An introduction to PK-Sim®: the open source platform for PBPK modeling

Sessions #1 through 4

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

Session #1

AIM: ensure participants understand the Open Systems Pharmacology (OSP) Suite as well as have an adequate level of knowledge and practical experience using the PBPK tool, PK-Sim, and its basic functionalities. This session aims to ensure that participants will be able to assimilate subsequent sessions, as these will assume this knowledge.

WHO: recommended for new users of PK-Sim as well as to anyone who needs to revive or complement existing knowledge about OSP.

Andrea Edginton, PhD
'Doing PBPK since 2004'
Hallman Director & Professor
School of Pharmacy
University of Waterloo +
VP, Design2Code Inc.

Paul Malik, PharmD
Doctoral Researcher
Pharmacist
School of Pharmacy
University of Waterloo

Erik Sjögren, PhD
Associate Professor,
Uppsala University +
Senior Consultant
Pharmetheus AB

Chat storm

- Name
- Scientific interest
- Hobby

Andrea Edginton, learning through modeling, cooking (and eating)

Learning Outcomes

1. Lecture on the OSP suite to provide a basic understanding of the software including governance and maintenance since the open-source release
2. Demonstration of how to build a PBPK drug model using PK-Sim including the *scientific basis* for PBPK modeling
3. Hands-on exercises: Task-based training to familiarize participants with the *structure* and *key functionalities* of PK-Sim as well as the modeling *workflow* using this platform

How will this session roll out?

1. OSP – governance and maintenance (10 min)
2. Small molecule structure, definition of terms, scientific basis of parameterization (40 min)
3. Large molecule structure, definition of terms, scientific basis of parameterization (20 min)
4. Open PK-Sim and navigate the workspace, building block philosophy (10 min)
5. Build a PBPK model for an IV administration (40 min)
6. Optimization, sensitivity analysis (20 min)
7. Generating a population and evaluating a population simulation (20 min)

Questions?

1. Put your questions in the chat. I will read as we go and answer verbally, or Paul or Erik will answer in the chat, OR
2. Raise your hand and I will call upon you

Open Systems Pharmacology

Vision

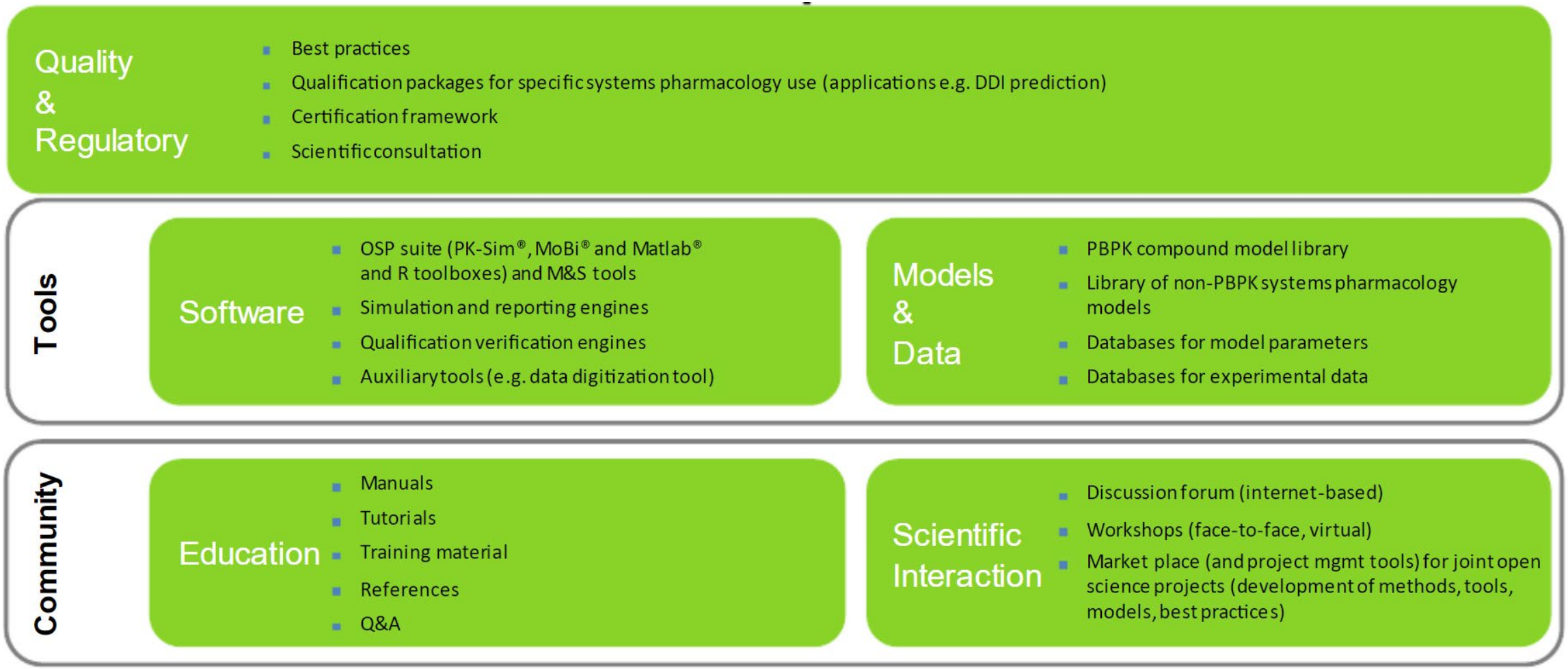
Robust and reliable, easy-to-use modeling & simulation tools, processes and models for pharmaceutical and other life-sciences applications qualified and accepted by a scientific community from academia, regulatory agencies and industry available and open to everyone.

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.

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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

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)

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)

Note Omics and Animal Physiology FGs currently moving through approvals process*

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.

www.open-systems-pharmacology.org

- Download PK-Sim®, MoBi®, GENEDBhuman, Qualification Framework, R-toolbox
- Access source code (if you're savvy like that)
- Find the manuals
- Watch/access tutorials
- Download models (e.g. bupropion model in PK-Sim, dermal absorption model 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)

ESSENTIALS

DOWNLOAD OSP SUITE

Explore the full functionality of the OSP suite. PBPK, PBPK/PD, QSP – the OSP Suite gives you the flexibility to build it all without having to start from scratch.

FORUM

Have your questions answered or provide answers to others. The Forum is a great way to stay up-to-date on the community buzz around OSP.

DOCUMENTATION

Need to find out how to use a feature? Looking to understand the inner workings of the model? Here you'll find the extensive OSP manual and qualification documents.

- How to model a biomarker in MoBi — 6
  #658 opened on Dec 18, 2020 by teutonicod
- Metoprolol-CYP2D6 PBPK Model
  #657 opened on Dec 17, 2020 by SRuedesh
- Reference concentration — 5
  #653 opened on Dec 9, 2020 by shapoo1
- Question about lympha flow and operation about PBPK modeling for large molecule answer question — 2
  #651 opened on Dec 4, 2020 by wangwei1619
- Equations for physiological parameters and PBPK model answer question — 6
  #650 opened on Dec 3, 2020 by hsuanpin
- Measure of variability around PK analysis? — 1
  #649 opened on Nov 30, 2020 by eburg007
- PBPK models of Probenecid and Furosemide to Predict Transporter Mediated Drug-Drug Interactions announcement — 2
  #648 opened on Nov 30, 2020 by HannahBri
- How to set QD in MOBI answer question — 1
  #647 opened on Nov 25, 2020 by csungeun
- Question about the definitions of several parameters (K_water_cell, K_water_int, K_rbc, K_int_pls, permeability and SA_pls_int) answer question — 8
  #646 opened on Nov 25, 2020 by jessechao830330
- How to Apply GFR Formula? answer question — 7
  #645 opened on Nov 24, 2020 by Wenjing1018
- Microdialysis concentrations question — 5
  #644 opened on Nov 20, 2020 by Vichelfer
- Trimethoprim PBPK model announcement
  #643 opened on Nov 18, 2020 by DeniTue
- Is chart editor not available in PK-Sim while conducting population simulations? question — 3
  #641 opened on Nov 15, 2020 by humblewarrior

main · 1 branch · 0 tags · Go to file · Add file · Code

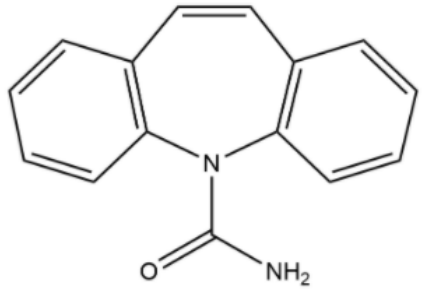
LMFuhr Model snapshot b197419 3 days ago 3 commits

Carbamazepine-Model.json	Model snapshot	3 days ago
README.md	Update README.md	3 days ago

README.md

Carbamazepine-Model

PBPK model of carbamazepine as CYP3A4 and CYP2B6 substrate and inducer



Within this repository we share a whole-body parent-metabolite PBPK model of carbamazepine and its main metabolite carbamazepine-10,11-epoxide. The model was developed using a large number of clinical studies and was evaluated with in a DDI modeling network. The model describes DDIs with carbamazepine as CYP3A4 and CYP2B6 substrate and/or inducer.

For a detailed documentation of model development, quantitative model evaluation and sensitivity analysis, please refer to [1].

Code of conduct

Everyone interacting in the Open Systems Pharmacology community (codebases, issue trackers, chat rooms, mailing lists etc...) is expected to follow the Open Systems Pharmacology code of conduct.

