Oral drug absorption modeling in PK-Sim®

April 16, 2021

Sessions # 1 through 4

1. Introduction to PK-Sim
2. **PK-Sim applied for modeling of oral drug absorption**
3. The Qualification Concept of Open System Pharmacology (OSP) and its exemplary application to pediatric predictions with PK-Sim
4. Application of PBPK modeling of locally acting drugs – possibilities and considerations

Session 2

AIM: The aim of this session is that participants will acquire knowledge and practical experience of the oral absorption model in PK-Sim.

WHO: This session is primarily recommended to those who want to increase their skills and experience in oral absorption modeling using PK-Sim.

Learning objectives

- Detail the GI absorption model in PK-Sim in terms of
  - Structure
  - Physiology
  - Functionalities for formulation assessments
- Explain how to address GI absorption in drug model development using PK-Sim with the purpose of formulation performance assessments.
- Summarize OSP Suite workflow for virtual bioequivalence highlighting work from the FDA grant "*PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform*"

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Questions?

Put your questions in the chat.

1. I will read as we go and answer verbally

   OR

2. Moriah, Enrica, Johanna or Tobias will answer in the chat

Session 2
- Oral drug absorption modeling PK-Sim®

- Welcome & OSP Intro *(20 min)*
- PK-Sim oral absorption model *(45 min)*

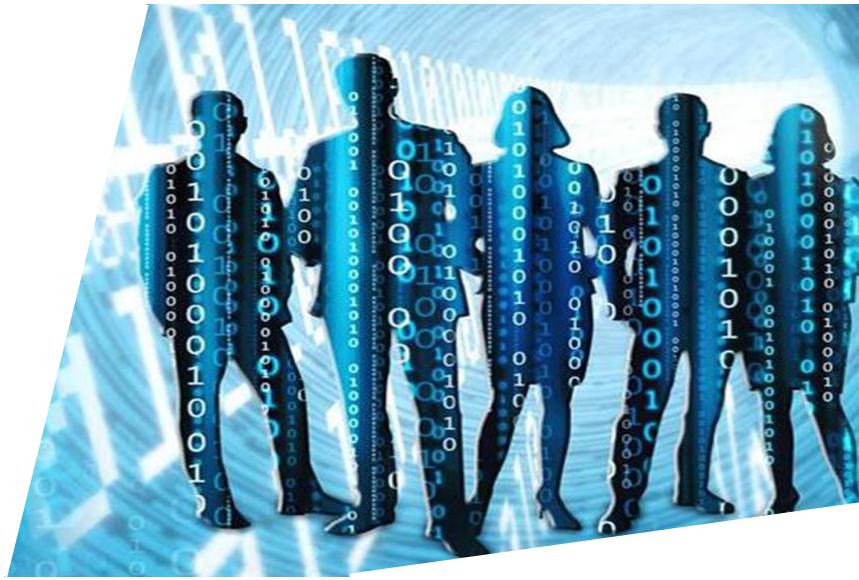
Break 10 min

- Hands-on exercises
  - Intro 1 *(5 min)*
  - Establish oral absorption model *(30 min - breakout rooms)*
  - Intro 2 *(5 min)*
  - Formulation performance in virtual populations *(30 min - breakout rooms)*

Break 10 min

- Virtual bioequivalence framework (FDA grant U01FD006549) *(45 min)*

Open Systems Pharmacology



Vision

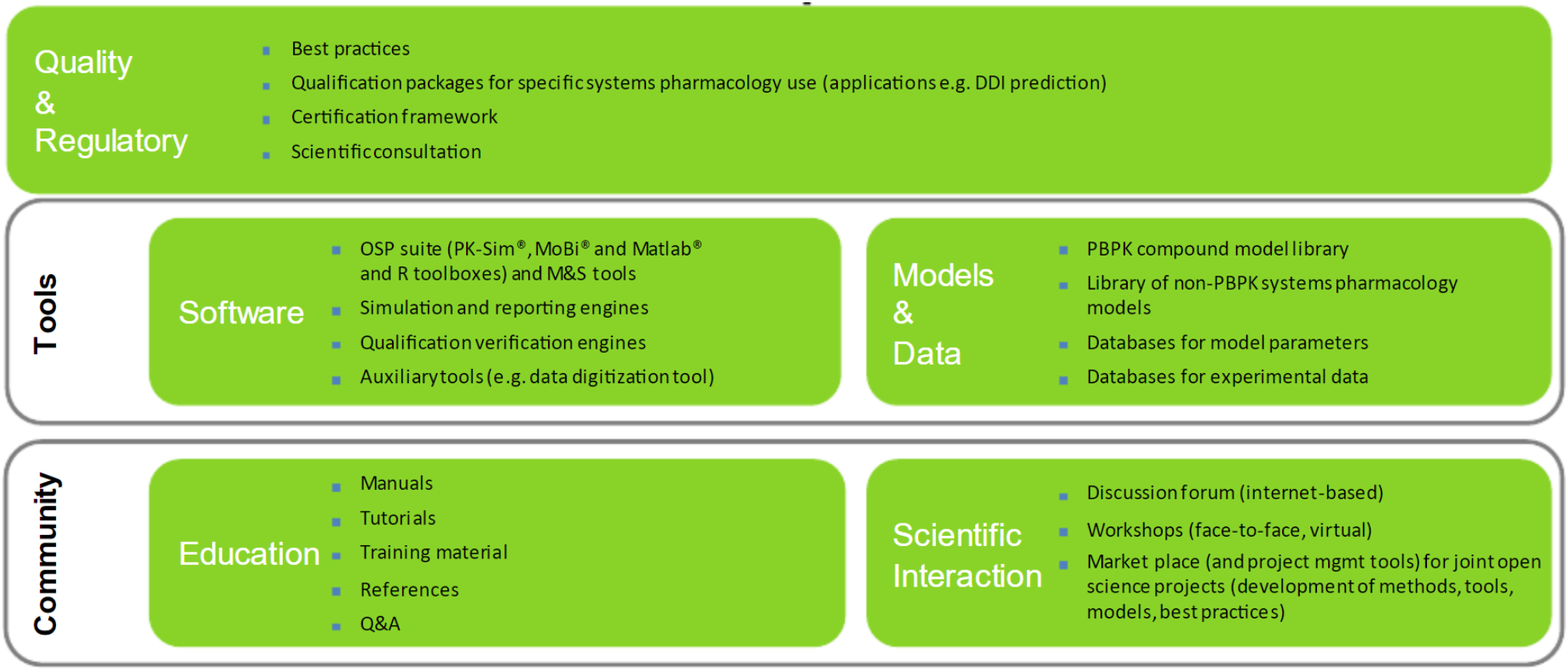
Robust and reliable, easy-to-use modeling & simulation tools, processes and models for pharmaceutical and other life-sciences applications qualified and accepted by a scientific community from academia, regulatory agencies and industry available and open to everyone.

Mission

Provide a platform for joint development, review & qualification, and application of state-of-the-art tools for PBPK and Systems Pharmacology modeling and an open library of models for application as well as method & tool qualification purposes. Promote the idea of pre-competitive open collaboration for the advancement of modeling & simulation sciences in pharmaceutical and life science.

Lippert et al. 2019. Open Systems Pharmacology Community-An Open Access, Open Source, Open Science Approach to Modeling and Simulation in Pharmaceutical Sciences. *CPT: Pharmacometrics and Systems Pharmacology*. 8: 878-882.

The scope of OSP addresses high priority applications of Systems Pharmacology and the need to continuously develop the scientific, methodological and regulatory foundation together with the software platform



OSP Management Team coordinates the interplay of focus areas and interfaces between them. Dedicated Focus Groups conceptualize, design and progress the individual areas.

OSP Management Team organize coordination and oversee all activities (bi-weekly meetings)

- Rolf Burghaus (Chair), Bayer AG
- Andrea Edginton, University of Waterloo
- Valvanera Vozmediano Esteban, University of Florida
- Andreas Kovar, Sanofi
- Thorsten Lehr, Universität des Saarlandes
- Jörg Lippert, Bayer AG
- José David Gómez Mantilla, Boehringer Ingelheim
- Matthew M. Riggs, Metrum Research Group
- Stephan Schaller, esqLABS
- Michael Sevestre, Design2Code
- Erik Sjögren, Pharmetheus, Uppsala University
- Juri Solodenko, Bayer AG
- Alexander Staab, Boehringer Ingelheim
- Donato Teutonico, Sanofi

OSP Sounding Board provides scientific/technical consultancy to MT and informs on trends

- Sebastian Frechen, Bayer AG
- Mats Karlsson, Uppsala University
- Peter Milligan, Pharmetheus
- Jan Schlender, Bayer AG
- Tobias Kanacher, Pharmetheus

Focus groups are expected to conceptualize and coordinate activities of the respective field. Includes a OSP MT sponsor, a chair and OSP community members.

