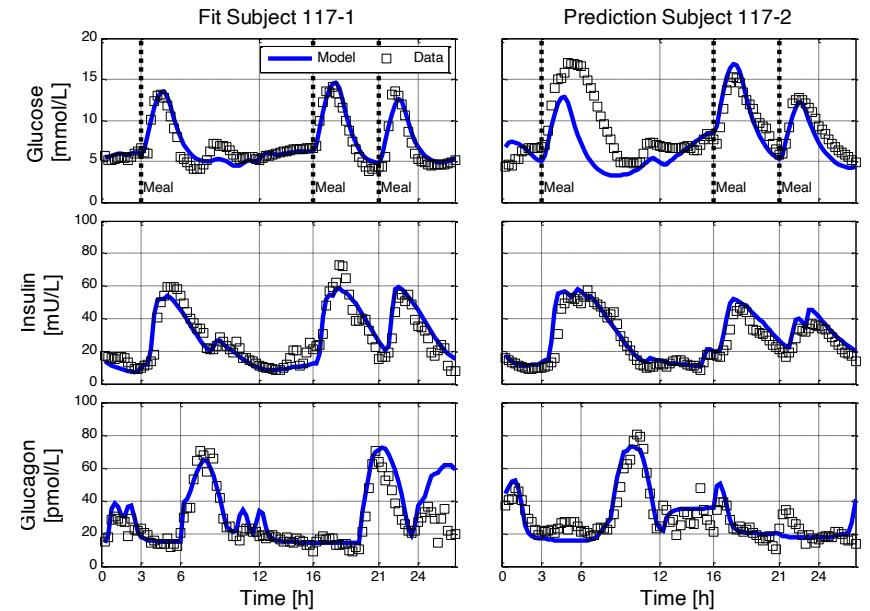
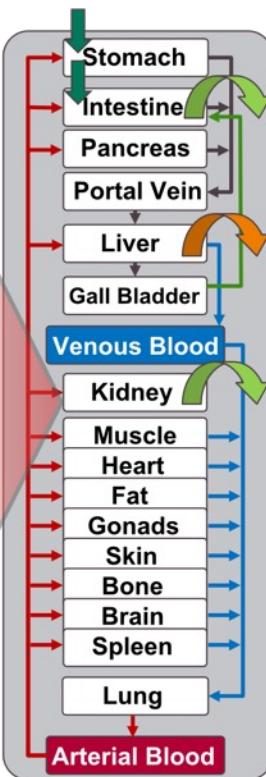
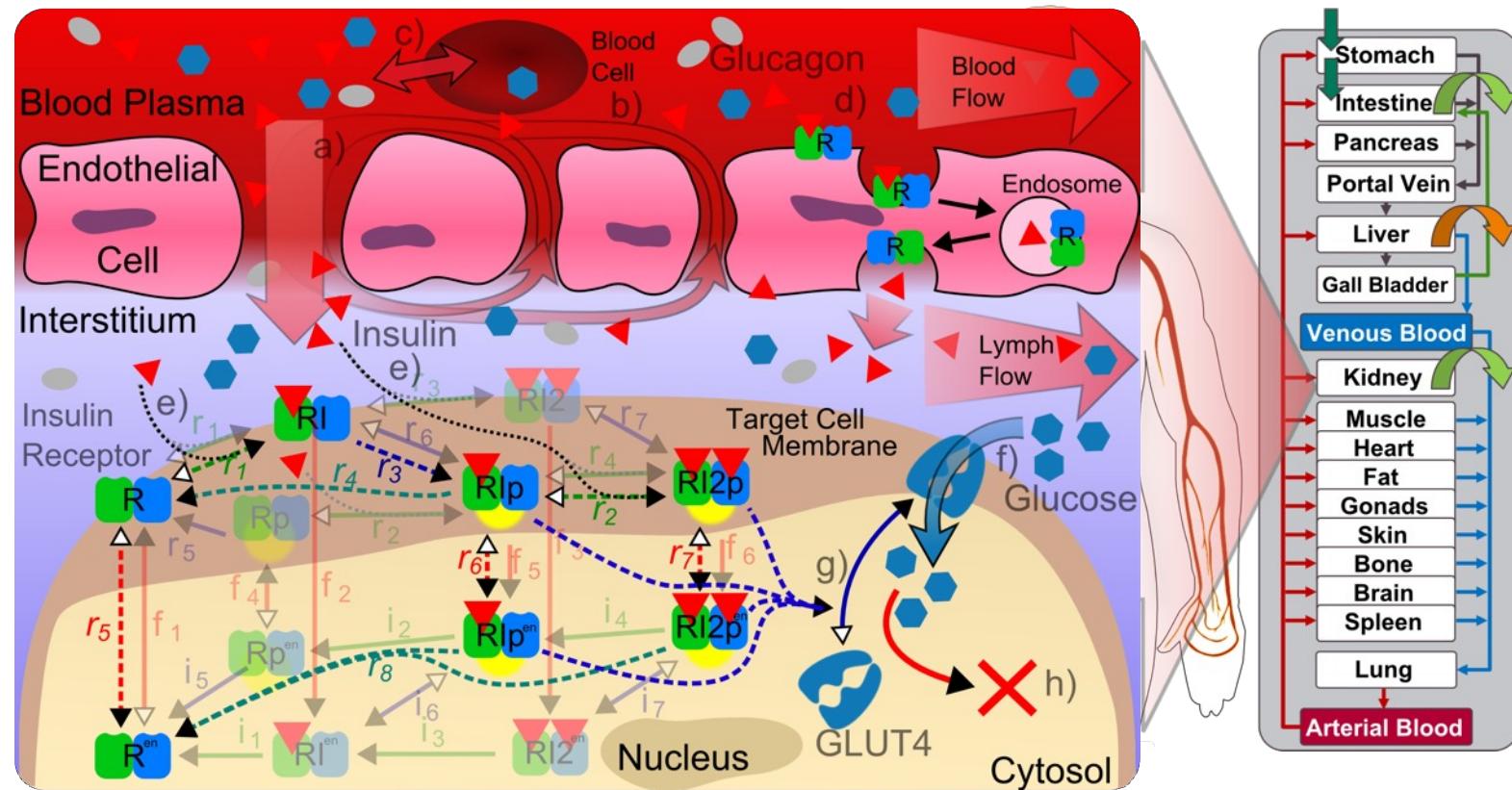


Complex: the computer simulates the interplay between DNA and numerous proteins (white and gray ovals) during DNA replication. The interactions of these molecules are symbolized by the connecting lines and the diamonds made up of blue, red and green dots.



Modeler: Dr. Bernhard Knab simulates the interaction of different enzymes in the cell.

Systems Pharmacology models in MoBi can become complex...



Schaller et al. CPT:PSP 2013

Model published on OSP GitHub

<https://github.com/Open-Systems-Pharmacology/Glucose-Insulin-Model>

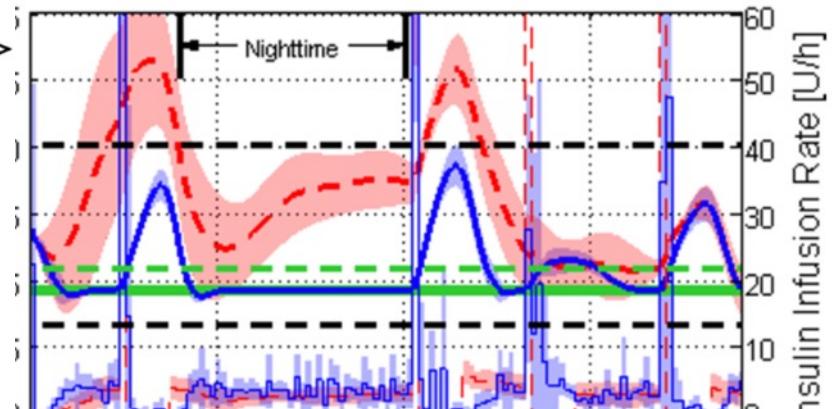
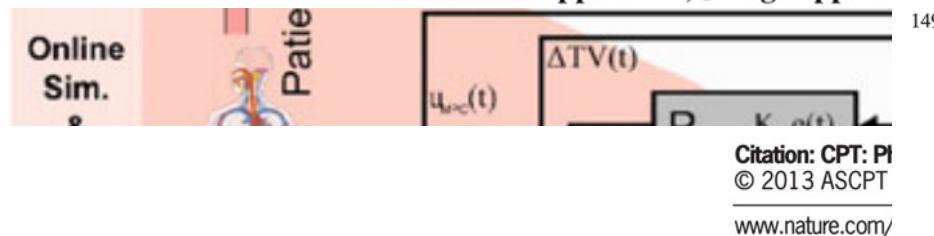
...and can still be used to represent individual patients and predict and control their glucose level