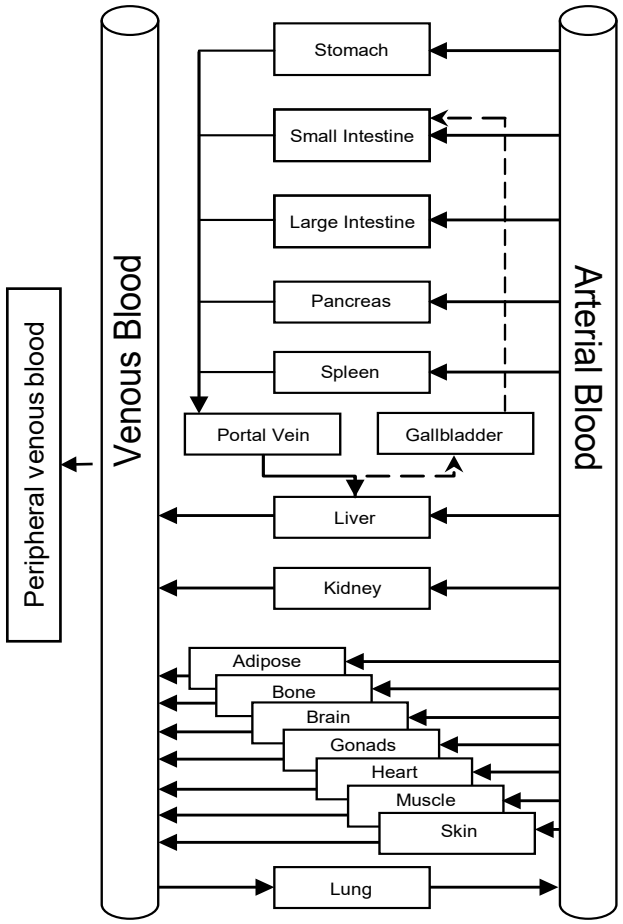
Contribution

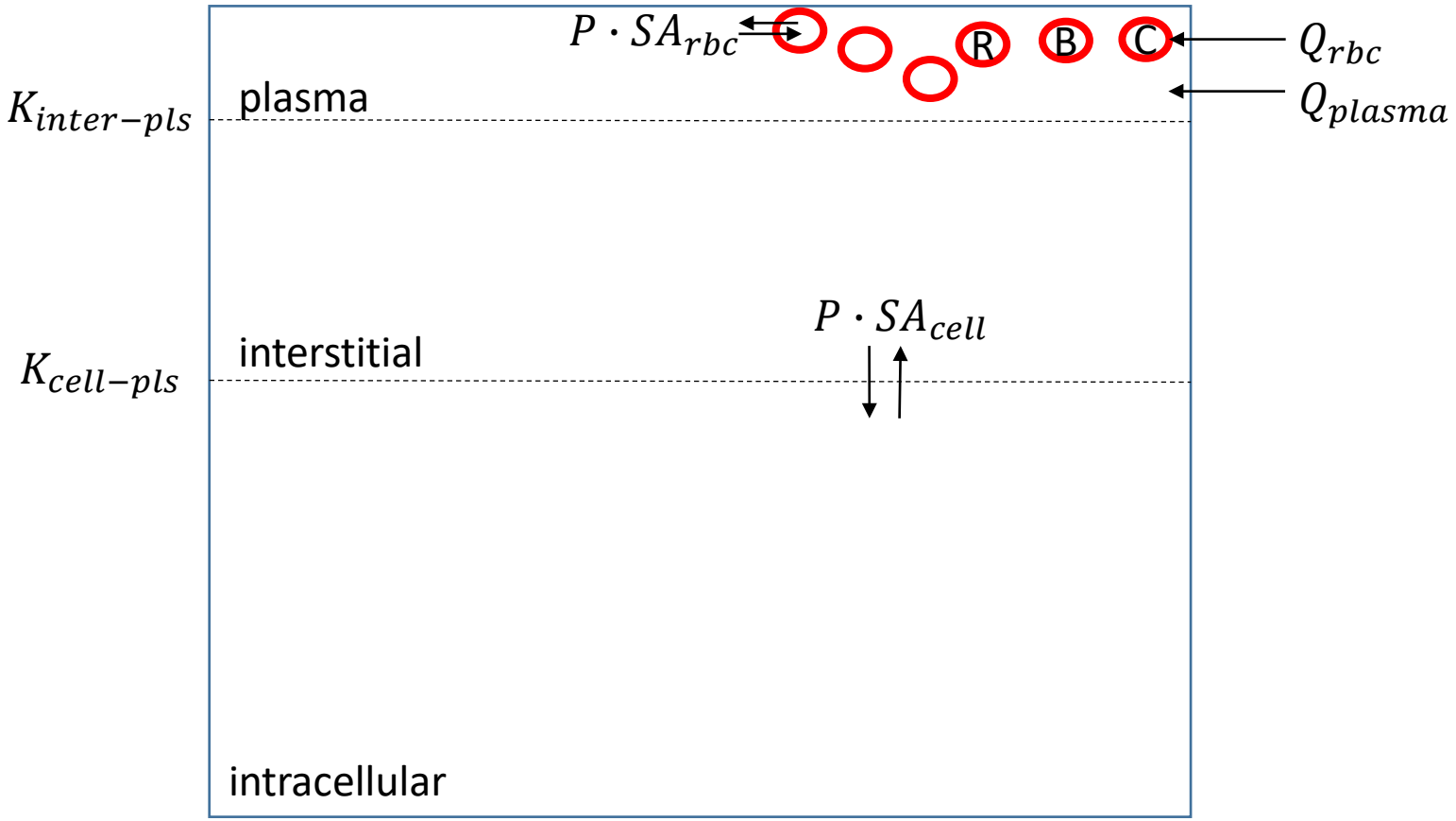
We encourage contribution to the Open Systems Pharmacology community. Before getting started please read the contribution guidelines. If you are contributing code, please be familiar with the coding standard.

The importance of the question!

- Drives workflow
- Drives structure
- Drives parameterization

Small molecule structure <5000 Da





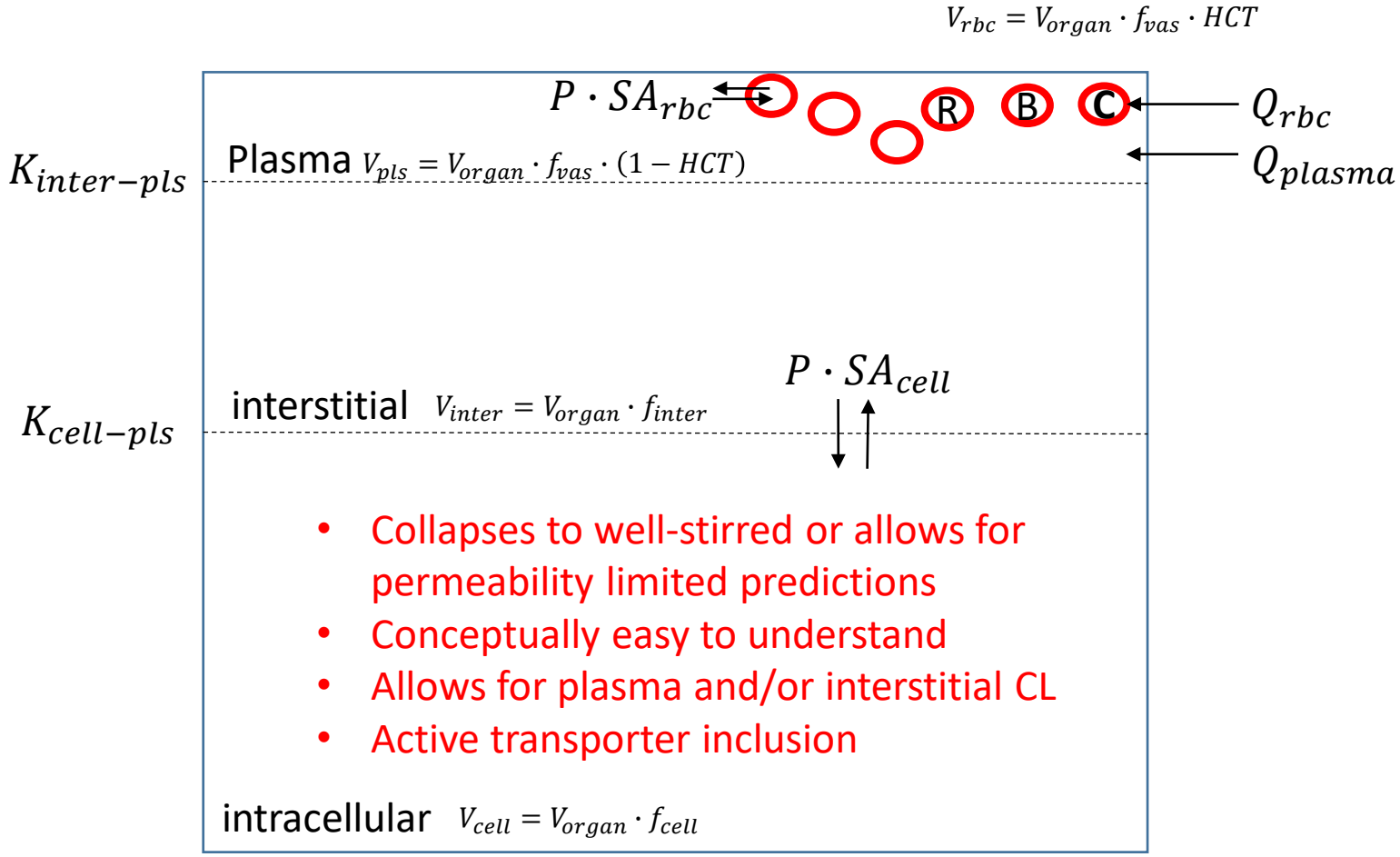
Small molecule structure

$K_{inter-pls}$: partition coefficient defined by binding protein concentration differential across endothelium