Current Focus Groups (1/2)

Focus Group	Objective	Lead (GitHub UserID)
Absorption	The addition of model structures defining additional routes of administration/absorption is required to expand the application scope of the software in a consistent manner across users. The overall objectives are to define processes for 1. Technical generation of new routes of absorption destined for the OSP Suite 2. Evaluation of those absorption modules.	Erik Sjörgren (Erik-Sjogren)
Automation	Automation is a strategic theme of the OSP MT. Automation obviously is a means to increase efficacy but also an enabler the execution large technical tasks like population or trials simulations that cannot be conducted manually. Due to its intrinsic transparency, automation is an element of quality by design.	Juri Solodenko (Yuri05)
Community engagement	• To streamline official outside communication channels of OSP – Social Media: LinkedIn / Twitter – Newsletter / OSP News Section – OSP Booth at conferences – OSP Events (Hackathon, …) • Use Communication Channels to increase community engagement • Sustain Community Collaboration Framework	Stephan Schaller (StephanSchaller)
DDI	Quantitative DDI predictions (CYPs as well as transporters) are one of the key applications for PBPK and are a prerequisite for designing efficient clinical development programs and studies. A comprehensive library of well documented, qualified perpetrators and victims is a prerequisite for acceptance of DDI predictions from regulatory authorities.	Sebastian Frechen (sfrechen)
IVIVE	• Improve and facilitate use of IVIVE in PK-Sim • Provide guidelines on how to conduct IVIVE in PK-Sim • Facilitate integration of in vitro data in prediction of DDI (e.g. integration of fraction metabolized) • Extrapolation of Caco-2 permeabilities to effective permeabilities	Donato Teutonico (teutonicod)

Focus groups are expected to conceptualize and coordinate activities of the respective field. Includes a OSP MT sponsor, a chair and OSP community members.

Current Focus Groups (2/2)

Focus Group	Objective	Lead (GitHub UserID)
PBPK best practices	Establishing Standards for PBPK Model Development and Application to Ensure Reliability, Reproducibility and Transparency, Independent of Modeling Platform. The standards should be considered when developing a PBPK model, regardless of the platform.	Matthew Riggs (riggsmm)
PD	• PBPK/PD & QSP modeling is a strategic theme of the OSP MT • Identify needs for enabling / facilitating PD/QSP modelling in PK-Sim and MoBi • To streamline PD efforts of OSP • Derive a strategy for / identify public or industrial collaborations or funding sources to sponsor roadmap implementation	Stephan Schaller (StephanSchaller)
Special populations	The addition of new or updated virtual populations is required to expand the application scope of the software in a consistent manner across users. The overall objectives are to define a process for 1) technical generation of populations destined for the OSP Suite and, 2) evaluation of those populations. This protocol will allow populations to be added more efficiently.	Andrea Edginton (Aedginto)
Statistical Modelling	Statistical Modeling is a strategic theme of the OSP MT. Statistical modeling is a key enabler for PBPK and QSP M&S. Respective capabilities are required for all application areas to quantitatively assess population variability and uncertainty in prior knowledge and posterior results.	Christian Diedrich (DiedrichC)
Suite Release Mgmt. / Software Usability	The software suite is a pillar and the nucleus of OSP. Development and maintenance of the suite is a core element of the OSP mission. Active Release Management is required to execute on this mission.	Juri Solodenko (Yuri05)

Managed Open Source

- OSP Suite uses **GitHub** (https://github.com) as a source control platform
- Release planning is realized via the GitHub “Projects” feature. Issues are organized by milestones and effort estimates are proposed and tracked. All of these efforts can be seen by anyone. Release planning and release are only done by the core development team that is supported by industry and academic partners.
- Approved “official” releases of the OSP Suite are published on the GitHub Platform and can be downloaded by any user (no GitHub account is required for this). Full release histories are available.
- Rigorous software development practices use Continuous Integration (CI) that includes test automation, build automation, code quality analysis and artifact repository. Nightly builds are accessible to anyone and thus always in beta mode for the future version.

For more details on software engineering, transparency and security :
https://github.com/Open-Systems-Pharmacology/Forum/wiki/OSP:-Software-engineering,-transparency-and-security

Managed Open Source

GitHub is the main place for OSP interactions:

https://github.com/Open-Systems-Pharmacology

- Download PK-Sim®, MoBi®, GENEDBhuman, Qualification Framework, R-toolbox
- Access source code
- Find the manuals
- Watch/access tutorials
- Download models (e.g. drug models in PK-Sim, or application models in MoBi)
- View qualification documents (subject of Session #3)
- Ask and answer questions on the community FORUM
- See the bug reports and fixes (ISSUES in PK-Sim or MoBi)

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- Virtual bioequivalence framework (FDA grant U01FD006549) *(45 min)*

PK-Sim oral absorption model

Where to find information.

PK-Sim®

MoBi®

4022 *J. Med. Chem.* **2004,** *47,* 4022−4031

A Physiological Model for the Estimation of the Fraction Dose Absorbed in Humans

Stefan Willmann,*,† Walter Schmitt,† Jörg Keldenich,‡ Jörg Lippert,§ and Jennifer B. Dressman||

Bayer Technology Services GmbH, Biophysics, 51368 Leverkusen, Germany, BAYER AG, Bayer HealthCare, Chemical Research, 42096 Wuppertal, Germany, Bayer Technology Services GmbH, Computational Solutions, 51368 Leverkusen, Germany, and Institute of Pharmaceutical Technology, University of Frankfurt, 60439 Frankfurt, Germany

Evolution of a Detailed Physiological Model to Simulate the Gastrointestinal Transit and Absorption Process in Humans, Part 1: Oral Solutions

KIRSTIN THELEN,[1,2] KATRIN COBOEKEN,[2] STEFAN WILLMANN,[2] ROLF BURGHAUS,[3] JENNIFER B. DRESSMAN,[1] JÖRG LIPPERT[2]

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[3]Clinical Pharmacology - Modeling and Simulation, Bayer Pharma AG, 42096 Wuppertal, Germany

Received 8 December 2010; accepted 14 July 2011

Research paper

Mechanism-based prediction of particle size-dependent dissolution and absorption: Cilostazol pharmacokinetics in dogs

Stefan Willmann [a,*], Kirstin Thelen [a,b], Corina Becker [a], Jennifer B. Dressman [b], Jörg Lippert [a]

[a] *Bayer Technology Services GmbH, Competence Center Systems Biology and Computational Solutions, Leverkusen, Germany*
[b] *J.-W. Goethe University, Institute of Pharmaceutical Technology, Frankfurt a.M., Germany*

Evolution of a Detailed Physiological Model to Simulate the Gastrointestinal Transit and Absorption Process in Humans, Part II: Extension to Describe Performance of Solid Dosage Forms

KIRSTIN THELEN,[1,2] KATRIN COBOEKEN,[2] STEFAN WILLMANN,[2] JENNIFER B. DRESSMAN,[1] JÖRG LIPPERT[2]

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PK-Sim oral absorption model

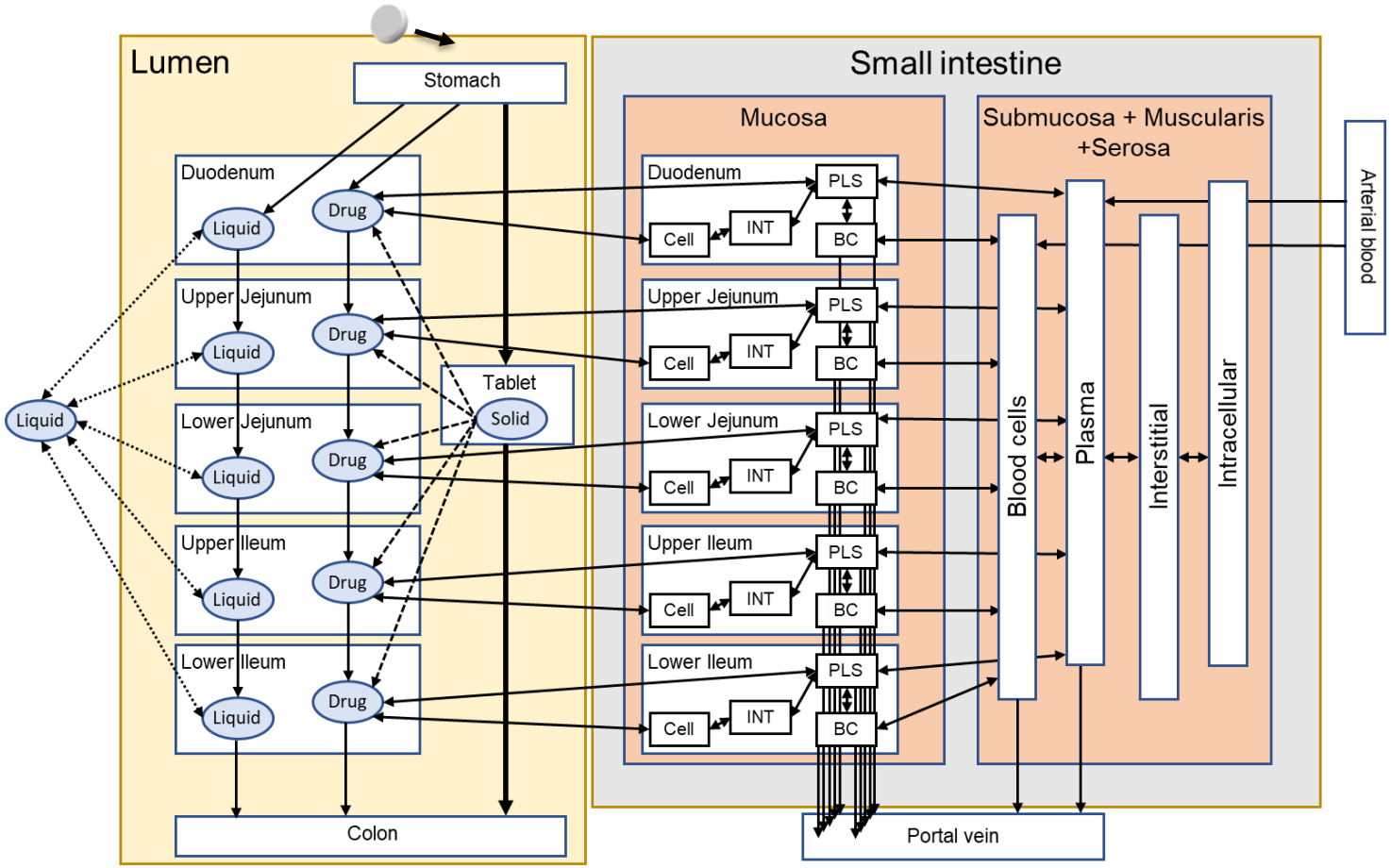
- Model structure and system parameters
  - Structure & Pathways, pH, Transit, Volumes, Areas, EHC
- Gut metabolism and transporters
- Solubility and dissolution
- Permeability
- Functionalities
  - Food effects
  - Formulations
  - Other