8th IFAC Symposium on Biological and Medical Systems
The International Federation of Automatic Control
August 29-31, 2012. Budapest, Hungary



A new Perspective on Closed-Loop Glucose Control using a Physiology-Based Pharmacokinetic / Pharmacodynamic Model Kernel

Stephan Schaller^{*/***}, Stefan Willmann^{*}, Lukas Schaupp^{***}, Thomas Pieber^{***},
Andreas Schuppert^{*/***}, Joerg Lippert^{*}, Thomas Eissing^{*}



IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, VOL. 63, NO. 7, JULY 2016

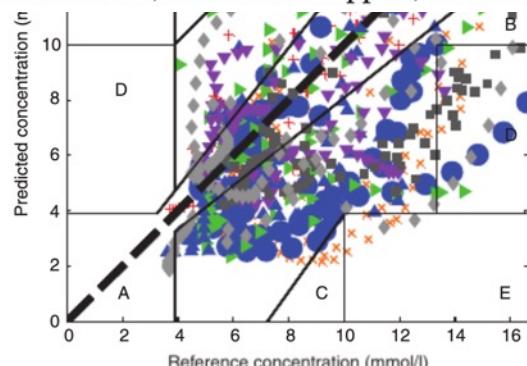
Robust PBPK/PD-Based Model Predictive Control of Blood Glucose

Stephan Schaller*, Jörg Lippert, Lukas Schaupp, Thomas R. Pieber, Andreas Schuppert, and Thomas Eissing

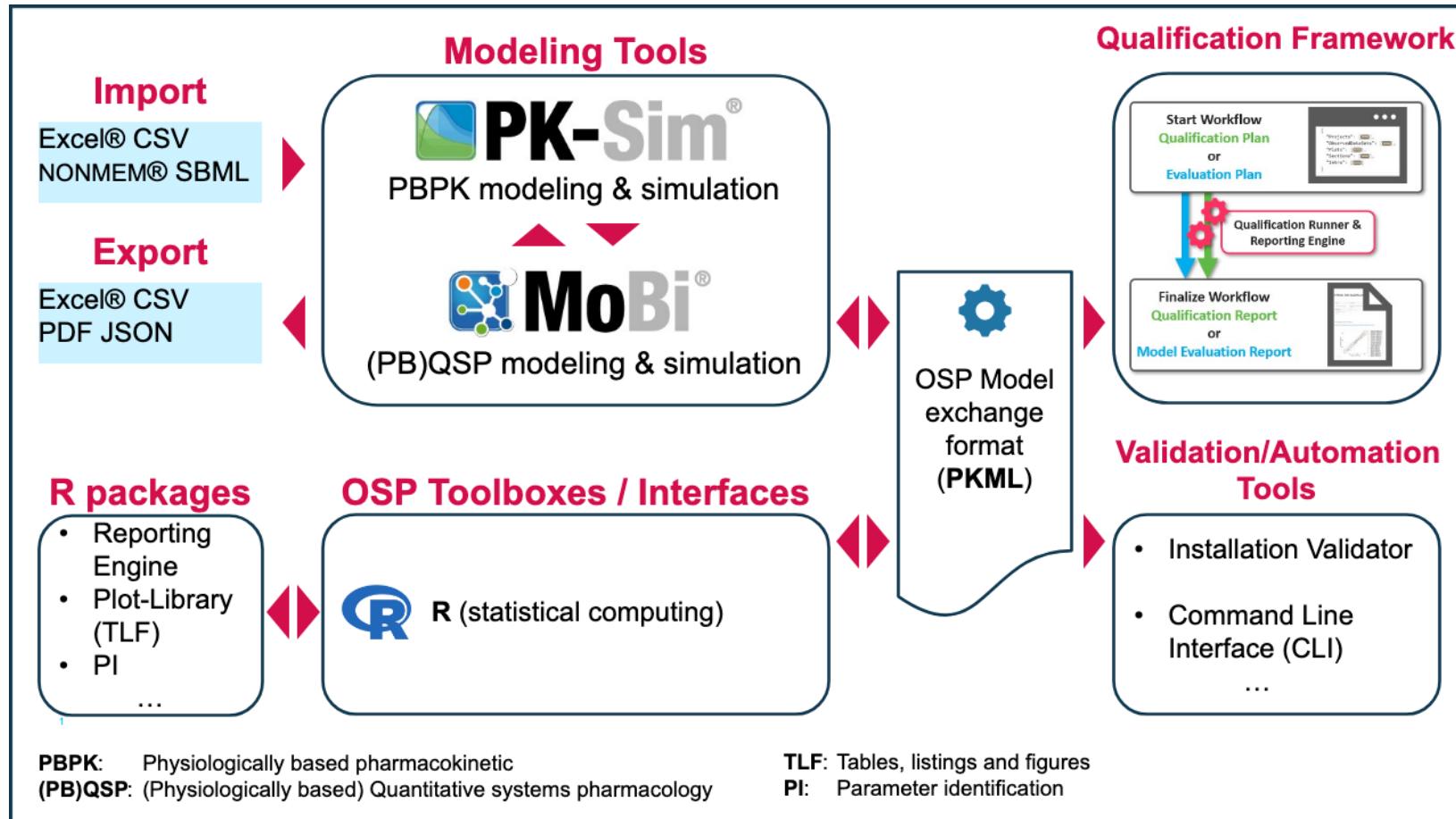
ORIGINAL ARTICLE

A Generic Integrated Physiologically Based Whole-body Model of the Glucose-Insulin-Glucagon Regulatory System

S Schaller^{1,2}, S Willmann¹, J Lippert¹, L Schaupp³, TR Pieber³, A Schuppert^{1,2} and T Eissing¹



PK-Sim & Mobi are embedded in a versatile platform





It started with PK-Sim, a commercial product, in 2003...

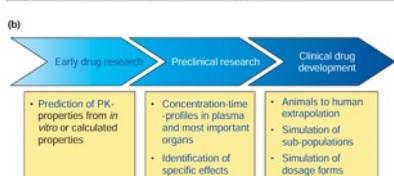
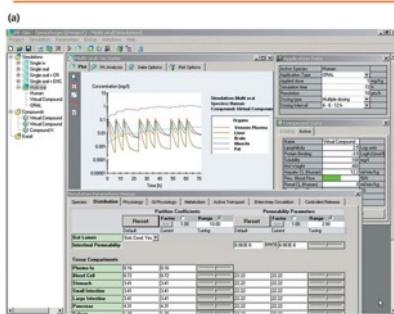
BIOSILICO Vol. I, No. 4 September 2003

UPDATE
BIO-TOOLS

PK-Sim®: a physiologically based pharmacokinetic ‘whole-body’ model

Stefan Willmann, Jörg Lippert, Michael Sevestre, Juri Solodenko, Franco Fois and Walter Schmitt

Stefan Willmann*, BAYER AG, Bayer Technology Services, Biophysics, Building 470 R. 217, 42096 Wuppertal, Germany, *e-mail: stefan.willmann.sw@bayertechnology.com. Jörg Lippert, Michael Sevestre, Juri Solodenko, BAYER AG, Bayer Technology Services, Computational Solutions, 51368 Leverkusen, Germany. Franco Fois, Walter Schmitt, BAYER AG, Bayer Technology Services, Biophysics, 40765 Monheim, Germany



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Figure 2. The graphical user interface (GUI) of PK-Sim® offers full control to all input parameters that are relevant for even sophisticated simulations. A compound window and an application window containing a menu bar and toolbars are shown. The application window contains a plot of concentration versus time for a single or multiple doses. Administration is represented by a single or multiple intravenous or oral doses are supported by PK-Sim®. The simulation parameter window consists of several independent modules allowing the definition of all substance and physiology related parameters. Examples are the substance specific distribution parameters, that are derived from the physicochemical input parameters, and the species dependent physiological parameters such as organ volumes or blood flow rates, or the dissolution kinetics of a controlled release oral dosage form. Consequently, the degree of complexity of a

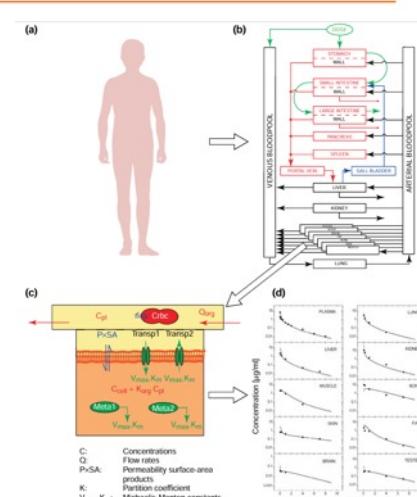


Figure 1. PBPK modeling aims to describe the pharmacokinetic behavior of a compound, including uptake, distribution and elimination in a living organism, based on substance-related and species-related anatomical and physiological information. The organism that is to be modeled, in this example, a human being (a), is divided into a number of compartments, each usually representing a single organ. The organs are mutually connected according to their physiological function. The absorption component (red) and the distribution component (black) were first developed and validated in tissues. They have now been linked together to make PK-Sim®. The simulation of enterohepatic circulation (blue) is also possible. To describe the distribution in the body, the organs are connected via their arteries and veins to the arterial and venous blood pool. Intercompartment mass transport occurs via organ-specific blood flow.