$K_{cell-pls}$: defined by tissue: plasma partition coefficient algorithms (tissue composition based: **lipophilicity, charge, fu**)

P: cellular permeability defined by algorithm using **lipophilicity, molecular weight and charge** (predicts permeability-limited vs. well stirred conditions)

SA: Surface area, quantified



Volume of distribution

$$V_{ss} = V_{plasma} + \sum V_{organ} \cdot Kp$$

$$Kp = \frac{fu_{plasma}}{fu_{tissue}}$$

fu_plasma is directly proportional to V for small molecules

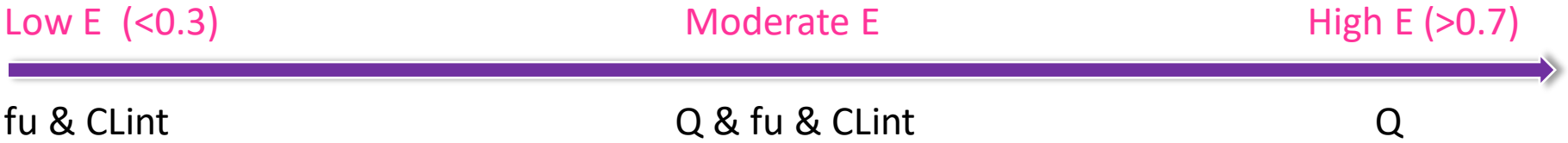
Empirical Kp algorithms vs. ***tissue composition based Kp algorithms***

TCB algorithms based on organ composition and drug phys-chem (lipophilicity, fu, acid/base)

Clearance $AUC = \frac{Dose \cdot F}{total\ CL}$

1. *What is the question?*
2. *How is it cleared or do I care?*
3. *How do I parameterize each process?*
   - Renal – filtration and potentially reabsorption or secretion (CLrenal > or < GFR*fu?)
   - Hepatic – plasma CL, liver microsomes, hepatocytes, recombinants, biliary (with EHC?)
   - Enzyme in plasma
   - Note* specific CL is what is used in all equations which is 'intrinsic CL/volume where the process occurs'

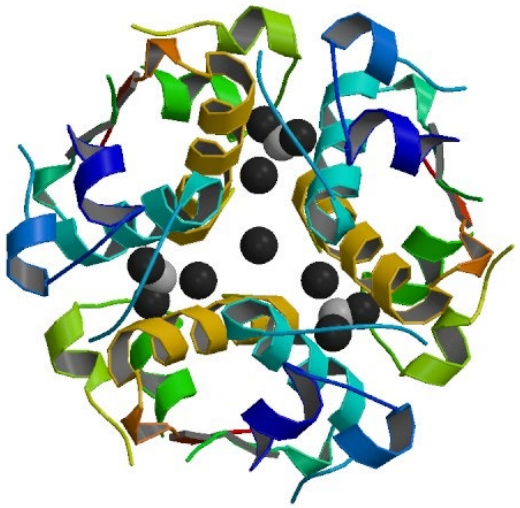
For active processes in organs these principles generally apply: $CL_{organ} = \frac{Q \cdot fu \cdot CL_{int}}{Q + fu \cdot CL_{int}}$



Metabolite tracking

- Clearance of one molecule becomes source of metabolite
- Need a PBPK model for metabolite
- One enzyme can create one or more metabolites
- No limit to the number of metabolites you can track