Model structure and system parameters

Structure and pathways

- 12 compartments representing the lumen of the GI tract from stomach to rectum.
- Regional properties (dimensions, surface area, pH, transit times)
- Stomach absorption currently not included

Upper gastrointestinal tract

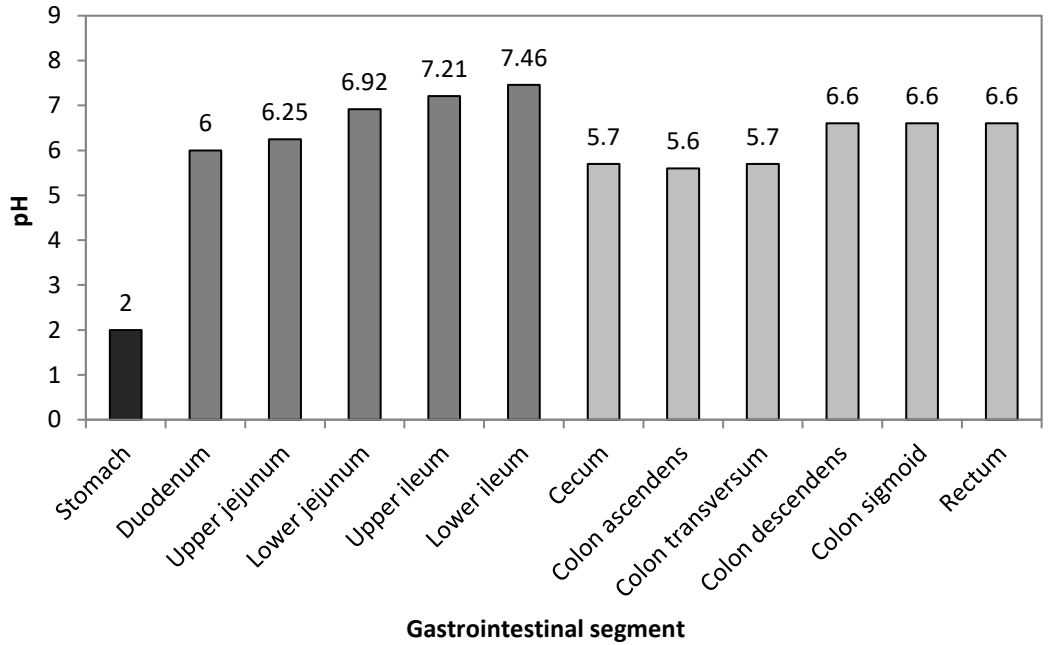


Thelen et al. 2011/2012

… similar structure for large intestine

Model structure and system parameters

- Luminal pH
  - Standardized for all typical healthy IDs

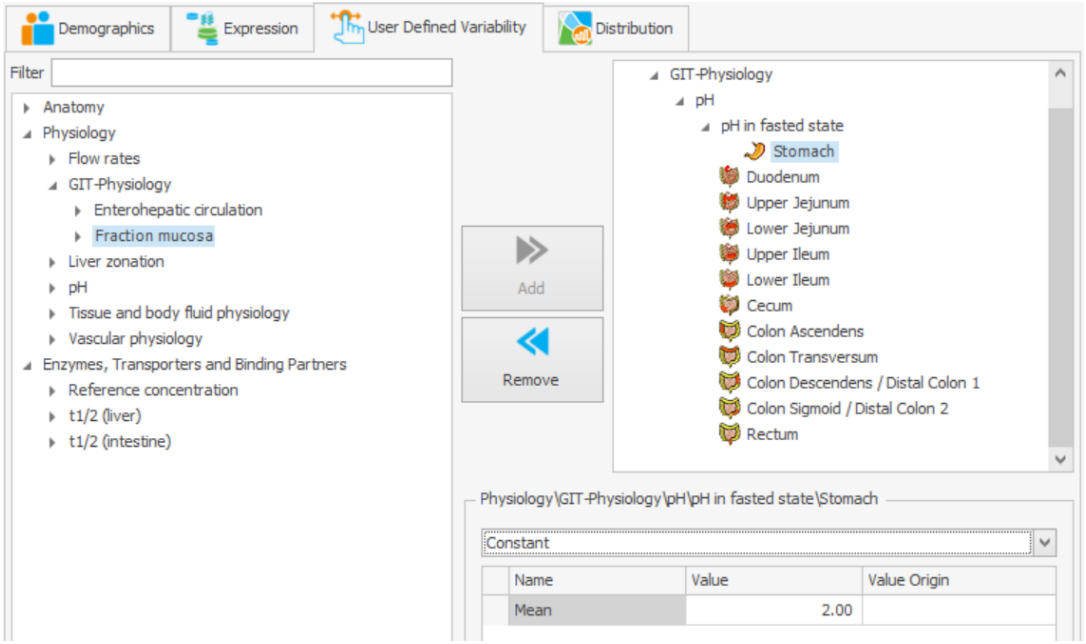


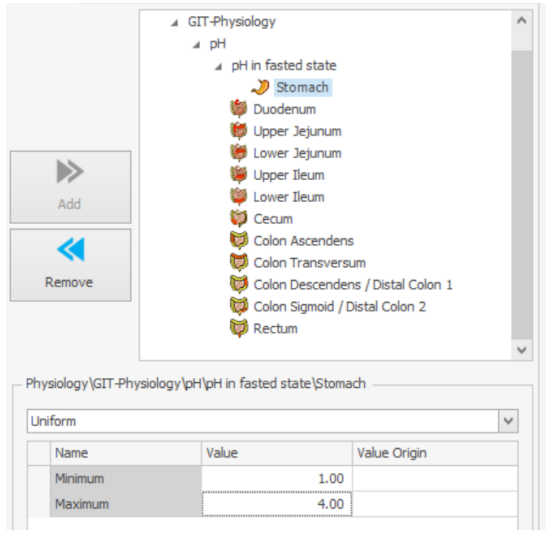
  - Variability not included in virtual population creation per default.

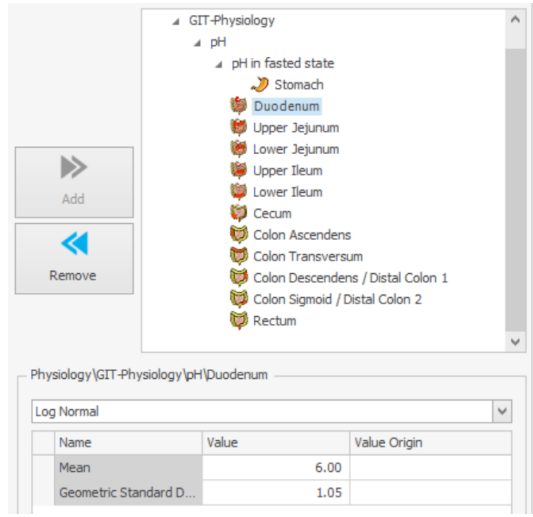
Model structure and system parameters

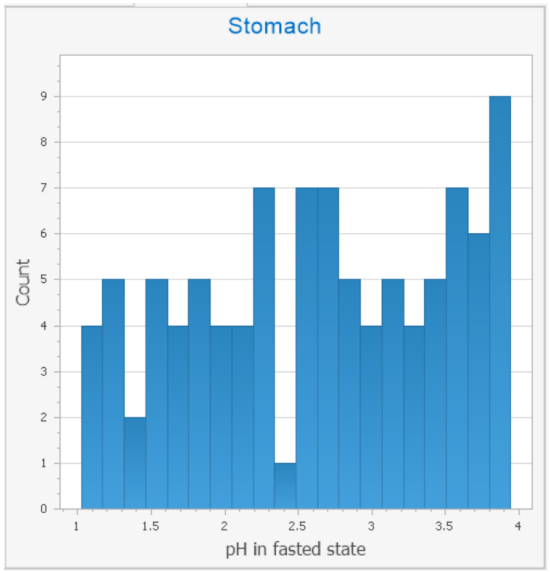
- Define population variability – example luminal pH