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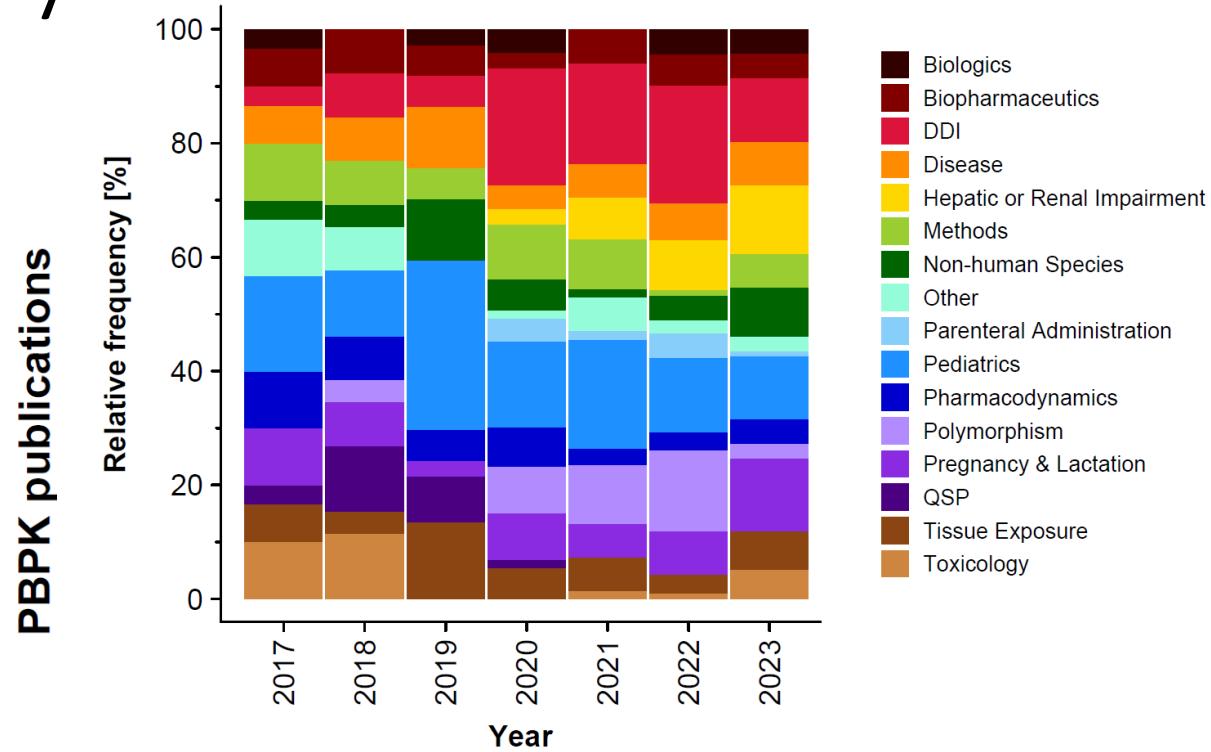
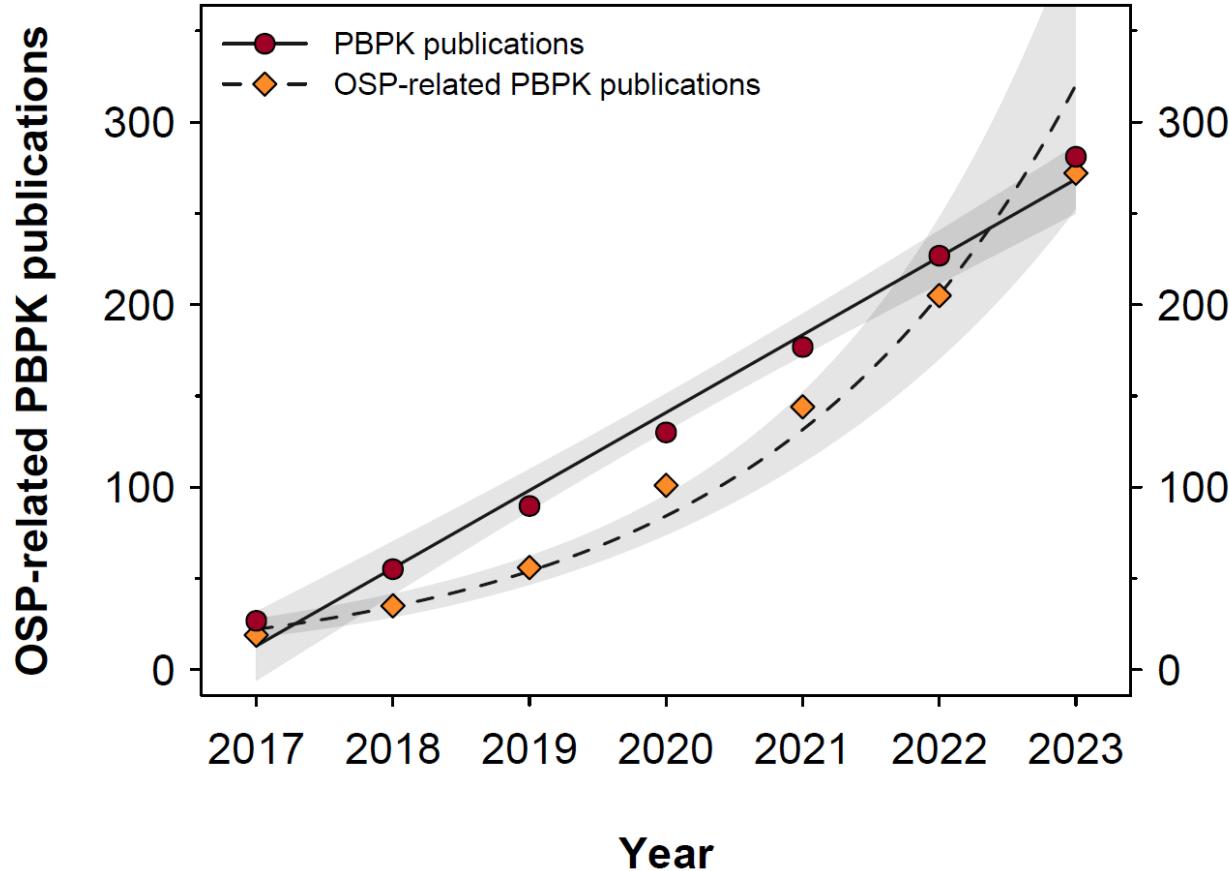
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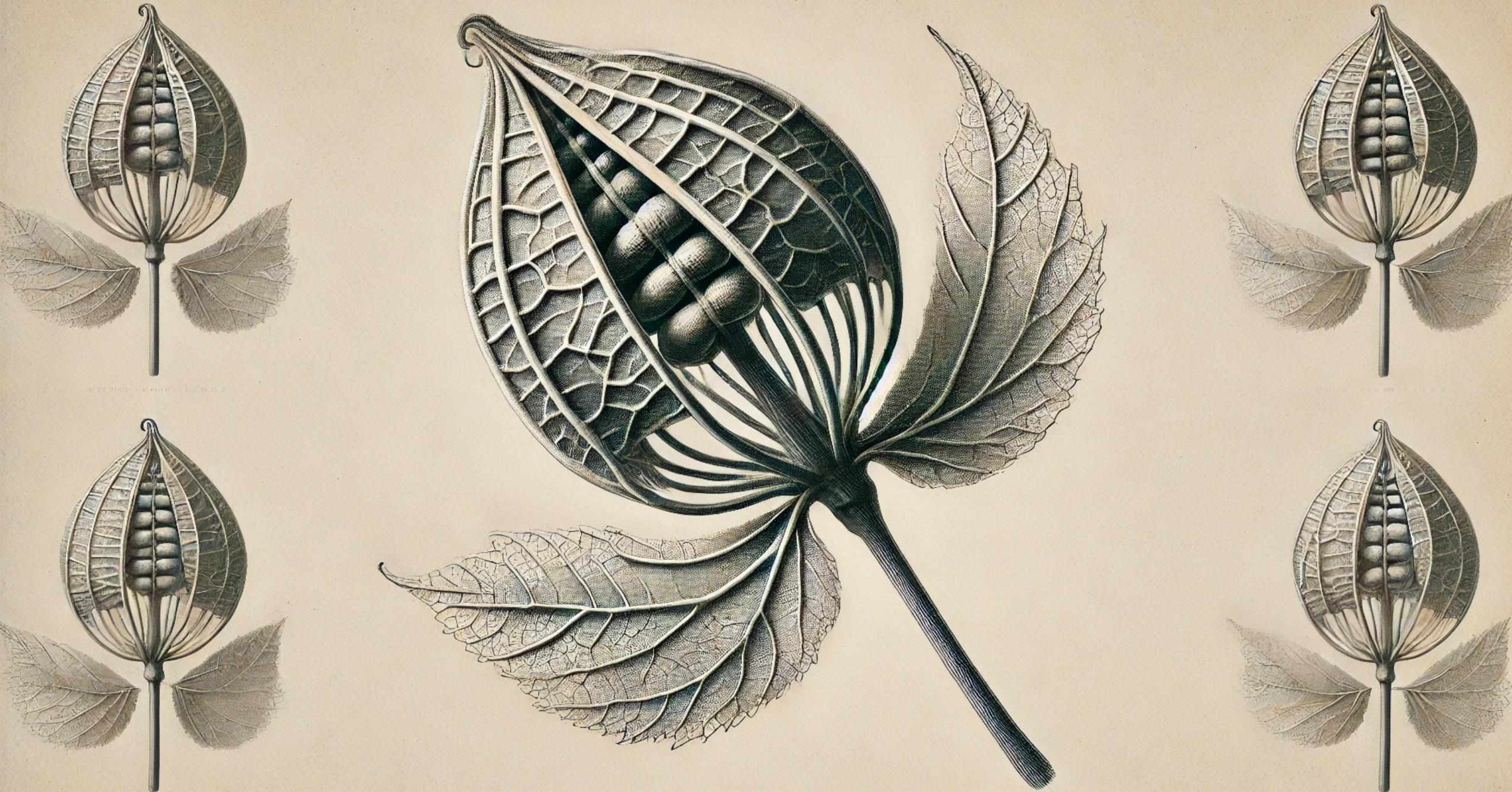
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...and has become a continuously growing Open Science Community