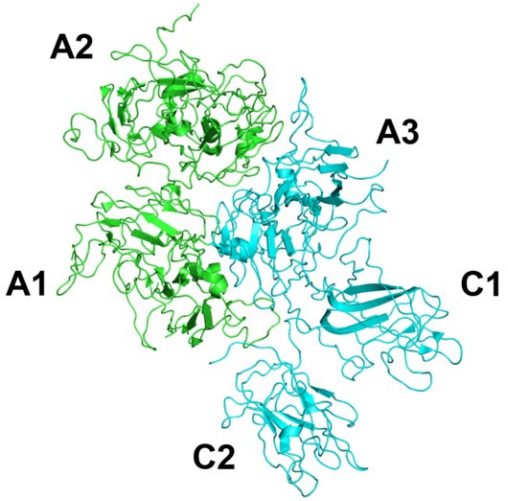
Therapeutic Proteins



Functional Peptides

Insulin Lispro, DrugBank

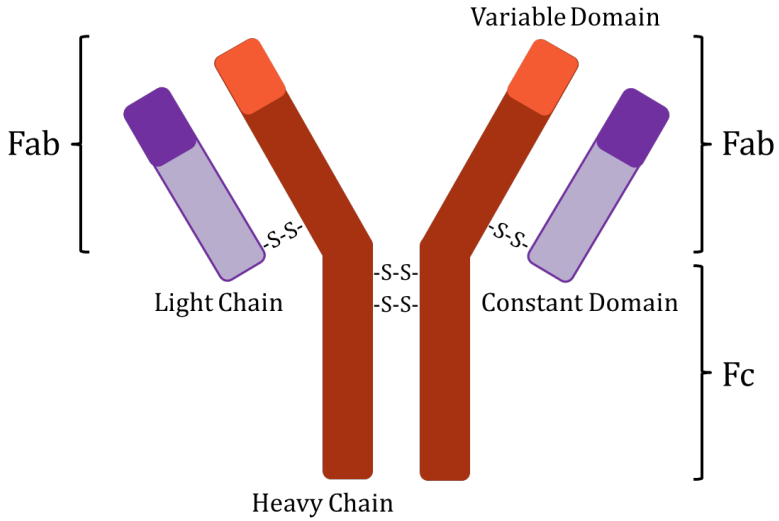
5.8 kDa



Coagulation Factors

Source: Matt Kosloski, 2013

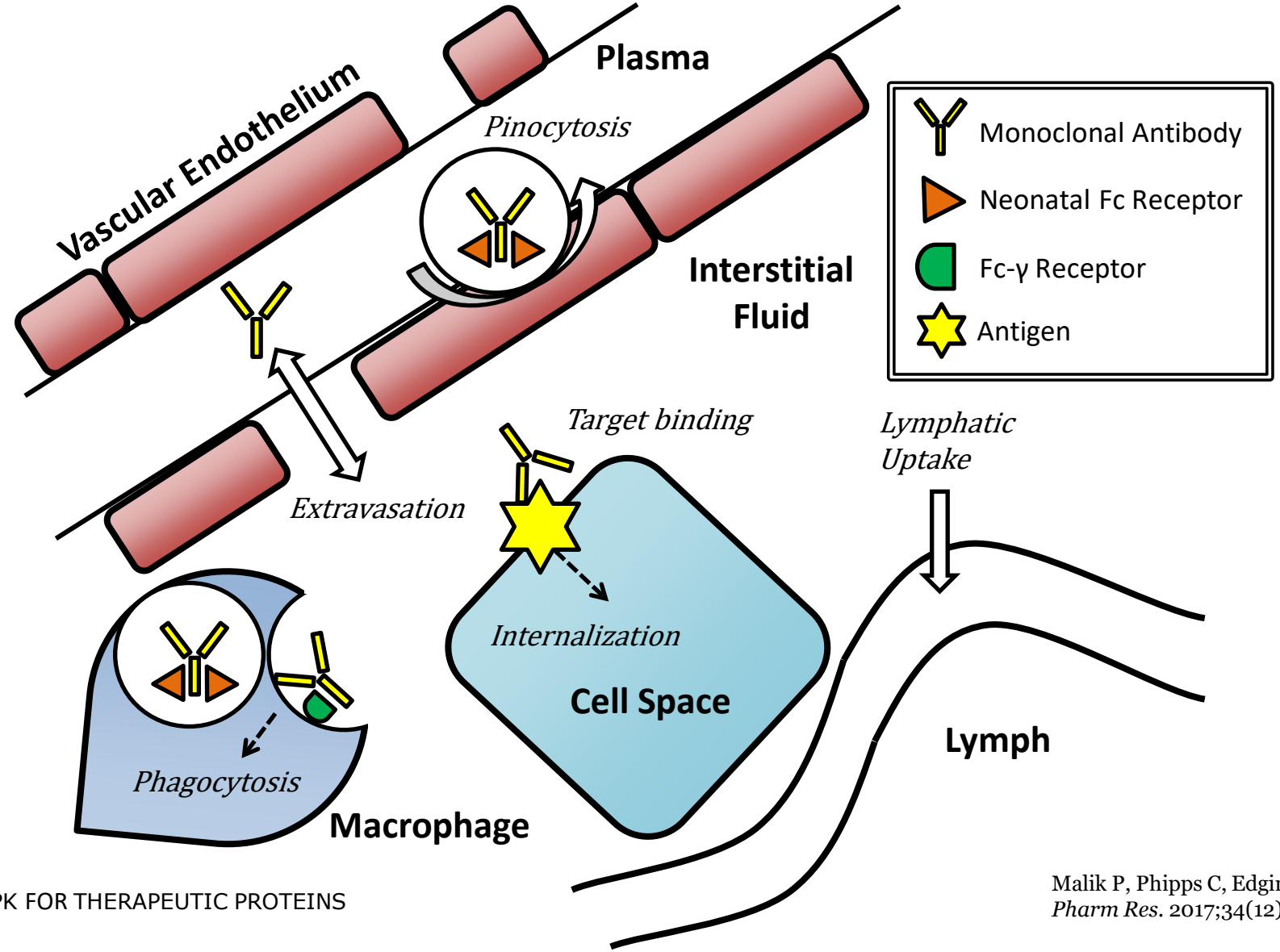
50 – 300 kDa

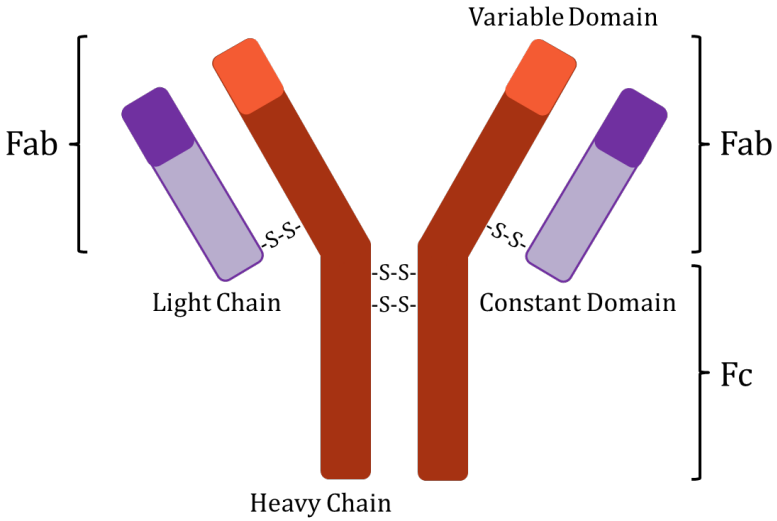


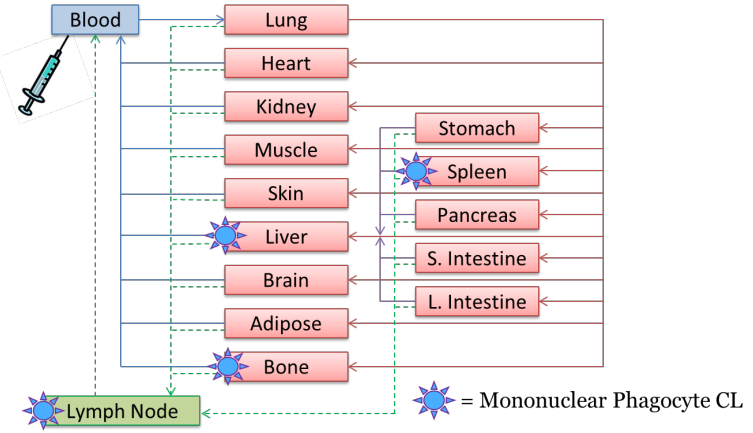
Monoclonal Antibodies

150 kDa

The Big Picture







Malik P, Phipps C, Edginton A, Blay J. *Pharm Res*. 2017;34(12):2579-95.

The Generic Model for Large Molecules

- Created by Niederalt et al., published in 2017 (JPKPD)

<u>Model features:</u>

Two pore extravasation

Lymph flow

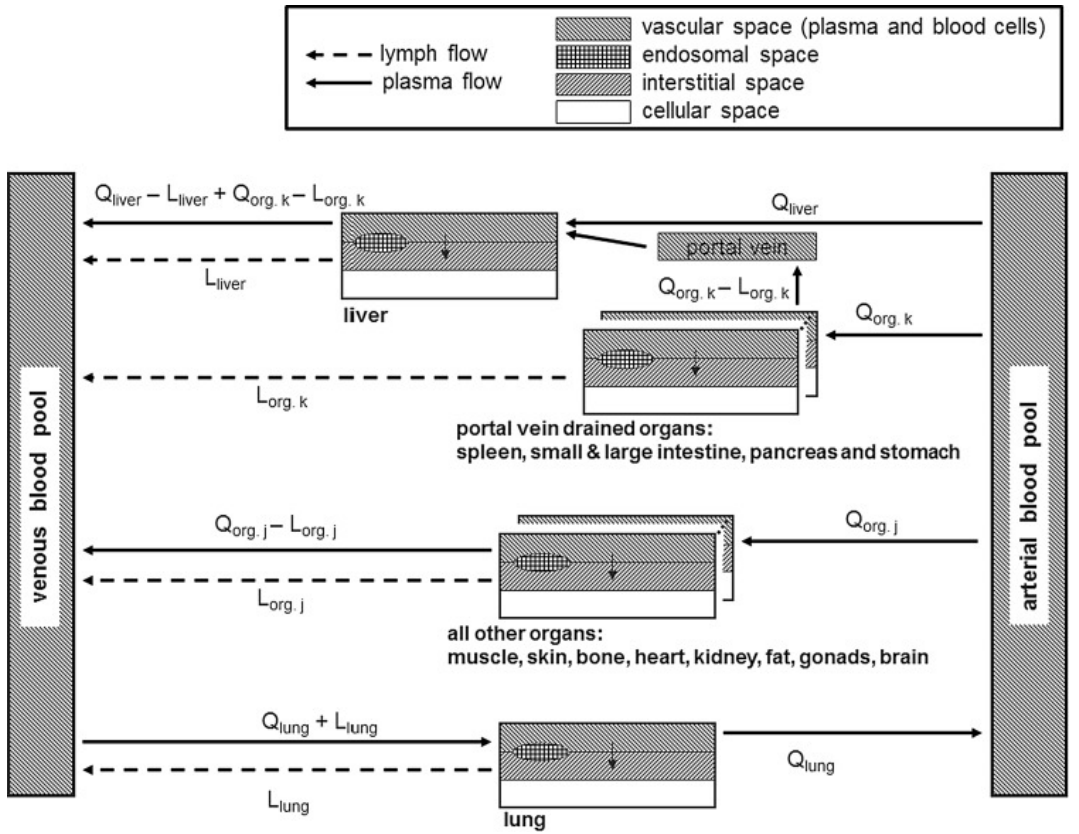
Endosomal clearance

FcRn-mediated recycling

Steady state Endogenous IgG

Fully transparent

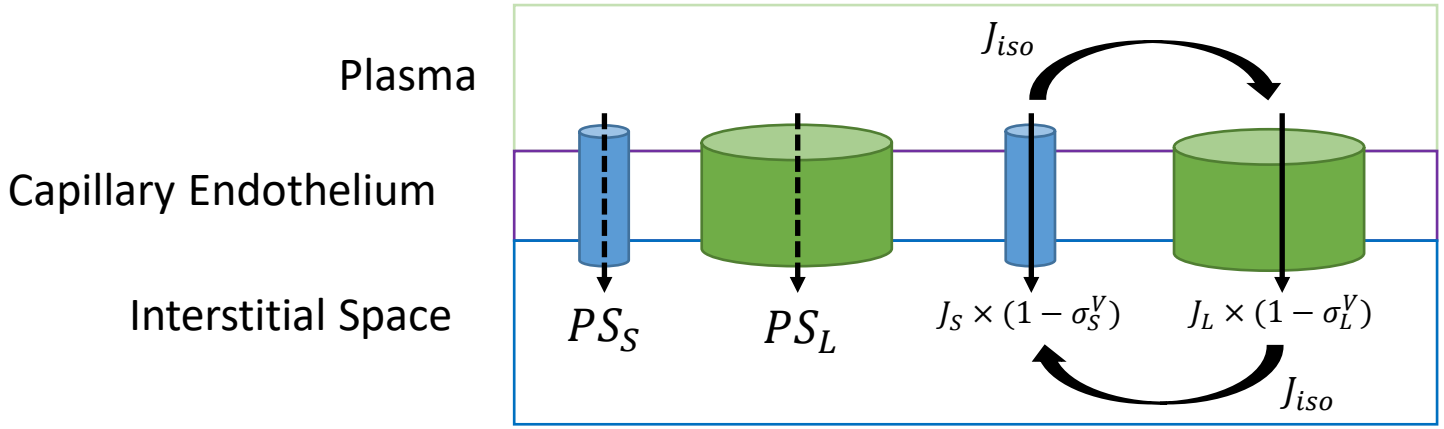
Validated in mouse, monkey, human



Niederalt C, Kuepfer L, Solodenko J, et al. *J Pharmacokinet Pharmacodyn*. 2018;45(2): 235-57.

Extravasation in OSP

- Two pore-formalism describes net flux across capillary beds by convection (lymph outflow, isogravimetric recirculation) and passive diffusion



- Lymph flows and isogravimetric flows are estimated as a fraction of organ plasma flow
- The OSP suite explicitly represents the vascular surface area available for protein exchange (S)

$$S_{org} = k \cdot f_{vas,org} \cdot V_{org}$$

Rippe B, Haraldsson B. *Physiol Rev.* 1994;74(1):163–219.