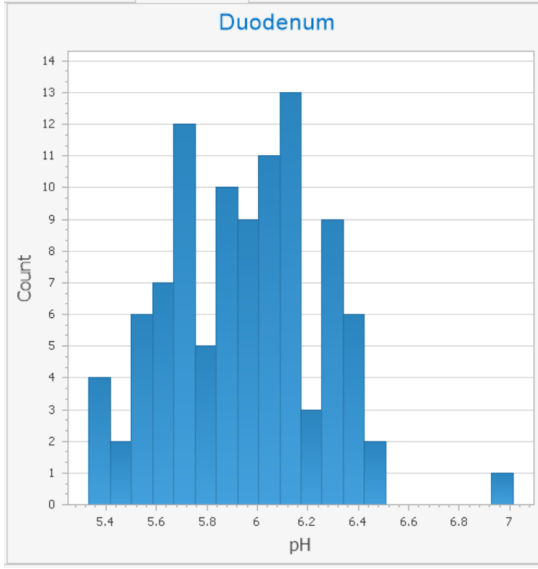
Population characteristics





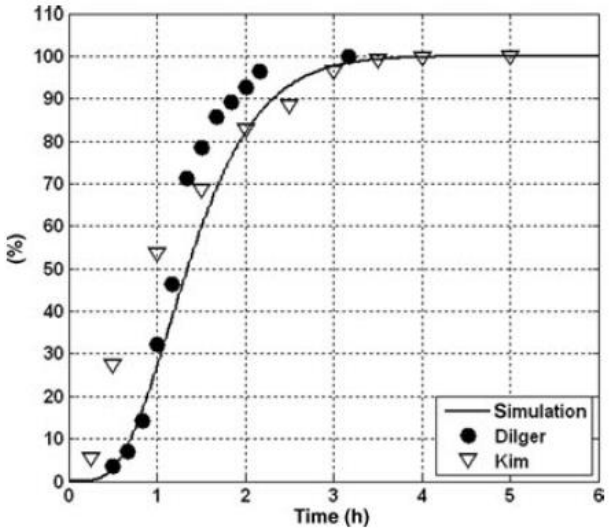






Model structure and system parameters

- Transit
  - Gastric emptying time (fasted state): 15 min
  - Small intestinal transit time: 2.1 h (complete at ~ 4h)
    (time from 63% entered duodenum and 90% has entered caecum)
  - Large intestinal transit time : 44.2 h
    (time from 90% entered caecum and 70% excreted into feces)
  - Total GITT: ~48 h → 70% excreted
    ~120 h → 100% excreted



Function used to describe the transit of the dissolved drug through the small intestine together with literature data

Thelen et al. 2011

- Gastric emptying time and SITT are standardized across age while LITT is age dependent (slight decrease by age).
- Variability in gastric emptying time and SITT is included in virtual population creation per default, but not for LITT.

Model structure and system parameters

- Transit
  - Gastric emptying time (fasted state): 15 min
  - Small intestinal transit time: 2.1 h (complete at ~ 4h)
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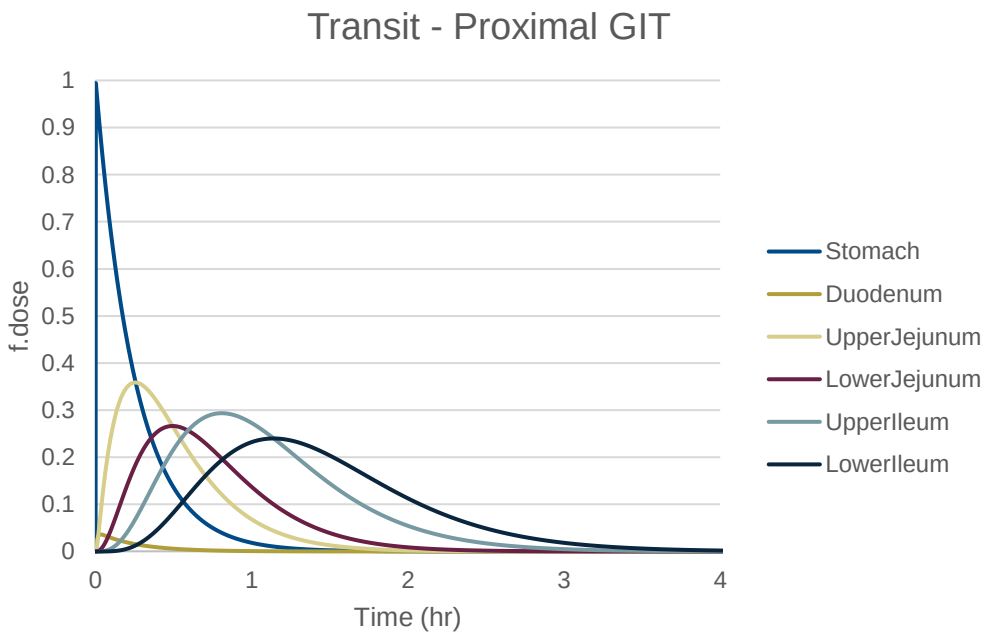
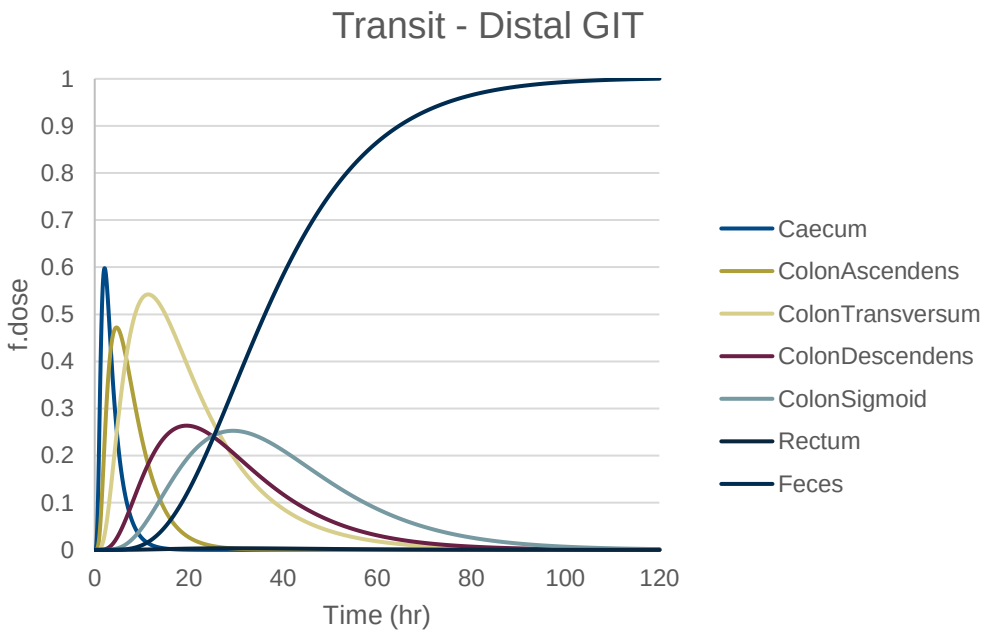
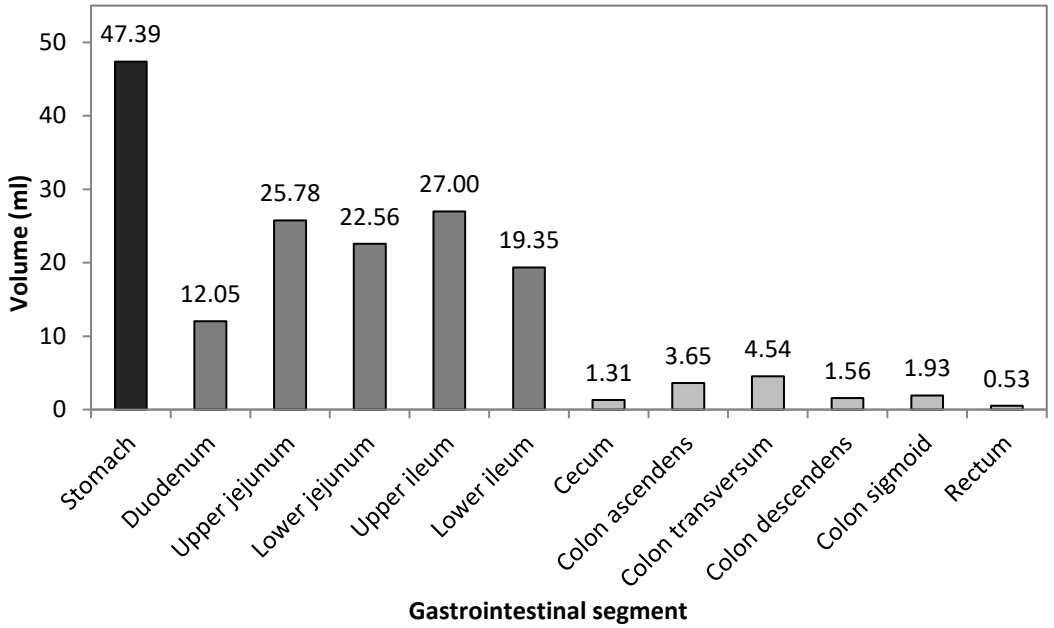