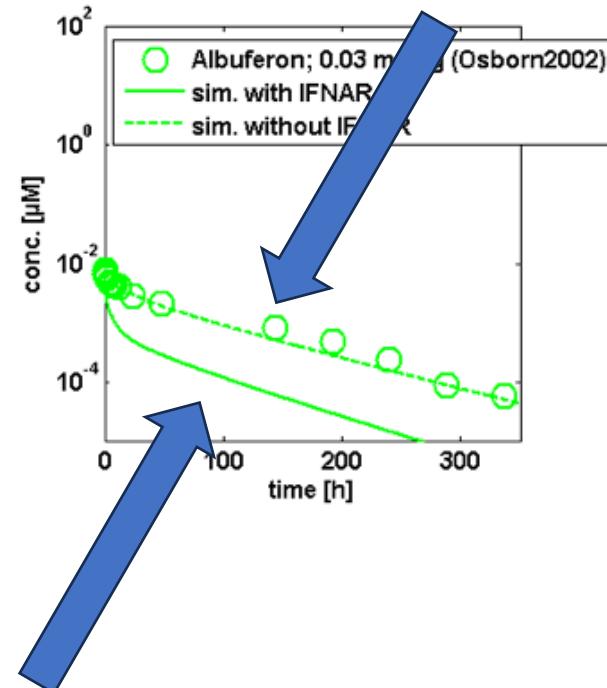
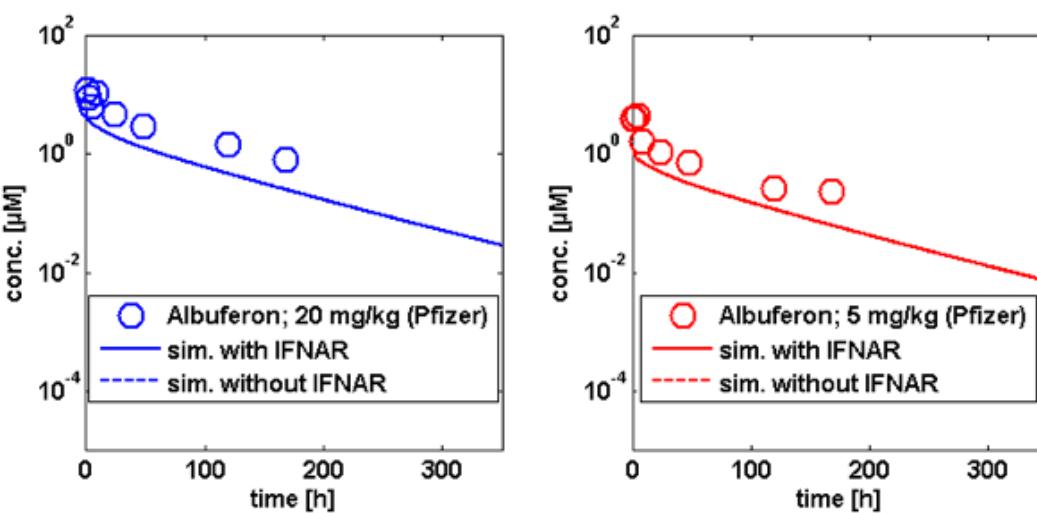


**In-depth analysis of the selection of
PBPK modeling tools: Bibliometric and
social network analysis of the Open
Systems Pharmacology community**





Integrated PBPK models for fusion protein detects modified target interaction



www.systems-biology.com

Mechanistic analysis of fusion proteins: PBPK applied in an Albuferon case study

Christoph Niederalt¹, Lars Kuepfer¹, Thomas Wendt¹, Stefan Willmann¹, Jörg Lippert¹, Victoria Flores² and Piet van der Graaf²

¹ Systems Biology & Computational Solutions, Bayer Technology Services GmbH, 51368 Leverkusen, Germany

² Pfizer, New Opportunities Unit, Sandwich CT13 9NJ, UK



Bayer Technology Services

Introduction

The pharmacokinetics of protein therapeutics is governed by a number of unspecific and specific processes, most of them having a minor or no role in small molecule drug kinetics. Processes which have to be considered to describe the pharmacokinetics of protein therapeutics include:

- 1) Exchange across the vascular endothelium by convection and diffusion.
- 2) Return of the drug from interstitial space of the organs to circulation by lymph flow.
- 3) Degradation and protection from degradation by neonatal Fc receptor (FcRn) in cellular endosomes.
- 4) Target-mediated deposition and clearance.

Objective

A physiologically-based pharmacokinetics (PBPK) model for Albuferon, an albumin-interferon-fusion protein, has been developed using generic sub-models adjusted to benchmarking on the available data. The main objective of this case study was to evaluate the influence on the PK of both the unspecific endothelial exchange and lymph flow as well as the specific effects of FcRn mediated recycling and target mediated deposition and clearance. The availability of data in monkey and human offers the opportunity to evaluate interspecies scaling with the established protein PBPK models.

Methods

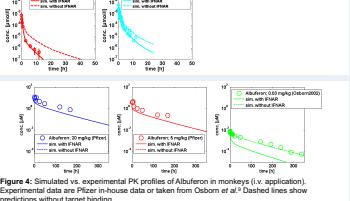
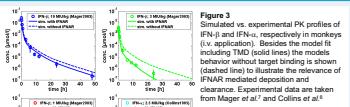
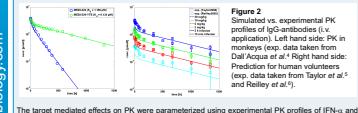
The model for Albuferon was build in a modular way using the parameterization first established for IgG antibody models (FcRn related processes) and interferons (target mediated processes). The PBPK models were implemented using the software tools PK-Sim[®] and Midilli[®]. Within PK-Sim[®] compound dependent parameters (permeabilities and osmotic reflection coefficients) are estimated from the hydrodynamic radius or the molecular weight of the compound. In the interstitial space the drug is transported back to circulation by lymph flow. To describe the protection from catabolism by binding to the FcRn, the recycling of the drug was set to a rate proportional to the concentration of endogenous FcRn ligand (albumin in case of Albuferon). The competitive binding of endogenous and exogenous IgG to FcRn was described to take place in the endosomes of endothelial cells in each organ. Once ligands are bound to the FcRn receptor in the endosome they are recycled to plasma and interstitial space of the organs. The unbound fraction is subject to degradation. The target-mediated deposition and clearance is described by reversible binding of drug to the IFNAR2 receptor (most abundant) and by an irreversible internalization of the drug-receptor complex. The drug as receptor is degraded once they are internalized (cf. Fig. 1).