Extravasation in OSP

Convection *Diffusion*

Two-Pore Model

$$J_{vi,org} = f_u \left(J_{L,org} \cdot (1 - \sigma_{L,org}) \cdot C_{v,org} + PS_{L,org} \cdot \left(C_{v,org} - \frac{C_{i,org}}{K_{iv,org}} \right) \cdot \frac{Pe_{L,org}}{e^{Pe_{L,org}} - 1} \right.$$
$$\left. + J_{S,org} \cdot (1 - \sigma_{S,org}) \cdot C_{v,org} + PS_{S,org} \cdot \left(C_{v,org} - \frac{C_{i,org}}{K_{iv,org}} \right) \cdot \frac{Pe_{S,org}}{e^{Pe_{S,org}} - 1} \right)$$

Reflection Coefficients

$$\sigma_{L,org} = 1 - \frac{(1 - \gamma_{L,org})^2 \cdot [2 - (1 - \gamma_{L,org})^2] \cdot (1 - \gamma_{L,org}/3)}{1 - 1/3 \cdot \gamma_{L,org} + 2/3 \cdot \gamma_{L,org}^2},$$

$$\sigma_{S,org} = 1 - \frac{(1 - \gamma_{S,org})^2 \cdot [2 - (1 - \gamma_{S,org})^2] \cdot (1 - \gamma_{S,org}/3)}{1 - 1/3 \cdot \gamma_{S,org} + 2/3 \cdot \gamma_{S,org}^2}$$

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Literature-informed parameters

Organs	Hydraulic conductivity, Lp (ml/min/N)	Fraction of flow via large pores, α_L	Radius of small pores, r_S (nm)	Radius of large pores, r_L (nm)
Bone	3.24E−04[a]	0.05[h]	4.5[h]	25[h]
Brain	1.80E−06[b]	0.05	4.5	25
Fat	3.24E−04[a]	0.05	4.5	25
Gonads	3.24E−04[a]	0.05	4.5	25
Heart	5.16E−04[b]	0.05	4.5	25
Kidney	4.5E−03[d]	0.05	4.5	25
Large intestine	6.73E−03[e]	0.05	4.5	25
Liver	1.40E−03[c]	0.80[i]	9[i]	33[i]
Lung	2.04E−04[b]	0.05	4.5	25
Muscle	3.24E−04[f]	0.05	4.5	25
Pancreas	1.16E−03[e]	0.05	4.5	25
Skin	7.01E−04[f]	0.05	4.5	25
Small intestine	5.54E−03[e]	0.05	4.5	25
Spleen	1.40E−03[c]	0.80[i]	9[i]	33[i]
Stomach	1.43E−03[e]	0.05	4.5	25

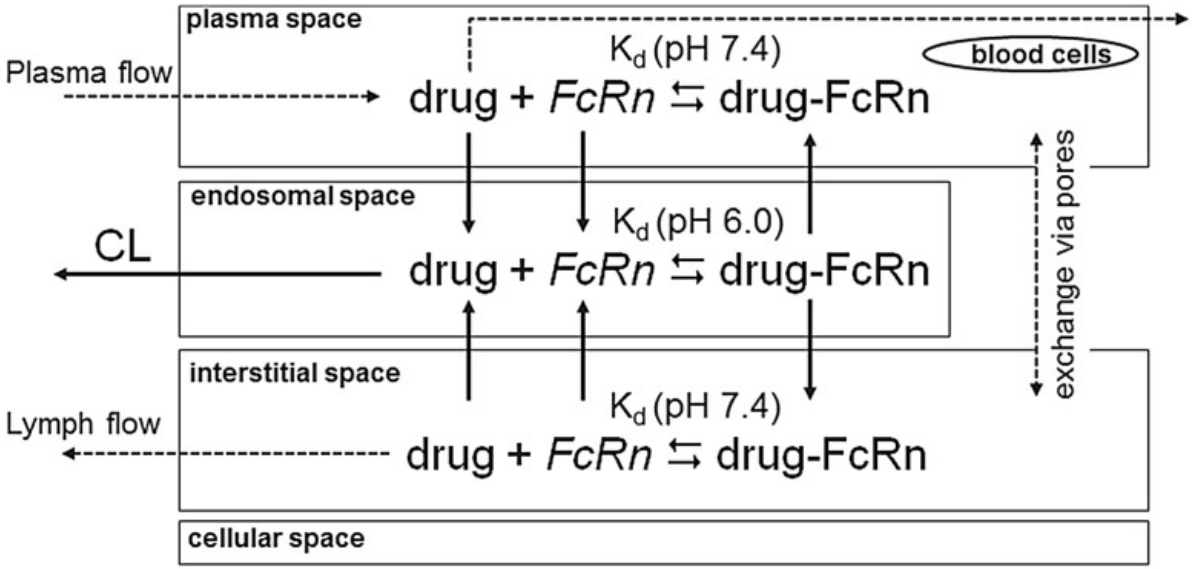
Niederalt C, Kuepfer L, Solodenko J, et al. *J Pharmacokinet Pharmacodyn*. 2018;45(2): 235-57.

Endosomal Clearance in OSP

- Capillary surface area is used to calculate volume of endothelial endosomes

$$V_{endo,org} = f_{endo} \cdot d_e \cdot S_{org}$$

- Cellular uptake is an estimated parameter
- pH-dependent FcRn-binding is represented with first order on and off rates
- Unbound mAb is degraded while FcRn-bound mAb may be recycled to plasma
- Endogenous IgG is present in parallel to compete for FcRn binding



Niederalt C, Kuepfer L, Solodenko J, et al. *J Pharmacokinet Pharmacodyn*. 2018;45(2): 235-57.

Practical Applications

- The generic model was calibrated with mAbs, Fabs and inulin, with a wide spread of hydrodynamic radii (1.39 – 5.34 nm) and Fc-binding properties, including Fc-specialized engineering

- In published literature the model has since been applied for:

Interferon alpha:	Kalra P, Brandl J, Gaub T, et al. *PLoS ONE*. 2019;14(2):e0209587.
Infliximab:	Malik PRV, Edginton AN. *CPT Pharmacometrics Syst Pharmacol.* 2019;8(11):835-44
Palivizumab, Pagibaximab, IVIG, MEDI8897:	Malik PRV, Edginton AN. *J Clin Pharmacol.* 2020;60(4):466-76.
Asunercept:	Hanke N, Kunz C, Thiemann M, et al. *Pharmaceutics*. 2019;11(4):152.
Bevacizumab & Palivizumab:	Basu S, Lien YTK, Vozmediano V. *Front Pharmacol*. 2020;11:868

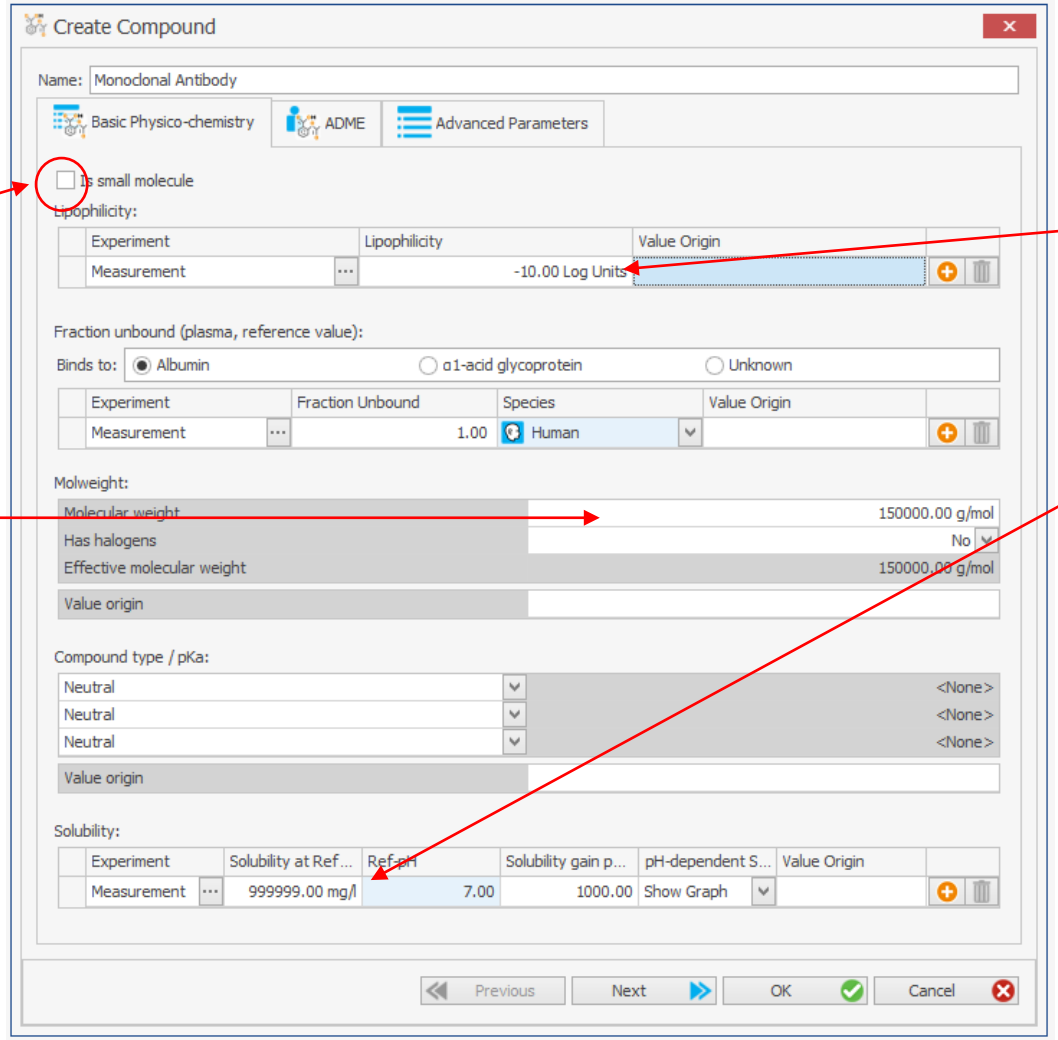
A Quick How To: The Compound Building Block

Uncheck!