Model structure and system parameters

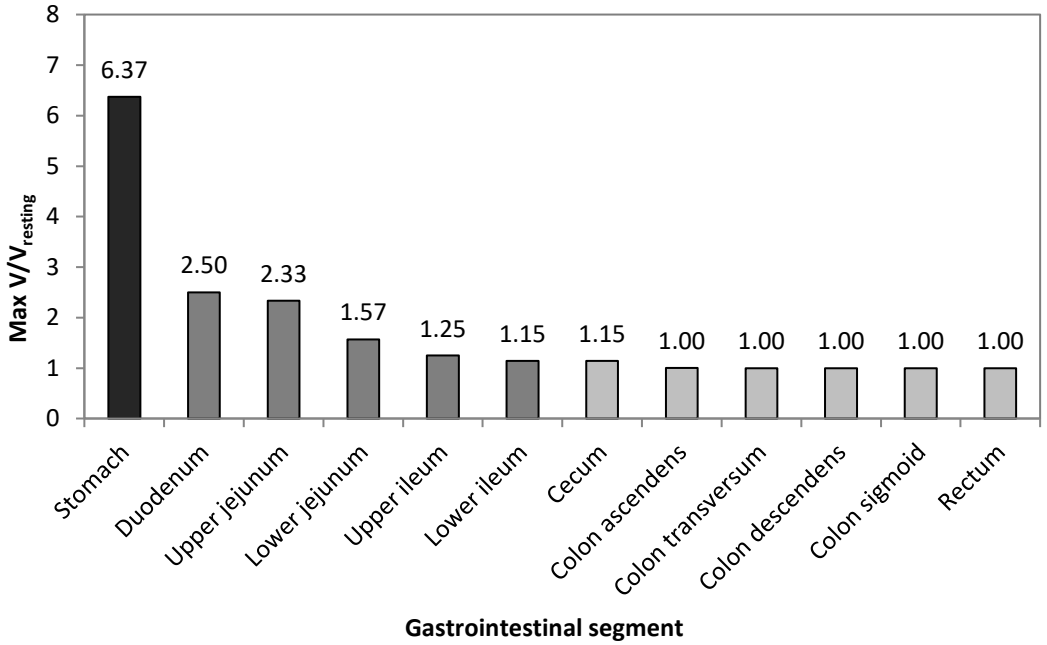
- GI fluid volumes
  (resting volumes, typical adult ID)
  - Gastric volume : ~50 ml
  - Small intestine: ~100 ml
  - LITT: ~14 ml

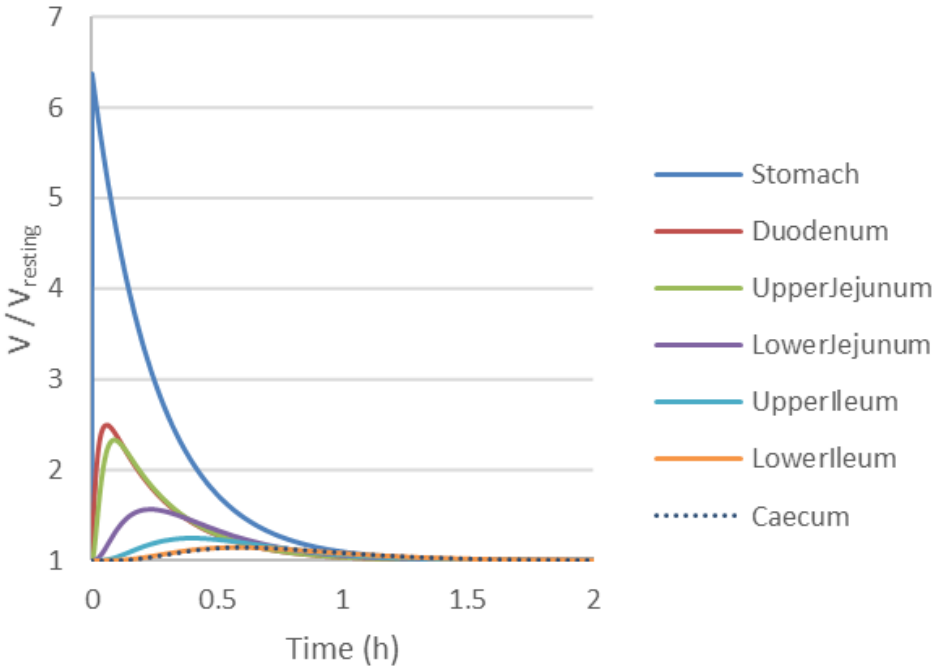


- Luminal volumes are determined by the size of respective GI segments and a parameter representing the geometric fraction filled (G=0.03, Duo= 0.06, Jej and Ile=0.065, LI=0.006)
- Dimensions etc are shown in PK-Sim per default, however effective luminal volumes are not.
- Inter individual variability in luminal volumes are included in virtual population creation per default as an effect of variabilities in organ dimensions and size.

Model structure and system parameters

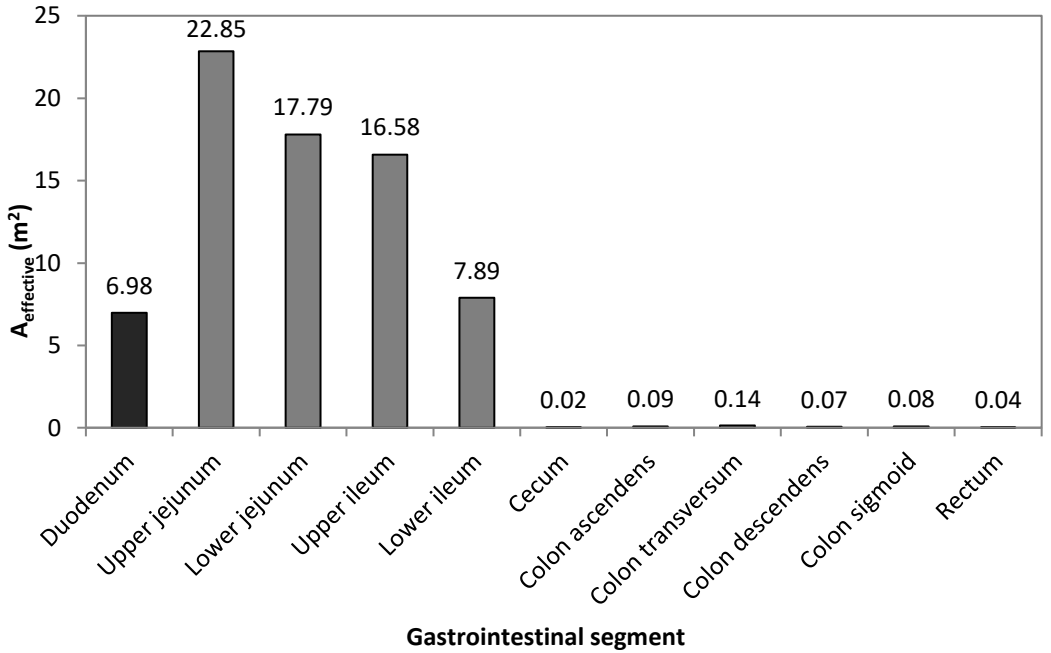
- GI fluid volumes
  (dynamic volumes)
  - Volume of co-administered water at oral administration dynamically change luminal volume.
  - Example using default volume of water taken at oral administration
    3.5 ml/BWT → 70 kg = ~250 ml





Model structure and system parameters

- Epithelial area
  - Surface in each compartment determined by geometric surface area and an area enhancement factor.
  - SI area: ~ 72 m^2
  - LI area: ~ 0.44 m^2



- Dimensions etc are shown in PK-Sim per default, however effective areas are not.
- Area enhancement factors are age dependent (decrease with age).
- Inter individual variability in effective areas are included in virtual population creation per default both in terms of variabilities in organ dimensions and size and a global surface area variability parameter.

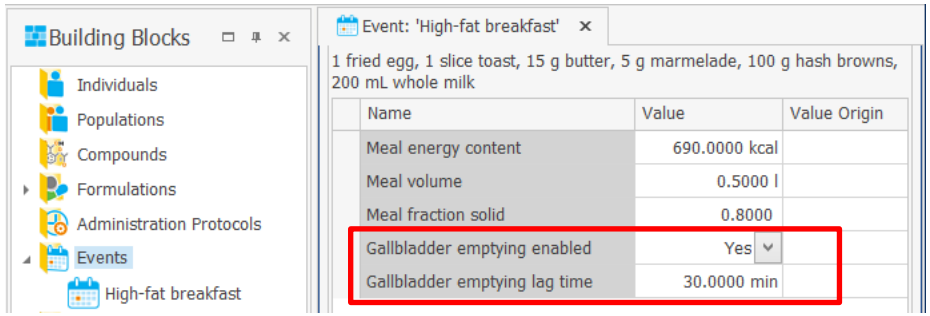
Model structure and system parameters

- Enterohepatic circulation

Gall bladder emptying is modelled as discrete mass flow from the gallbladder into the duodenum by either

- Continuous mass flow (EHC continuous fraction)
- Triggered by an event (such as a meal)

Name	Organ	Value
Gallbladder ejection half-time	Gallbladder	19.70 min
EHC continuous fraction	Liver	0
Gallbladder ejection fraction	Gallbladder	0.65