Figure 1

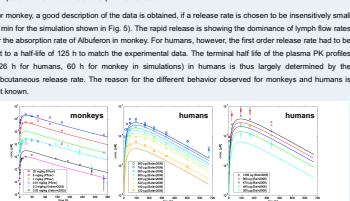


Results

To describe the FcRn mediated PK, models for IgG antibodies were established first. The concentration of FcRn receptor in the endothelial compartments and formation rate of endogenous IgG were fitted to PK profiles of therapeutic IgG antibodies and the steady state concentration of endogenous IgG in cynomolgus monkey. Based on the model for monkeys, a prediction for humans was made using the same FcRn concentration as for monkeys and a rate of formation of endogenous IgG scaled proportional to body weight. Cf. Fig. 2 for results.



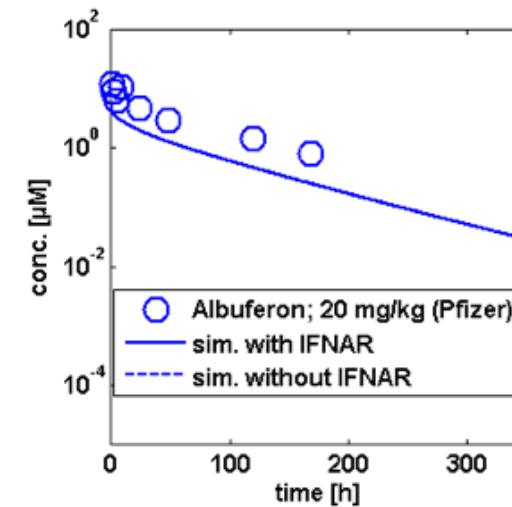
For monkeys, a good description of the data is obtained, if a release rate is chosen to be immensely small (1 min for the simulation shown in Fig. 5). The rapid release is showing the dominance of lymph flow rates for the absorption rate of Albuferon in monkey. For humans, however, the first order release rate had to be set to a half-life of 125 h (60 h for monkey in simulations) in humans is thus largely determined by the subcutaneous release rate. The reason for the different behavior observed for monkeys and humans is not known.



Conclusions
The pharmacokinetics of Albuferon could be predicted using PBPK sub-models which were established independently from Albuferon using benchmarking compounds and prior knowledge only. A detailed analysis revealed that IFNAR mediated deposition plays a minor role for Albuferon while it is highly relevant for "naked" reference interferons. Following subcutaneous application of Albuferon the terminal half-life of the plasma PK is determined by the subcutaneous release rate in human but not in monkey.

- References**
- ¹ E.D. Lobo et al., *J. Pharm. Sci.* 93 (11), 2645–2668 (2004).
 - ² L. Baxter et al., *Cancer Research* 54 (6), 1517–1528 (1994).
 - ³ B. Ropke and B. Haralsson, *Physiol. Rev.* 74, 163–219 (1994).
 - ⁴ W.F. Dall'Acqua et al., *J. Biol. Chem.* 281 (33), 23514–23524 (2006).
 - ⁵ S. Taylor et al., *Drug Metab. Dispos.* 28 (27–28), 263–269 (2000).
 - ⁶ S.E. Mager et al., *Antimicrob. Agents Chemother.* 49 (3), 969–972 (2005).
 - ⁷ B.L. Osborn et al., *Cancer Drug Deliv.* 2 (4), 247–253 (1995).
 - ⁸ B.L. Osborn et al., *J. Pharmacol. Exp. Ther.* 303 (2), 540–548 (2002).
 - ⁹ V. Balan et al., *Antivir. Ther.* 11 (1), 35–45 (2006).
 - ¹⁰ V. Bain et al., *J. Hepatol.* 44 (4), 671–678 (2006).

Integrated PBPK models for fusion protein detects modified target interaction



Human Genome Sciences Announces Withdrawal of European Marketing Authorization Application For JOULFERON® (ZALBIN) For the Treatment of Chronic Hepatitis C - Yahoo! Finance

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GET QUOTES Finance Search Fri, Jun 4, 2010, 6:47AM EDT - U.S. Markets open in 2 hrs 43 mins

Human Genome Sciences Announces Withdrawal of European Marketing Authorization Application For JOULFERON® (ZALBIN) For the Treatment of Chronic Hepatitis C

Companies: Human Genome Sciences Inc.

Related Quotes

Symbol	Price	Change
HGSI	26.46	0.00
HGSI	26.5	-26.0

Press Release Source: Human Genome Sciences, Inc. On Monday April 19, 2010, 7:00 am EDT

ROCKVILLE, Md.--(BUSINESS WIRE)--Human Genome Sciences, Inc. (Nasdaq: HGSI - News) today announced that Novartis has withdrawn a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for approval to market JOULFERON® (albinterferon alfa-2b, known in the United States as ZALBINTM) for the treatment of chronic hepatitis C.

The decision to withdraw the application was based on feedback from European regulatory authorities in preliminary response to the EMA application, indicating that additional new data would be requested which could not reasonably be generated within the timeframe allowed in the European Centralized Procedure. Feedback included whether the therapeutic benefit offered by JOULFERON dosed once every two weeks is sufficient relative to risk.