Molecular weight is used to calculate hydrodynamic radius

If radius is known, you can enter it in advanced parameters

For all mAbs, radius should be fixed at 5.34 nm

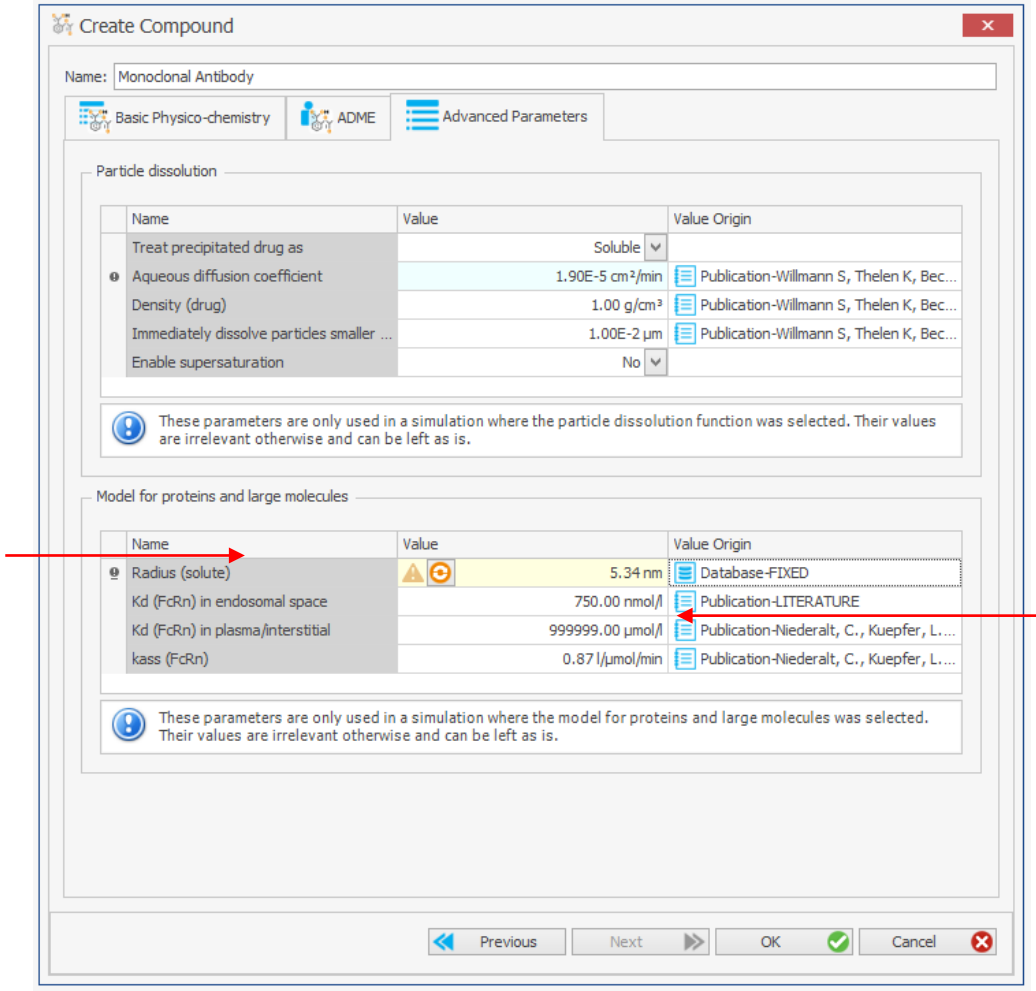


Lipophilicity and solubility are not used in the simulation

All proteins have a fraction unbound of 1 in plasma

A Quick How To: The Compound Building Block

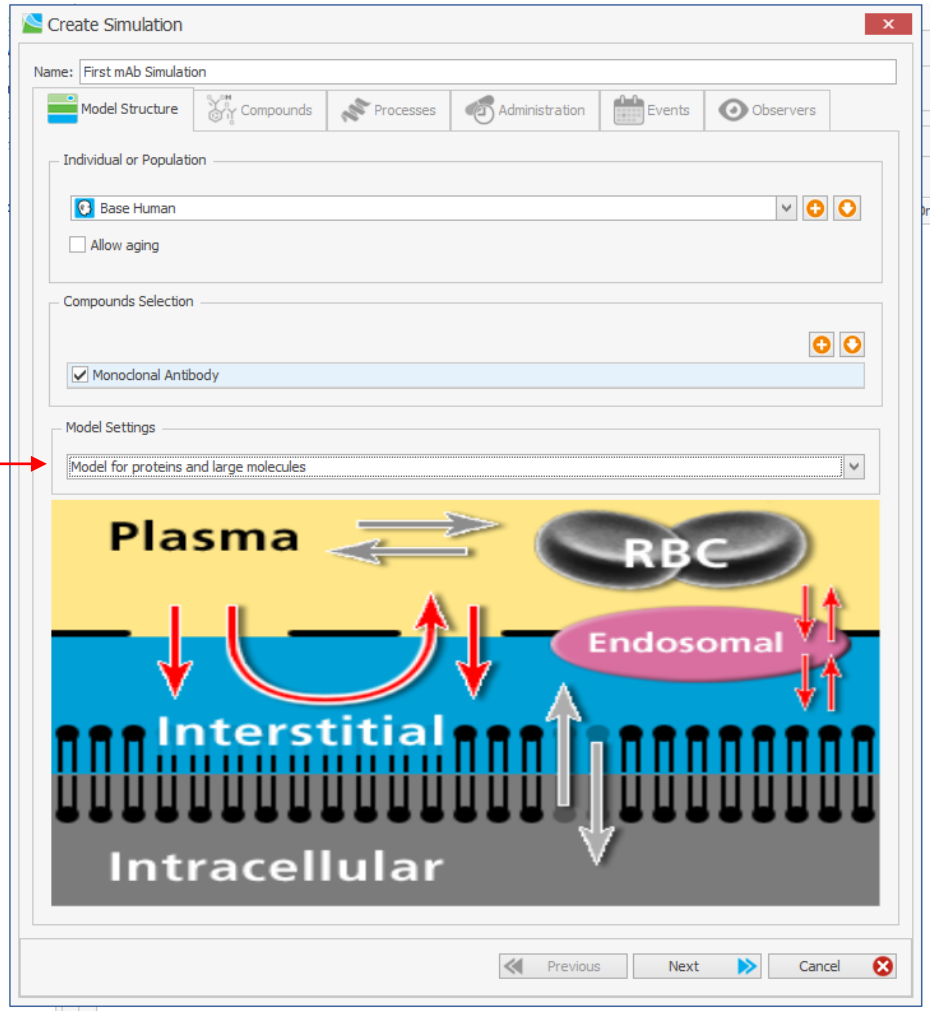
You can override radius here



Set K_D for FcRn binding
K_{on} is fixed
K_{off} will be calculated

A Quick How To: Configuring Your Simulation

Select the large molecule model here!



TMDD or extravascular administration can be added in Mobi…

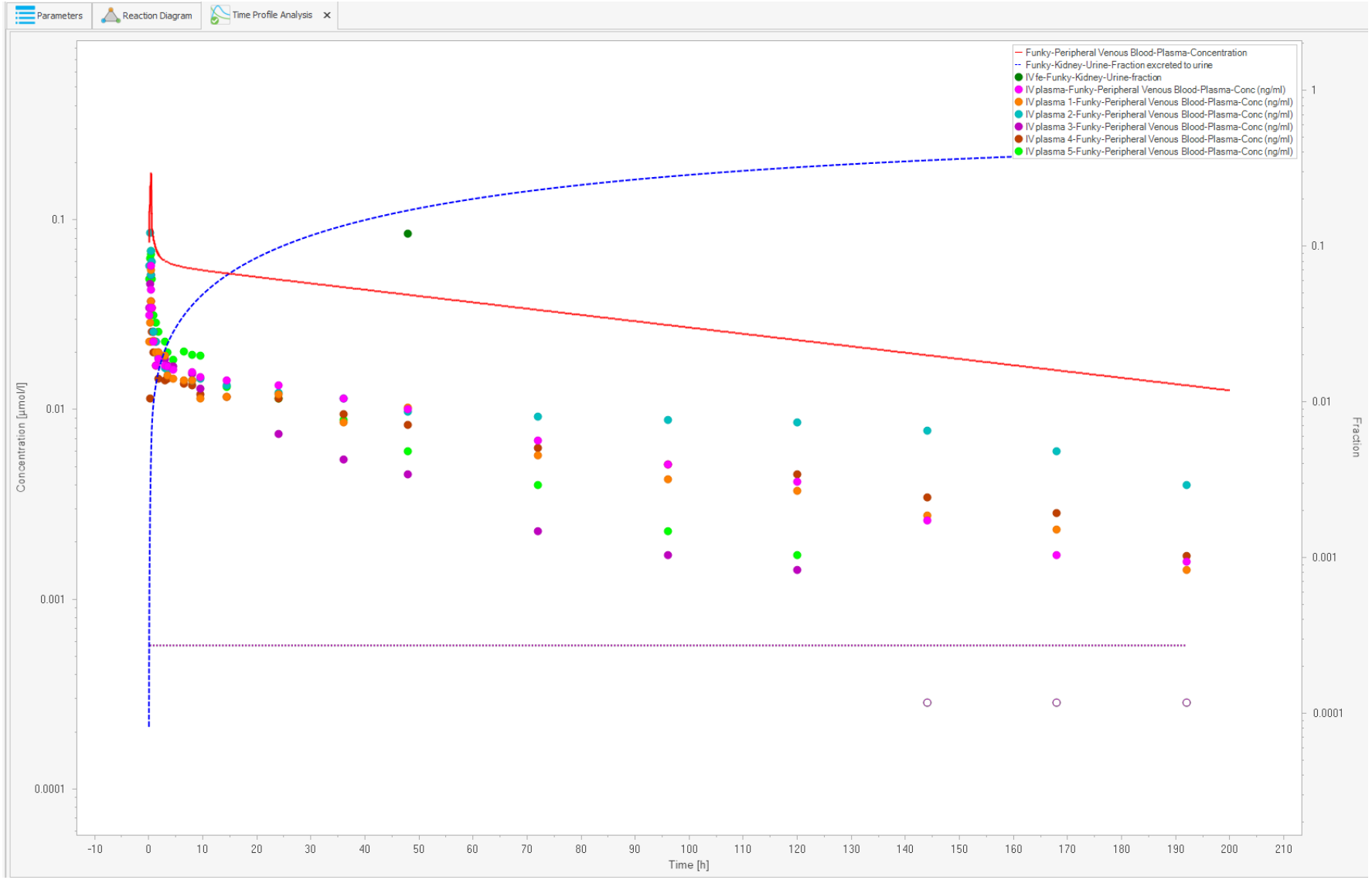
15 min break and breakout rooms

1. OSP management and software development – Erik
2. Small molecule structure/parameterization – Andrea
3. Large molecule structure/parameterization - Paul