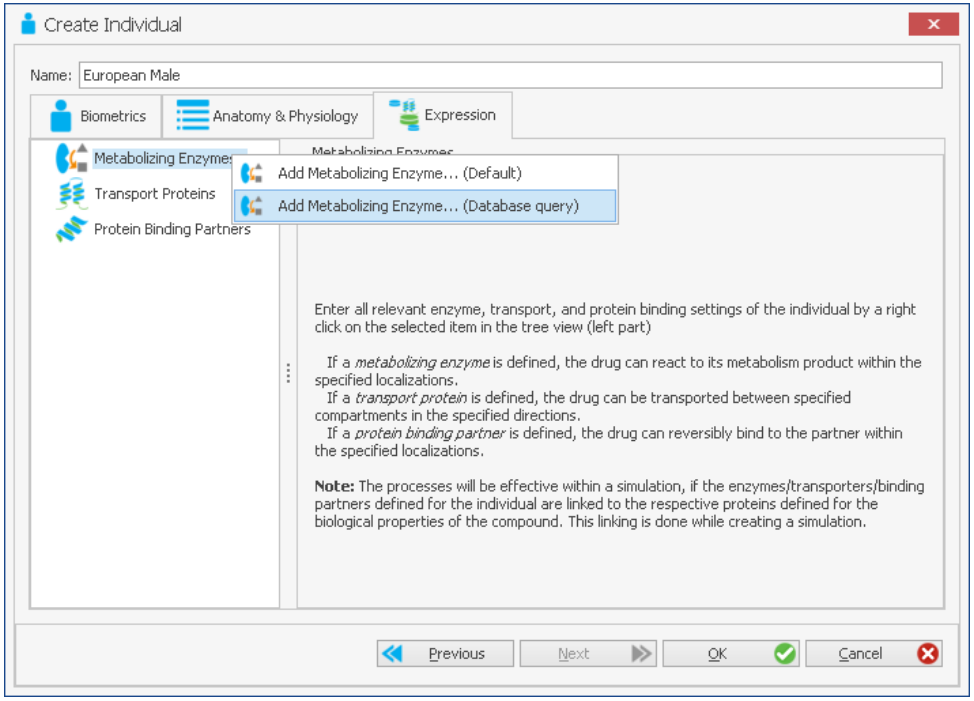
Parameters standardized for all typical healthy IDs,
Inter individual variability is not included in virtual population creation per default

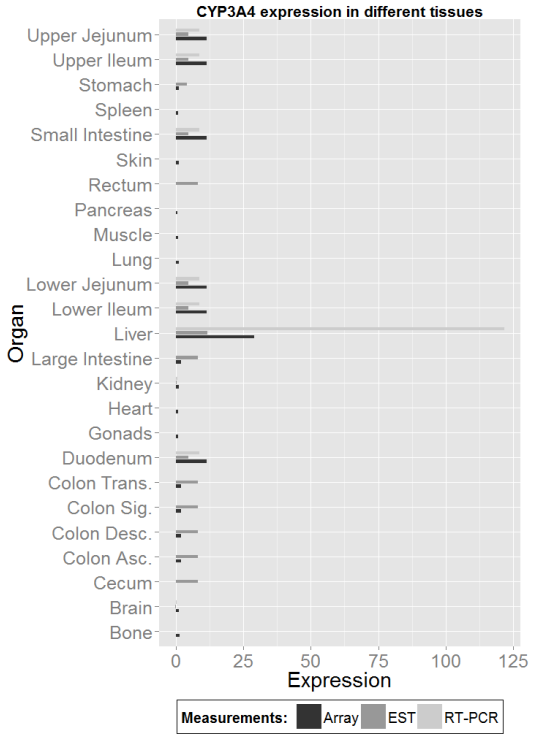
Gallbladder emptying does not automatically imply active secretion of the compound into the bile!

- In order to enable active secretion into the bile either implement generic biliary excretion or an efflux transport process at the apical side of the liver

Gut metabolism and transporters

- Metabolism can be specified in any of the mucosal intracellular compartments of the intestine
- Relative enzyme abundany along the GI tract can be loaded from the internal gene expression database (Meyer et al. 2012) or defined manually:

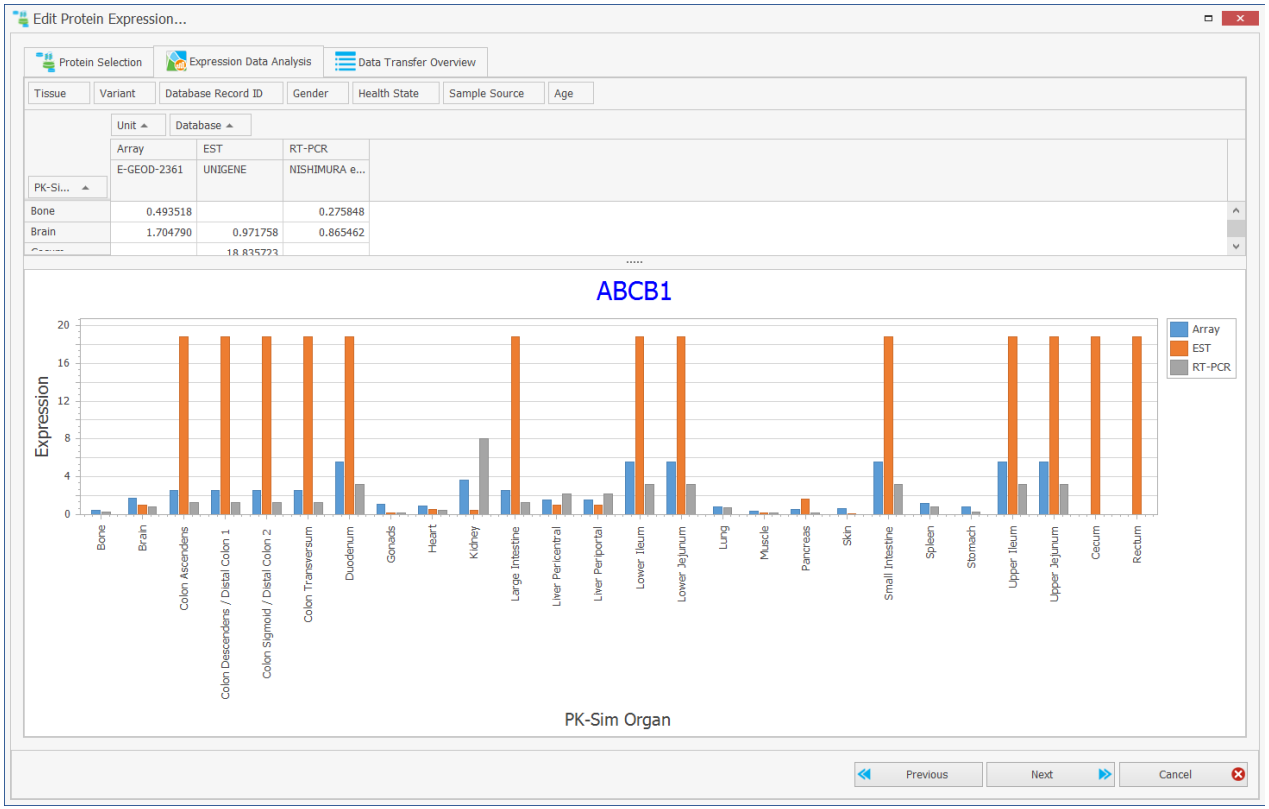


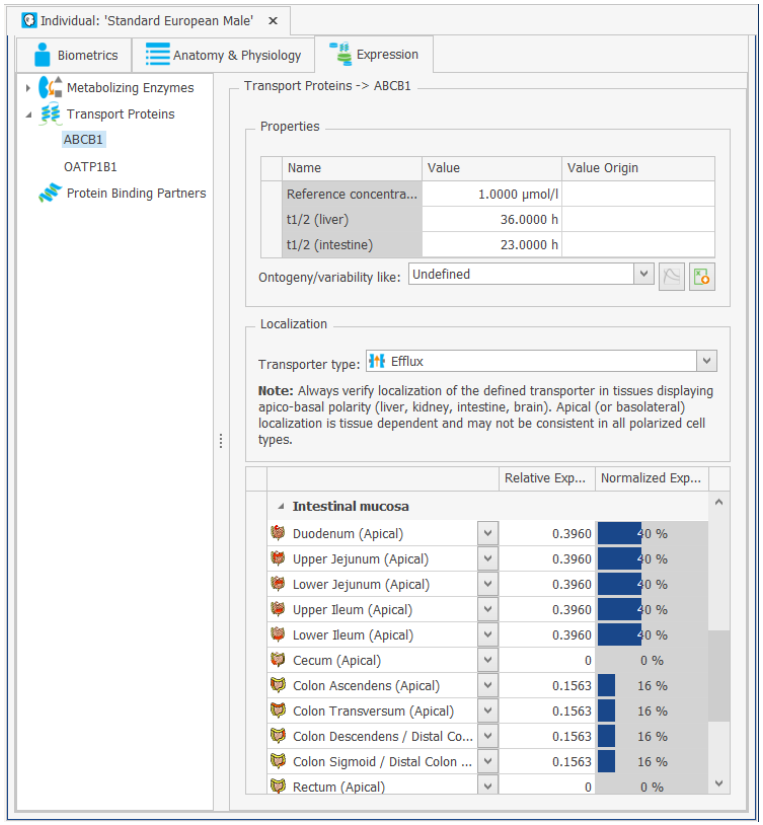


Meyer et al. 2012

Gut metabolism and transporters

- Similarly, to enzymes, drug transporters can also be loaded from the internal gene expression database
- Apical or basolateral localization defined