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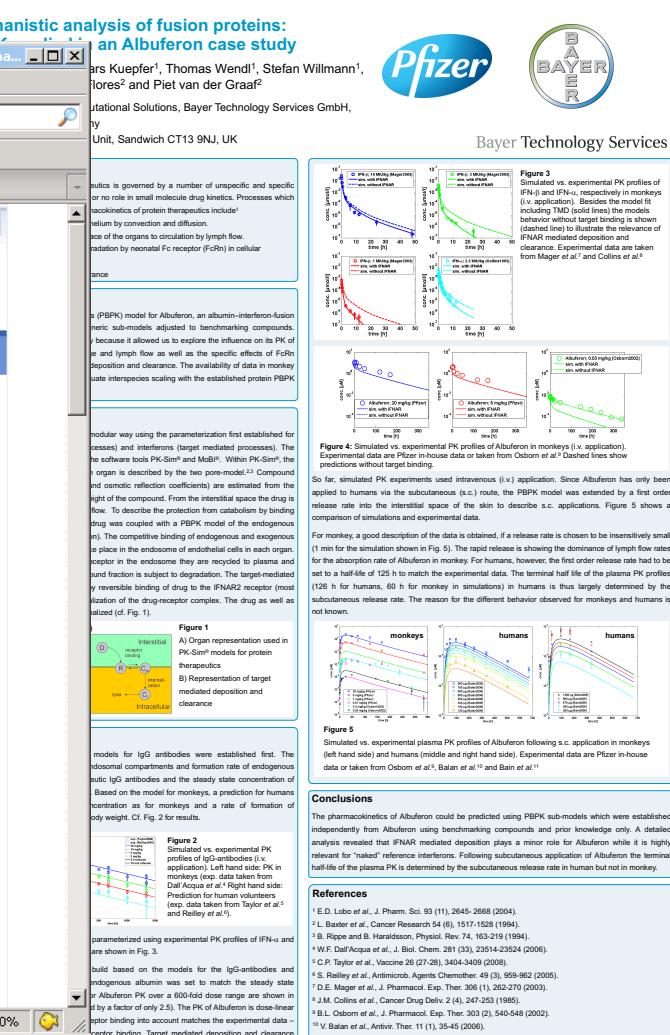
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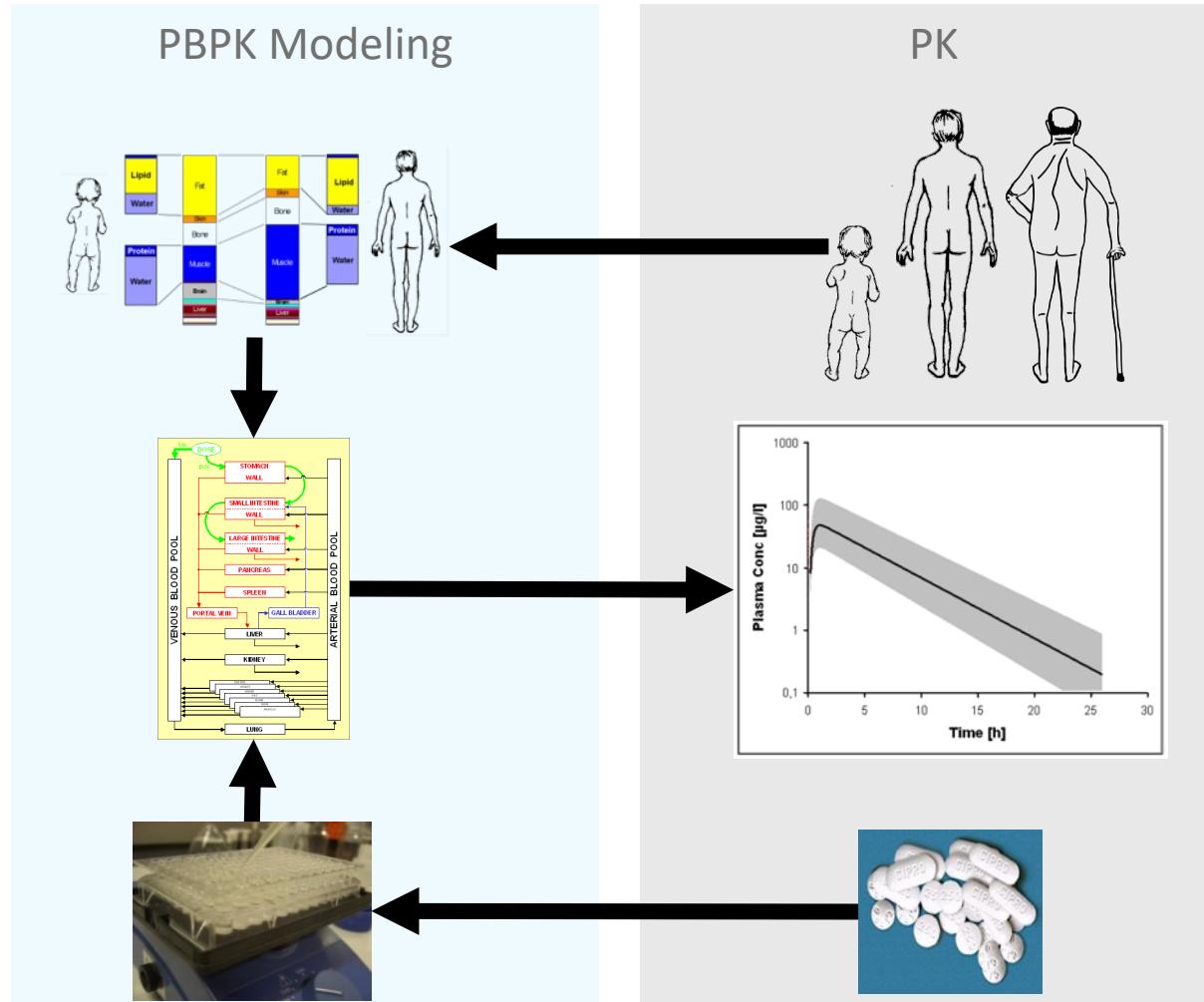
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Some features in PK-Sim 1.0

- Fully integrated whole-body PBPK model with
 - continuous flow GI tract model (no colon) with fasted / fed dependent transfer and pH parameterization and detailed representation of intestinal physiology
 - sub-compartmentalized organ representations with permeability limited exchange between interstitial space and cells
 - efflux and influx transporters in all organs and GI tract
 - Anatomy & physiology models for
 - mice
 - rat
 - dog
 - monkey
 - man
 - Proprietary prediction models for
 - tissue partition coefficients
 - tissue and GI permeability coefficients
 - SD and MD simulation of intravenous and oral administration
 - Visualization of simulation results and experimental data
- **No parameter estimation tool**

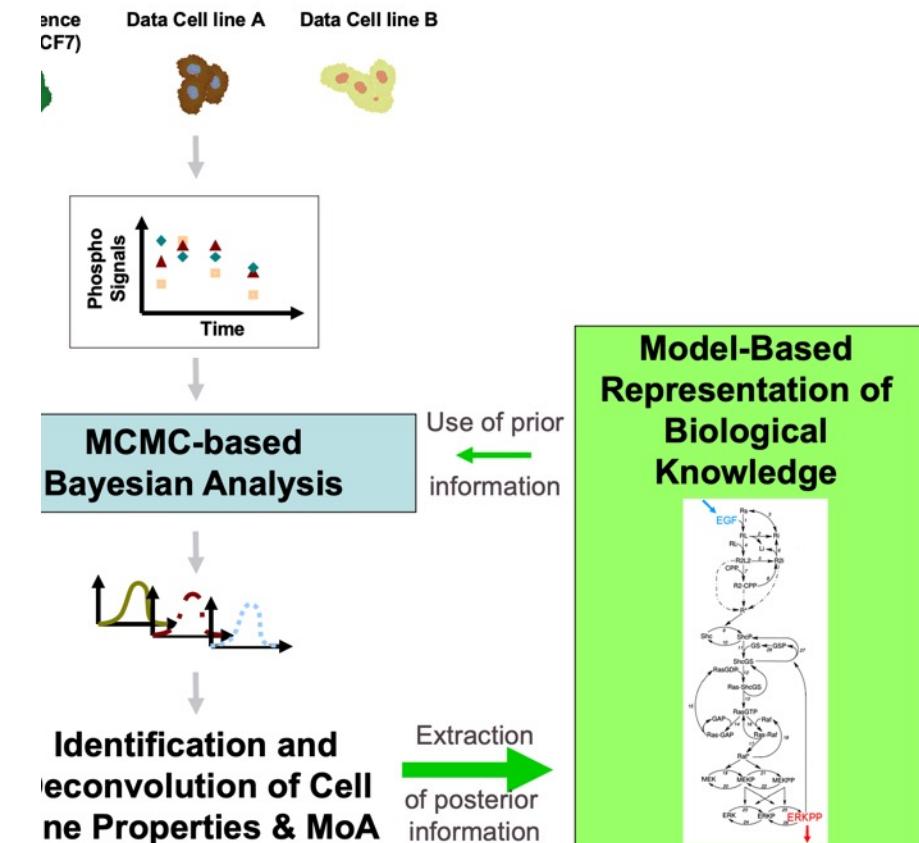
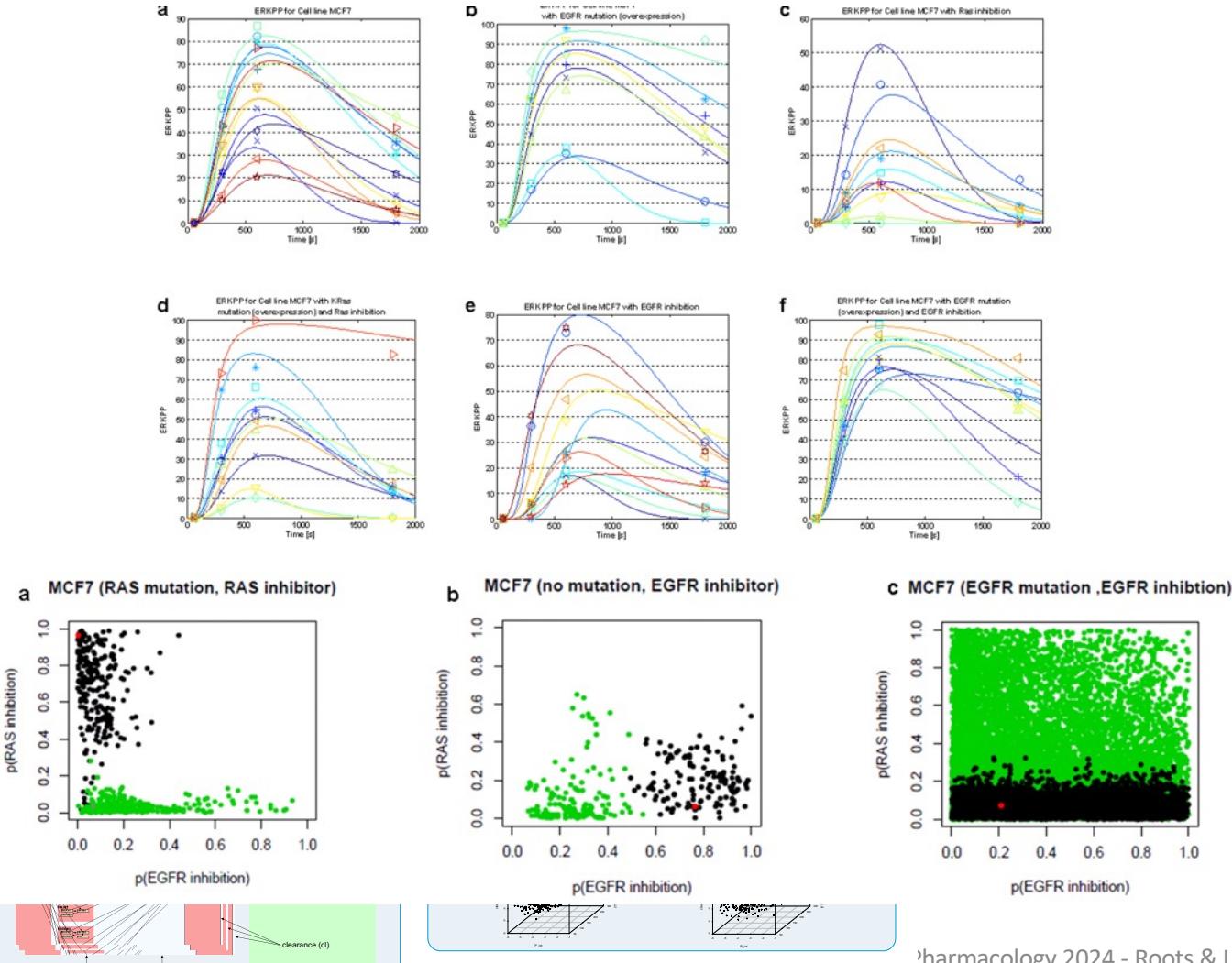
PBPK, a mechanism-based prediction tool not meant to be used for inference