Creating a Simulation

- End use of model = pediatric extrapolation
- LogP = 3.5
- 350 g/mol (1F)
- base with pKa=8.7
- water solubility = 200 mg/ml (only used for absorption models)
- fu_plasma_human = 0.04; fu_plasma_rat = 0.06; binding partner AAG
- Hepatic (CYP3A4 – guess CLint = 0.1 L/min)
- Renal (glomerular filtration and tubular secretion – guess Vmax and Km both 1000) with fe=0.12 @ 48H post-IV administration
- Observed adult data = 30-min IV infusion (7.5 mg) administration

This is what you should have for the non-optimized model

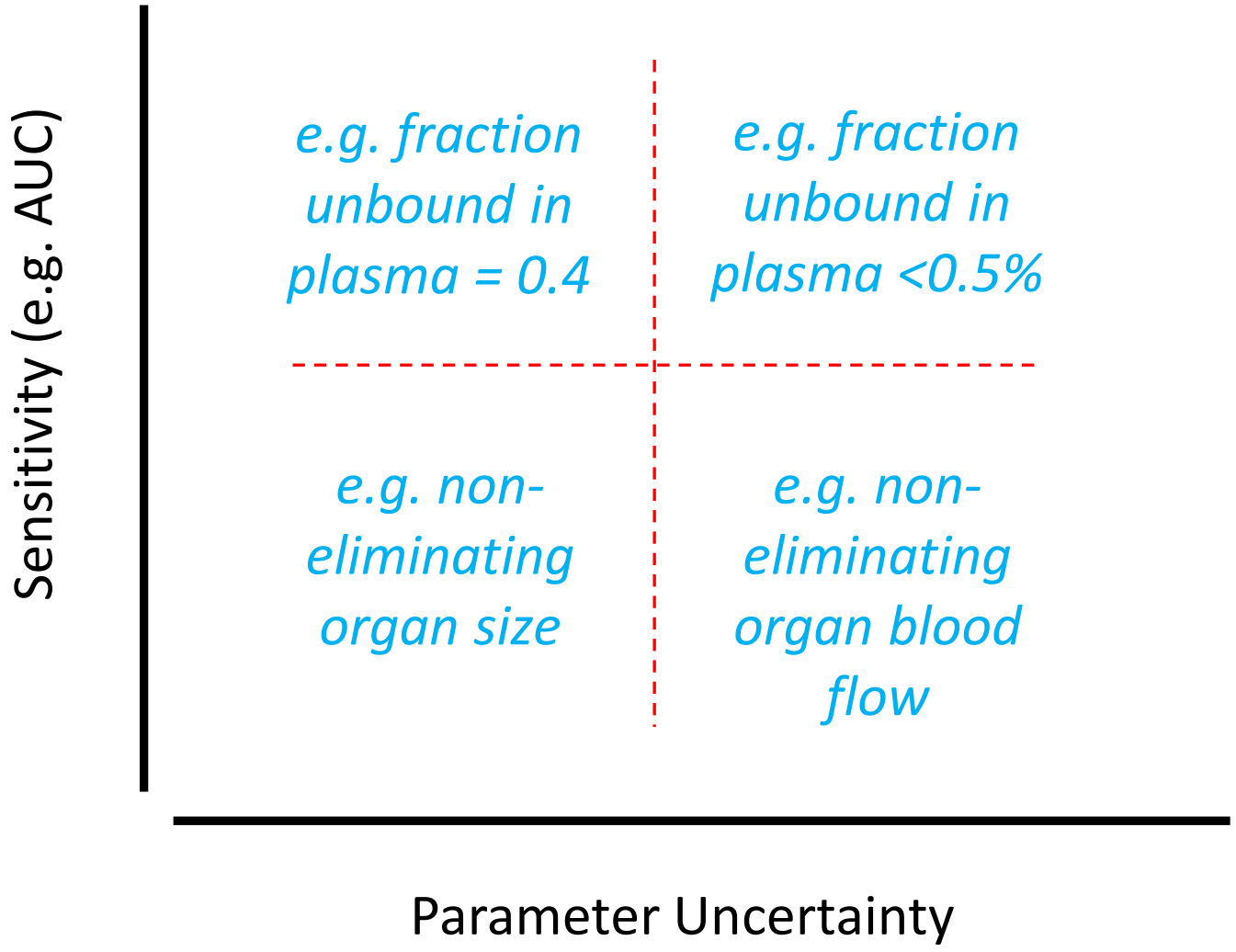


Sensitivity analysis in model development and evaluation

If you care about plasma AUC, you care about all parameters used to calculate **F and CL**

If you care about peaks and troughs, you care about all parameters used to calculate **rate of absorption, F, CL and V**

Model Evaluation: sensitivity & uncertainty

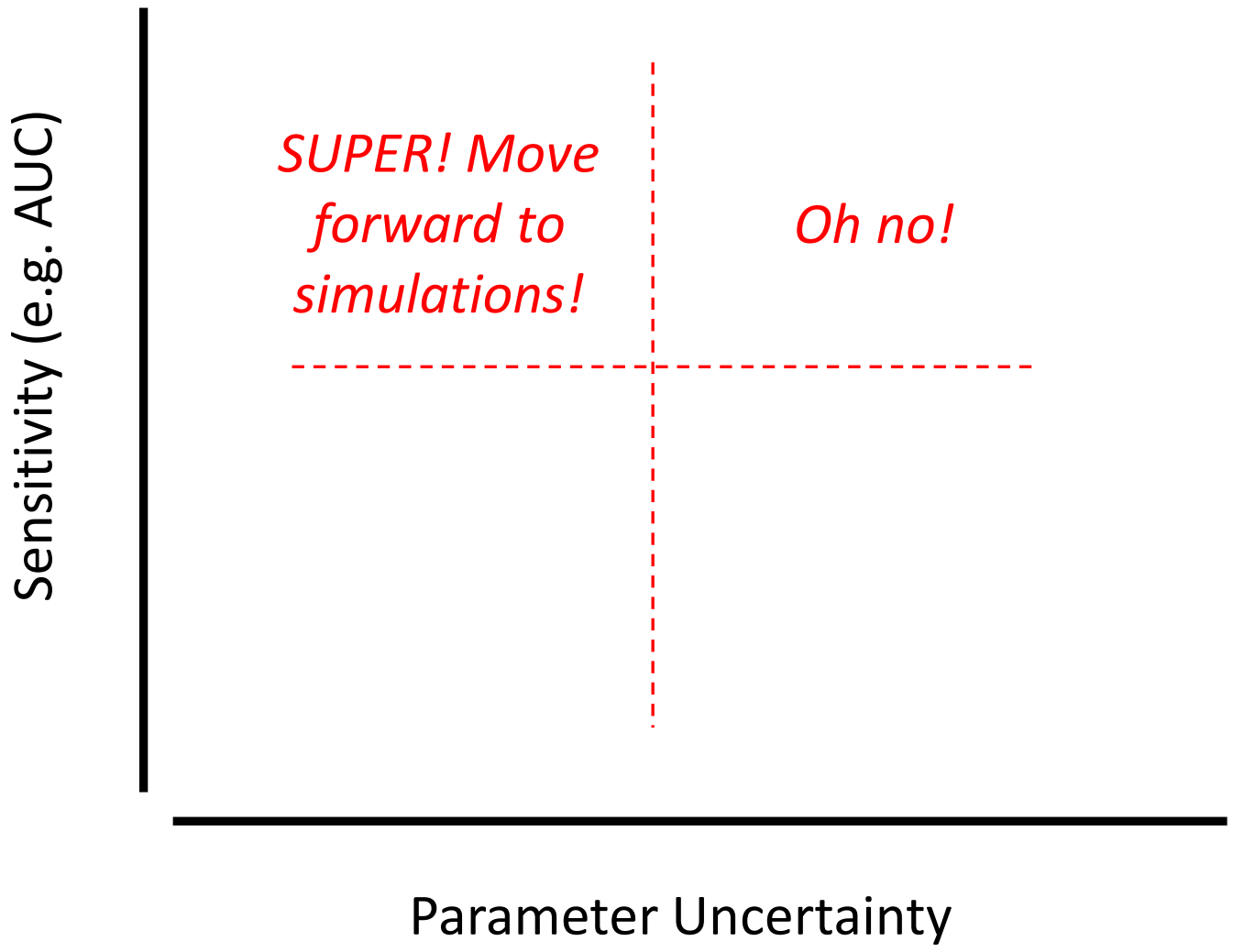


Description of uncertainty and sensitivity: WHO 2010. Characterization and application of physiologically based pharmacokinetic models in risk assessment. IPCS harmonization project document; no. 9.