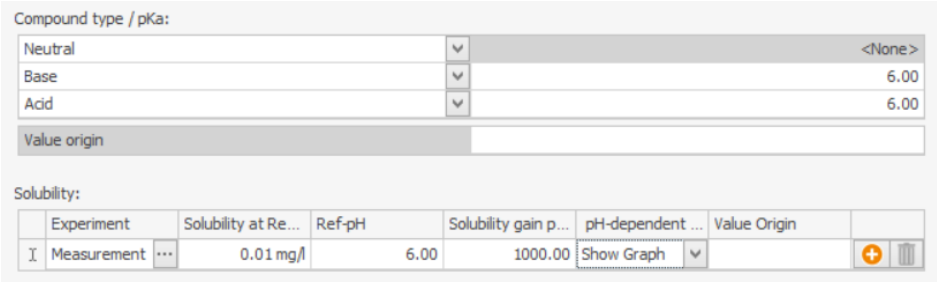


Solubility and dissolution

Drug solubility in the GIT is per default defined by the solubility input, ionization and luminal pH

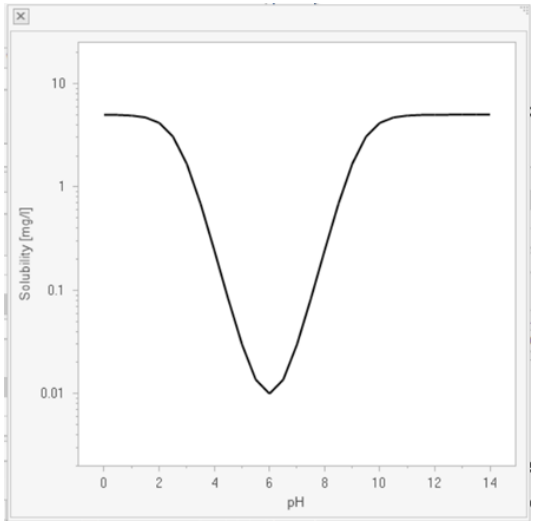
A minimum of one solubility value must be entered to establish a drug BB

- Up to three pKa input
- Solubility gain per charge
- Input option 1: Solubility at reference pH
- Input option 2: pH - Solubility table



Regional solubility can manually be modified in simulations

Regional GIT solubility given by drug input and pH



Compartment	Value
Stomach	4.17 mg/l
Duodenum	0.01 mg/l
Upper Jejunum	0.01 mg/l
Lower Jejunum	0.03 mg/l
Upper Ileum	0.05 mg/l
Lower Ileum	0.08 mg/l
Cecum	0.01 mg/l
Colon Ascendens	0.01 mg/l
Colon Transversum	0.01 mg/l
Colon Descendens ...	0.02 mg/l
Colon Sigmoid / Dis...	0.02 mg/l
Rectum	0.02 mg/l

Manual modification

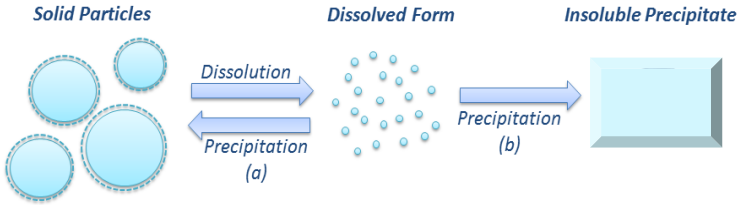
Compartment	Value
Stomach	4.17 mg/l
Duodenum	0.20 ...
Upper Jejunum	0.20 ...
Lower Jejunum	0.20 ...
Upper Ileum	0.20 ...
Lower Ileum	0.20 ...
Cecum	0.01 mg/l
Colon Ascendens	0.01 mg/l
Colon Transversum	0.01 mg/l
Colon Descendens ...	0.02 mg/l
Colon Sigmoid / Dis...	0.02 mg/l
Rectum	0.02 mg/l

Solubility and dissolution

The Particle dissolution model apply dissolution kinetics of spherical particles with a predefined particle size distribution based on the Noyes-Whitney equation (Willmann et al. 2010).

Drug specific parameters:

- How to treat precipitated material (soluble/insoluble)
- Aqueous diffusion coefficient
- Density of drug material
- Threshold for particle radius of immediate dissolution
- Allow for supersaturation



Willman et al. 2010

Formulation specific parameters:

- Thickness of the unstirred water layer (thickness of the diffusion layer)
- Type of particle size distribution (either monodisperse or polydisperse),
- Particle size distribution for polydisperse particles (normal, log normal) including:
  - Standard deviation of the particle radius
  - Number of bins
  - Minimum and maximum particle radius

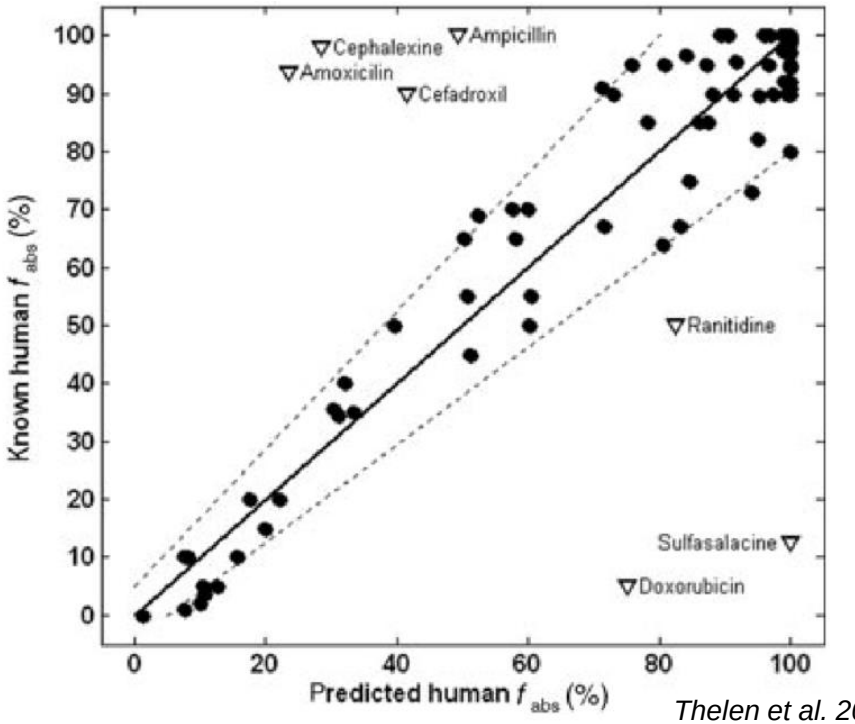
Permeability

- Intestinal permeability as input is defined as a function of effective Mw and membrane affinity in relation to the structural model (area and transit).
- Relationship estimated to capture observed fraction absorbed.
- Not based on in vivo permeability measurements

$$P_{\mathrm{int}}(\mathrm{MW_{eff}}, \mathrm{MA}) = A \times \mathrm{MW_{eff}^{-\beta}} \times \mathrm{MA}\,(\mathrm{cm/s})$$

<u>Default</u>

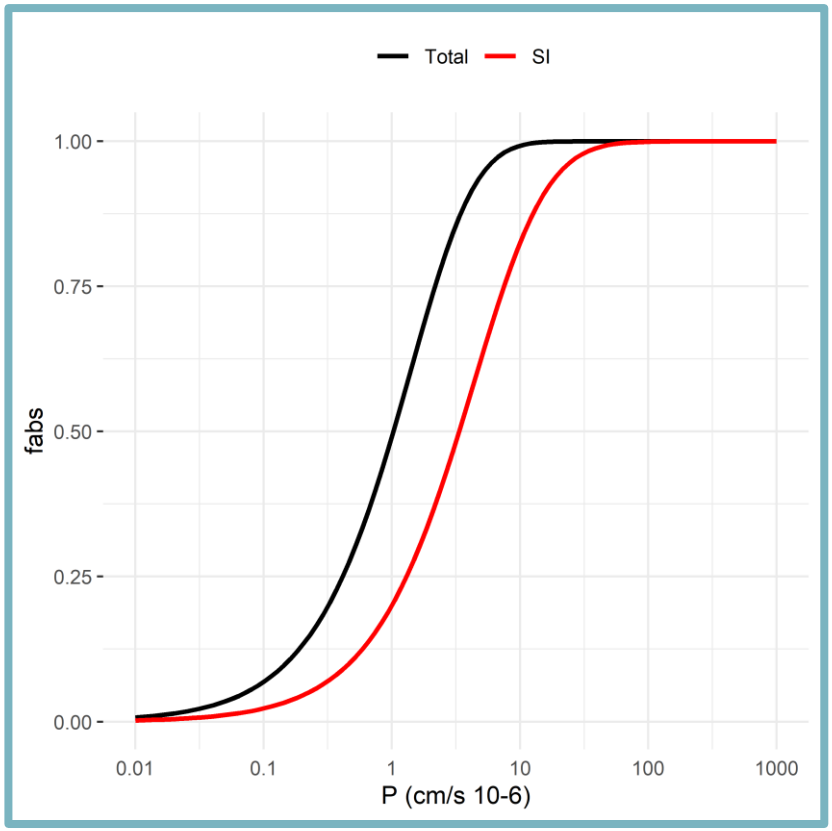
- Transcellular absorption
- Unidirectional passive membrane translocation
- No pH-effects (charge independent)
- No regional differences in permeability