PBPK Approach:

1. Prior anatomical & physiological knowledge
2. In-vitro drug properties
3. Mechanism-based prediction

For more than a decade Bayesian inference with full parameter MCMC is available but...



...deconvolution & translational learning based on PBPK and SysPharm has not become standard practice

Krauss et al. In Silico Pharmacology 2013, 1:6
<http://www.in-silico-pharmacology.com/content/1/1/6>

In Silico Pharmacology
 a SpringerOpen Journal

ORIGINAL RESEARCH

Open Access

Using Bayesian-PBPK modeling for assessment of inter-individual variability and subgroup stratification

Markus Krauss^{1,2}, Rolf Burghaus³, Jörg Lippert³, Mikko Niemi^{4,5}, Pertti Neuvonen⁵, Andreas Schuppert^{1,2}, Stefan Willmann¹, Lars Kuepfer¹ and Linus Görlich^{1*}

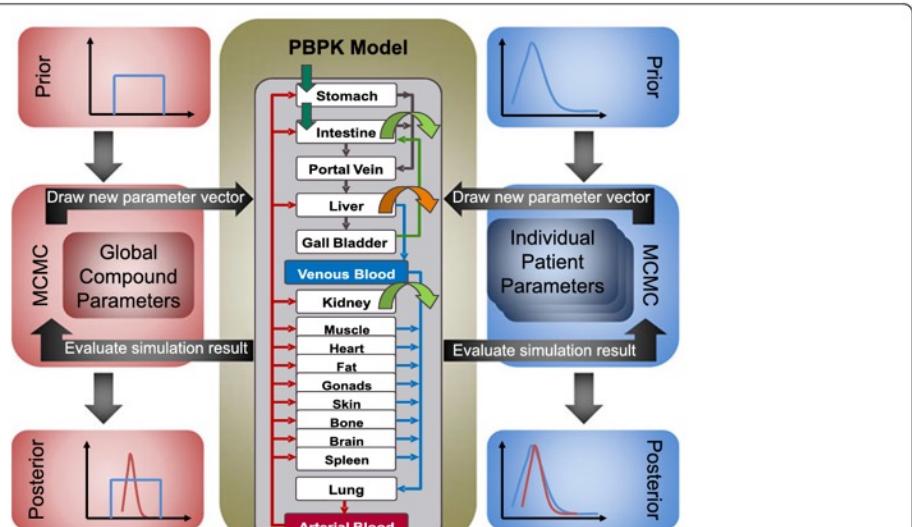


Figure 1 Schematic representation of the combined Bayesian-PBPK approach. A block-wise Metropolis-Hastings Markov chain Monte Carlo algorithm was used to sample the posterior distribution of individual patients' physiology on the one hand and global compound parameters on the other hand. The underlying model kernel was provided by detailed mechanistic physiologically-based