Methods for sensitivity analysis (Zhang et al. 2016. CPT Pharmacometrics Syst Pharmacol. 4, 69–79)

- Local sensitivity analysis
- Global sensitivity analysis
  - Sobol
  - Partial rank correlation coefficients

Application of uncertainty and sensitivity: Edginton et al. Cancer Chemother Pharmacol. 2016. 77(5):1039-52.

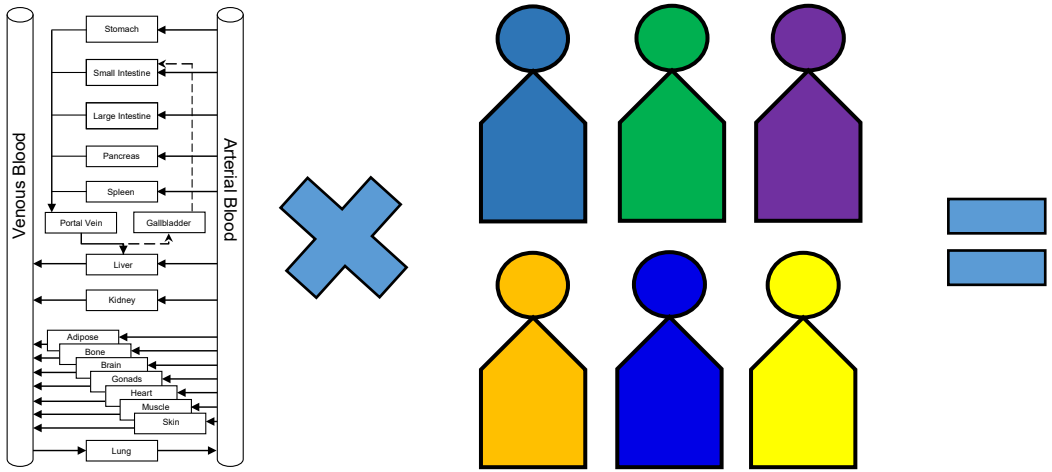


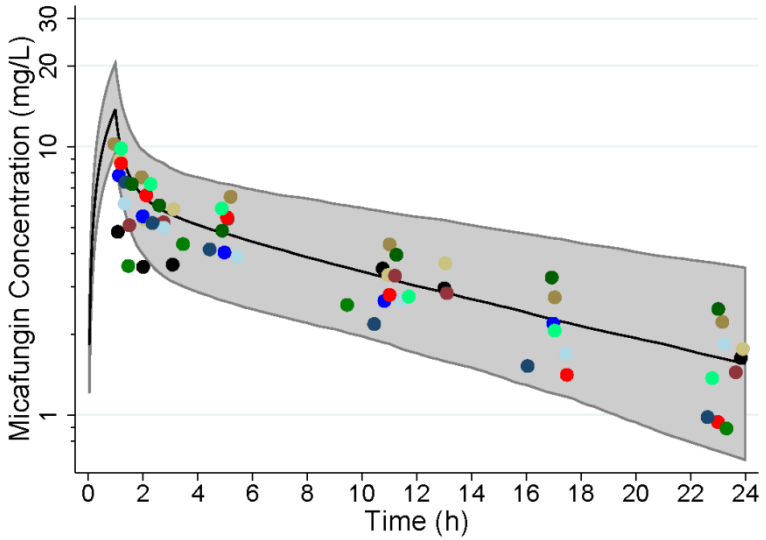
Oh no! can be dealt with by:

1. Benchmarking with another compound that is similar in the parameter/scenario of interest
2. Assessing the implications in the resulting dosing algorithm and altering trial design (dose titration)
3. Experimentation

Population Generation

- **One dose does not fit all**
- It is equally important to consider the variability in PK as well as the mean profile when designing dosage regimens or performing a risk assessment
- With Population PBPK modeling we can understand and predict inter-individual variability in PK as a composite output of inter-individual variability in key input parameters





Population Generation

- **Primary parameters** have anthropometric variability incorporated by default in the OSP suite

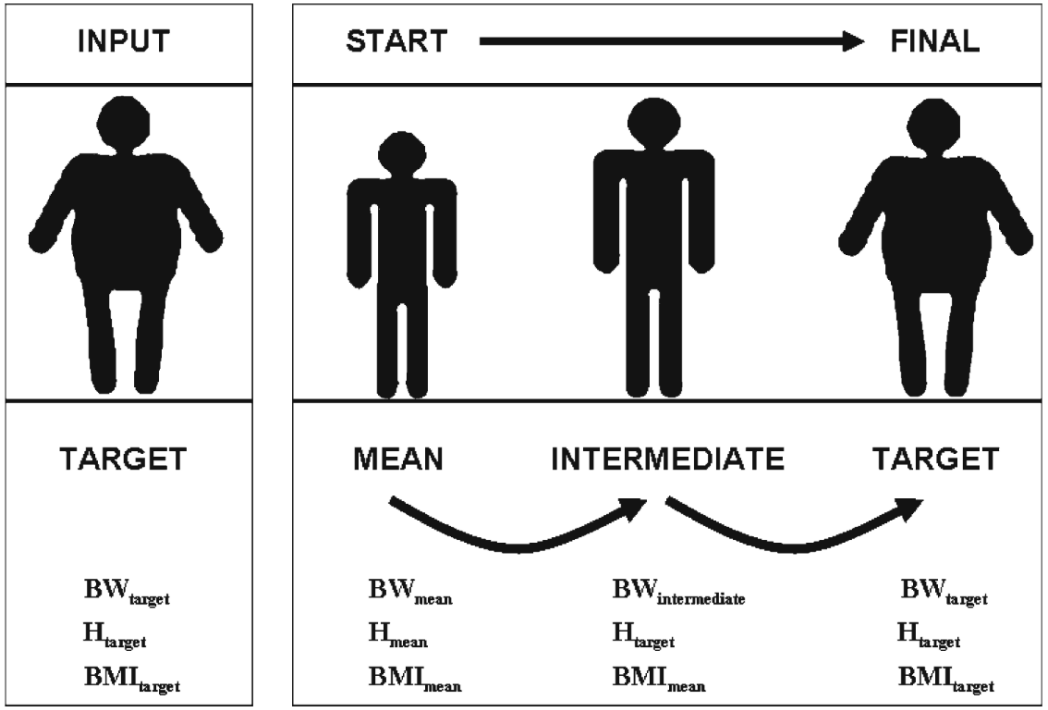
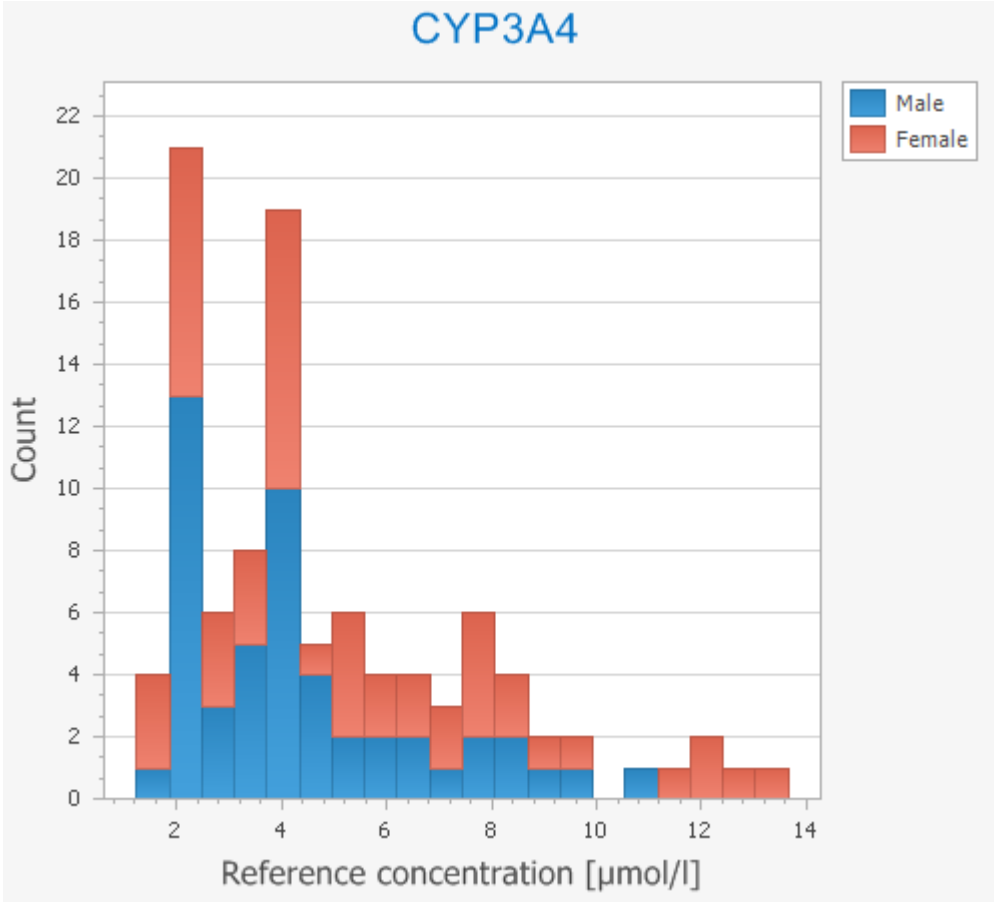


Fig. 1. Process for adjusting a single 'mean' virtual individual to a 'target' individual with a user-defined body weight (BW), height (H) and body mass index (BMI).

- If not already pre-defined in the database, variability in **secondary parameters** must be specified with a mean and SD (*normal distribution*) or geoSD (*lognormal distribution*)



Willmann S, et al. (2007) Journal of pharmacokinetics and pharmacodynamics 34 (3):401-431.