Thelen et al. 2012

Permeability

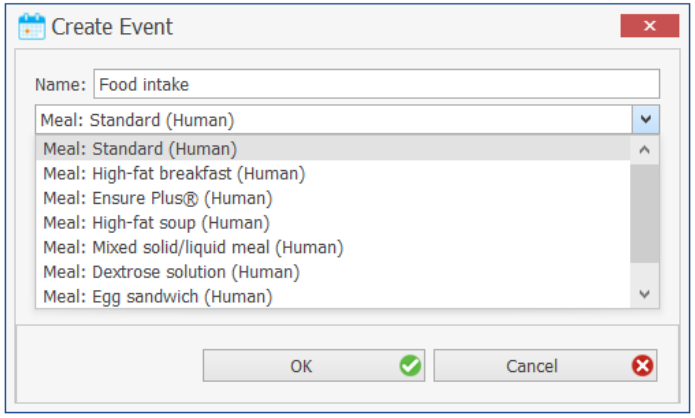
- Specific intestinal permeability automatically calculated based on Mw and logP
- To enable modification to intestinal permeability an additional permeability input needs to be added manually.
- Colonic absorption enabled per default

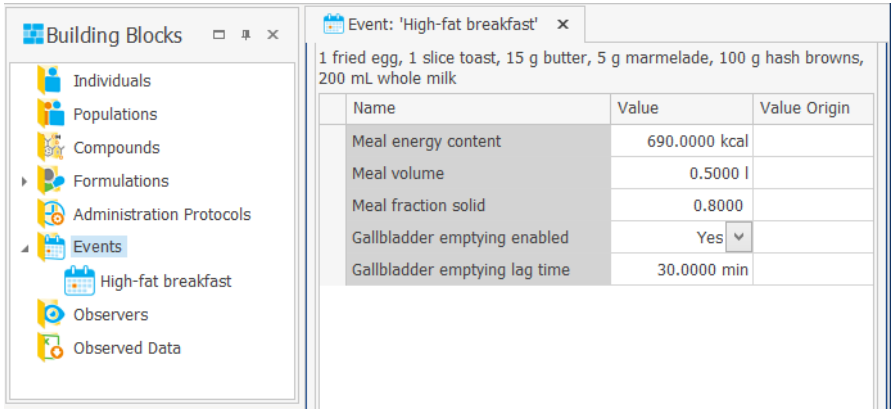


Functionalities – Food effects

Food intake can be defined in the Event Building Block section:

- Meal energy, meal volume and the solid fraction of the meal are predefined for several food types
- Relevant parameters of the food can also be manually modified by the user
- Food intake triggers the following physiological changes in the GI tract (Thelen et al. 2012, Willmann et al. 2014):
  - Initial liquid volume in stomach is increased by food volume
  - Gastric pH is increased and then decays exponentially
  - Gastric emptying time is slowed based on an empirical function fitted to >100 experimental gastric emptying profiles observed in healthy adults
  - Optionally: Gallbladder emptying

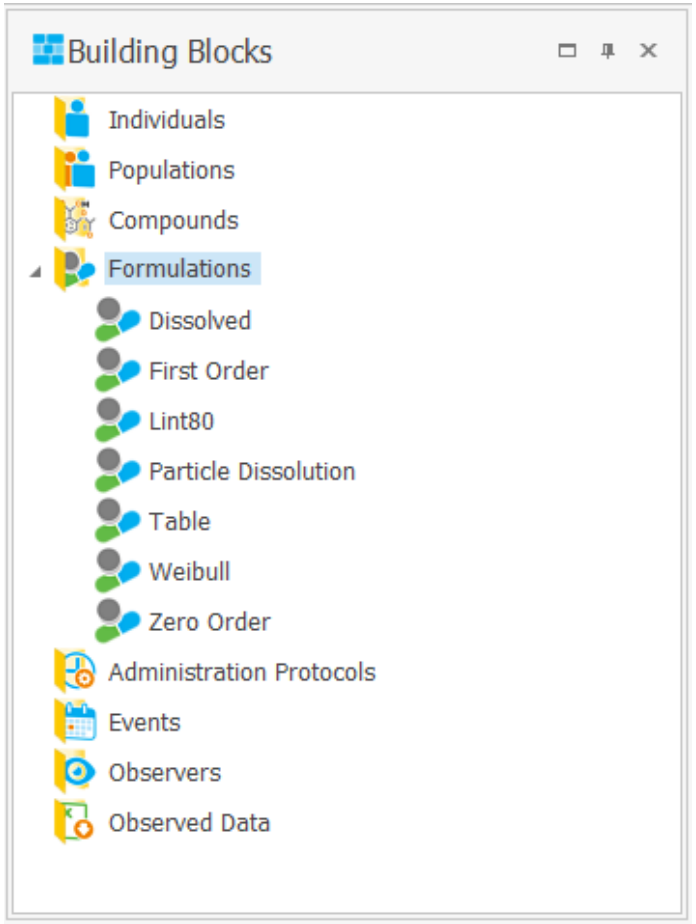




Functionalities – Formulations

Predefined options to define a formulation/drug release function in the Building Block section:

- Dissolved: Drug is administered in solution
- Zero order release: Empirical function assuming zero order release kinetics
- First order release: Empirical function assuming first order release kinetics
- Lint80 release: Empirical function assuming linear release until 80% of the administered dose is dissolved
- Weibull: Empirical function for drug dissolution with high flexibility
- Table read-in: Import of user-defined dissolution/release data
- Particle dissolution: Monodisperse or polydisperse particle distribution (up to 20 bins)



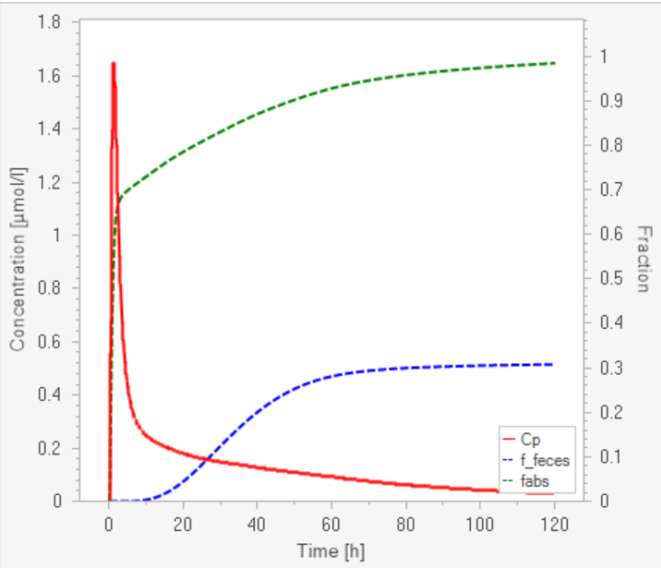
Functionalities – Other

- GET of non-disintegrated moiety
  - Time point at which a Single unit system leaves the stomach and enters duodenum

Name	Compartment	Value
Paracellular absorption sink condition		Sink Condition
Transcellular absorption sink condition		Sink Condition
GET of non-disintegrated moiety	Stomach	60.00 min

- Bi-directional flow over the epithelial
  - Activate possibility for passive secretion from system to lumen
- Bioavailability
  - The bioavailability is only calculated on request. A second simulation with an i.v. short infusion is carried out using identical parameters. The bioavailability is then calculated from AUCinf (p.o.)/AUCinf (i.v.) in the venous blood compartment. May be necessary to simulate as long as the total gastrointestinal transit takes (120 h).
- Fraction excreted in feces
  - For oral administrations, fraction excreted in feces enables an additional assessment of the absorption process

Bioavailability	0.55
Fraction absorbed	0.98



Session 2
- Oral drug absorption modeling PK-Sim®

- Welcome & OSP Intro *(20 min)*
- PK-Sim oral absorption model *(45 min)*

Break 10 min

- **Hands-on exercises**
  - Intro 1 *(5 min)*
  - Establish oral absorption model *(30 min - breakout rooms)*
  - Intro 2 *(5 min)*
  - Formulation performance in virtual populations *(30 min - breakout rooms)*

Break 10 min

- Virtual bioequivalence framework (FDA grant U01FD006549) *(45 min)*

Session 2 - Hands on
Part 1 – Establish oral absorption model

Task: Establish oral absorption model for “Drug” using data after oral solution administration as reference.

Systemic disposition already established.

Information of relevance for oral absorption model development

- Internal data (not shown) suggests
  - Incomplete absorption
  - Gut wall metabolism in small intestine
  - Negligible absorption in colon (colon ascendens - rectum)

If time allows: Investigate transporters and EHC. Reflect on potential impact on systemic disposition

Session 2 - Hands on
Part 2 – Formulation performance in virtual populations

Task: Evaluate formulation performance in virtual population with established model.

- Create a representative trial population (Age, BWT, and HT)
  - Optional: Add variability in metabolism (liver and/or intestine)
- Perform virtual trial simulations for Reference and Test formulations (n=3).
  - Run simulations
  - Assess output visually.

If time allows:

- Evaluate impact of population variability on AUC and Cmax.
  - After intra venous administration
  - After oral administration

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