armacology 2024 - Roots & Leafs - JL

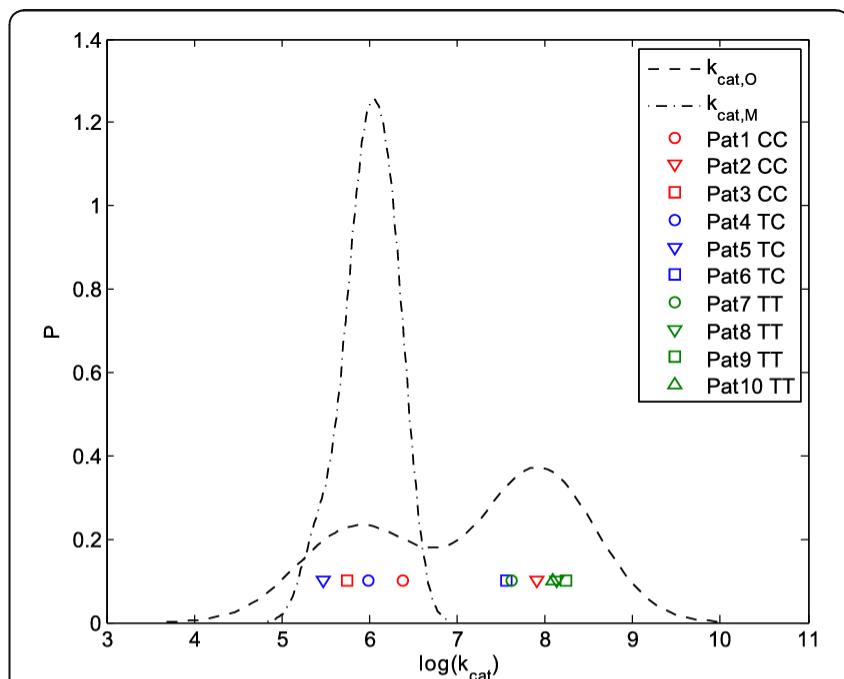
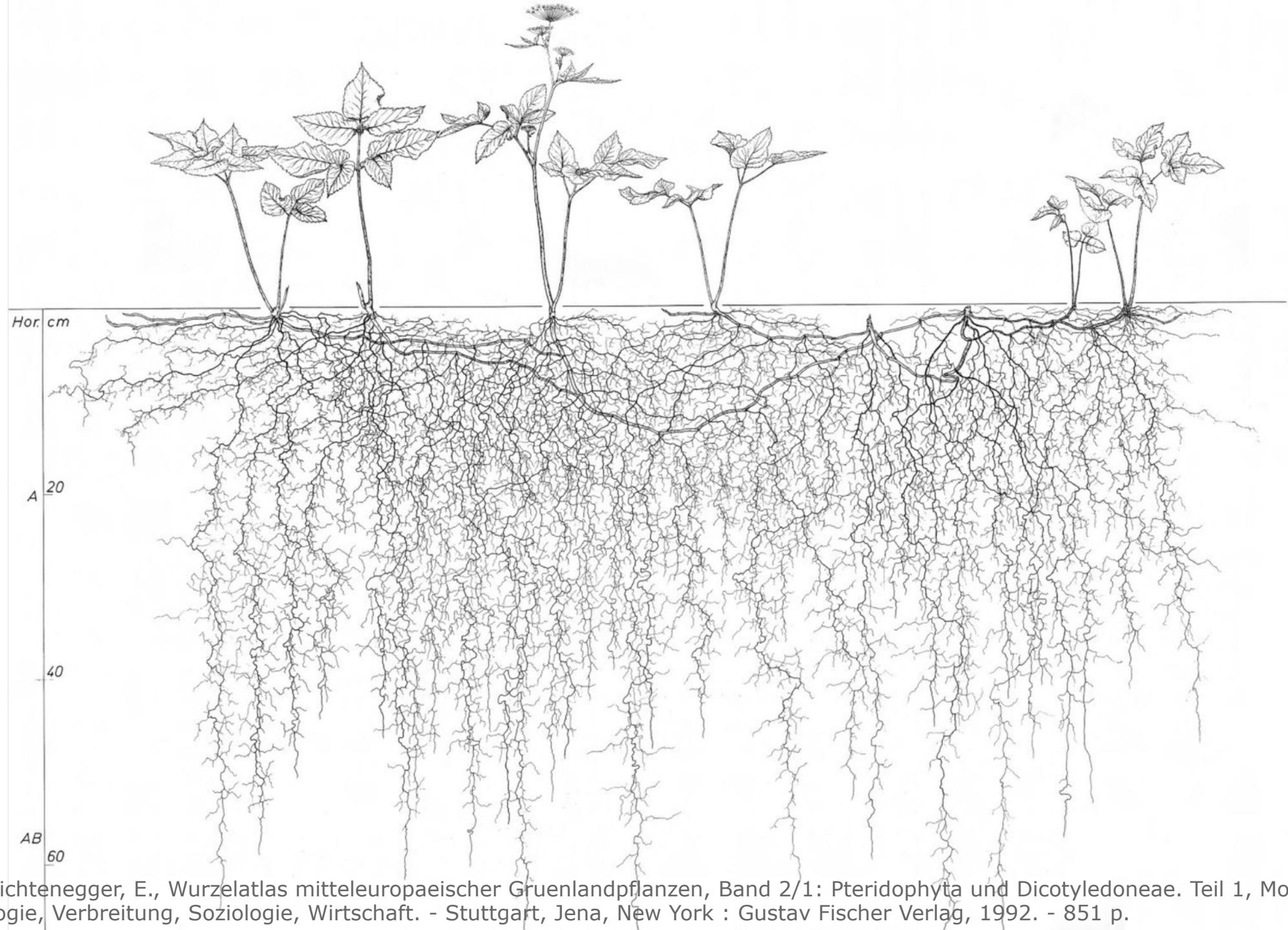
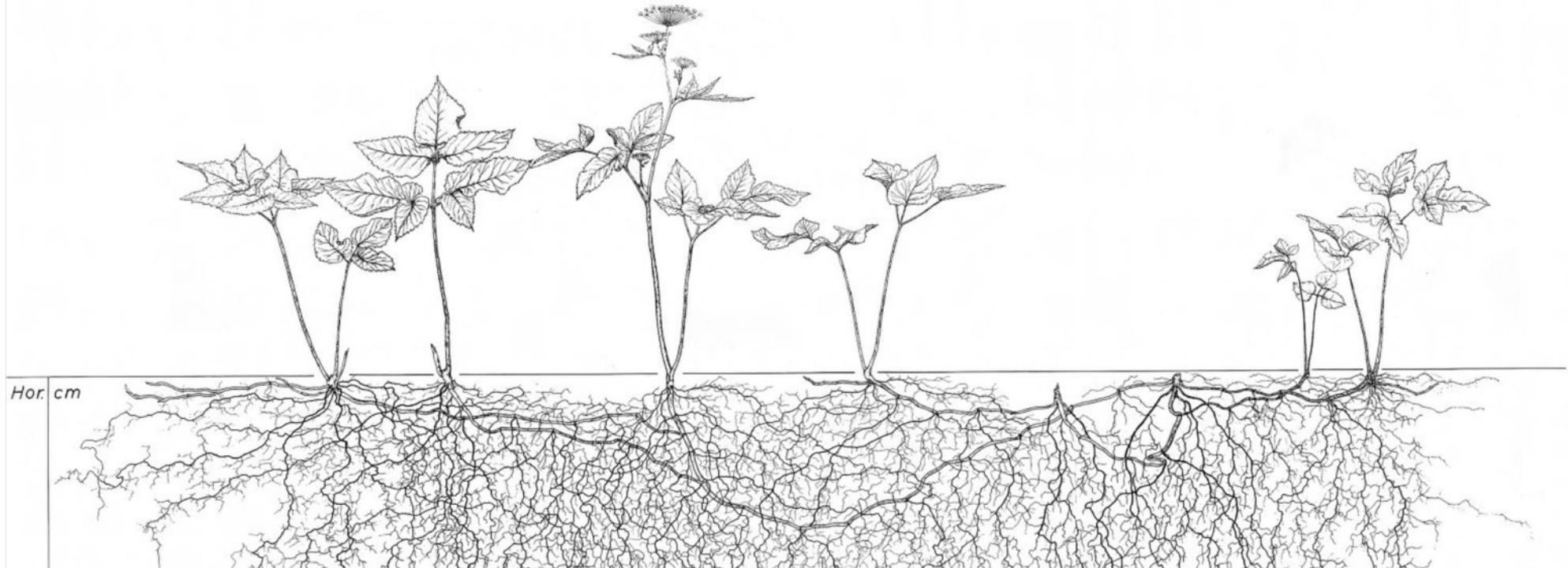


Figure 7 Identification and assignment of patient subgroups by monitoring the logarithmic mean for each patient. A density estimation of the logarithmic mean values supported the identification of specific patient subgroups. The logarithmic mean values of the transporter activities for MRP2 and OATP1B1 were calculated from the subsample of the posterior and the kernel densities were quantified. Since the density for OATP1B1 provided the separation of the patient logarithmic mean values into two groups, single values were also plotted with symbols. Additionally, they were colored related to their specific genotype.

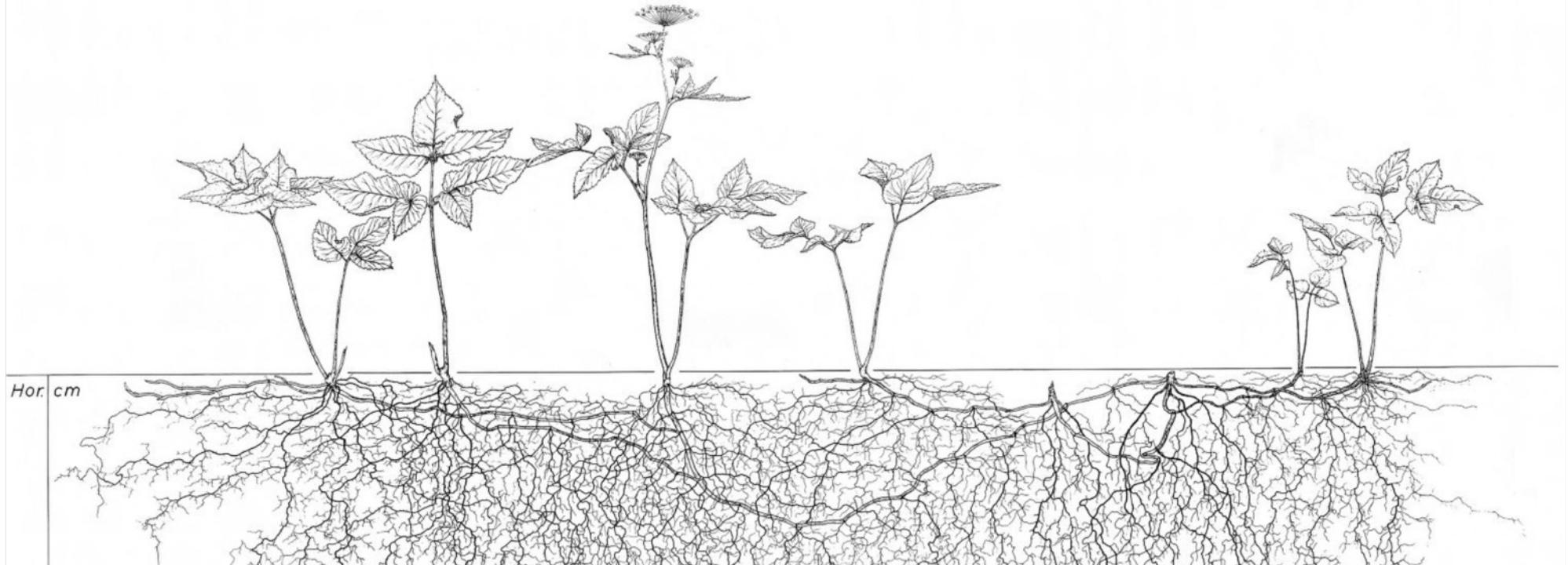


Kutschera, L.; Lichtenegger, E., Wurzelatlas mitteleuropaeischer Gruenlandpflanzen, Band 2/1: Pteridophyta und Dicotyledoneae. Teil 1, Morphologie, Anatomie, Ökologie, Verbreitung, Soziologie, Wirtschaft. - Stuttgart, Jena, New York : Gustav Fischer Verlag, 1992. - 851 p.



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