Topic II: Physiology based Pharmakokinetic Modelling

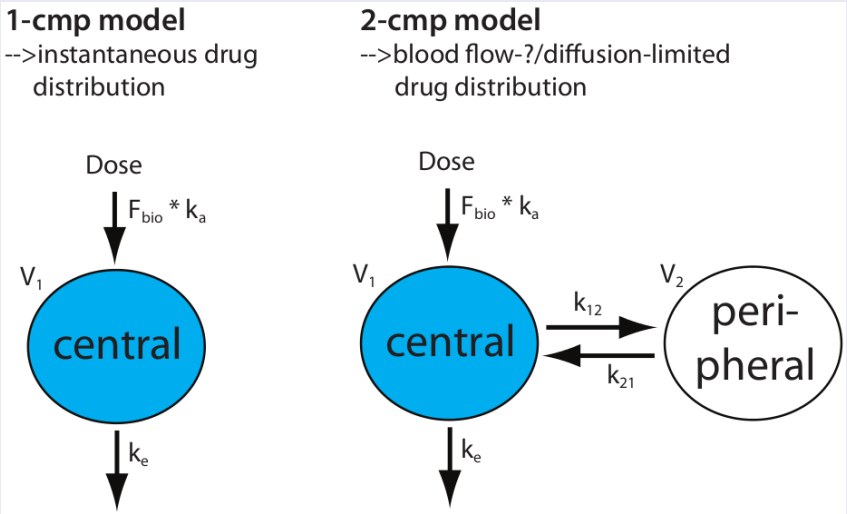
Johanna Tiemann

26.06.2014

Introduction

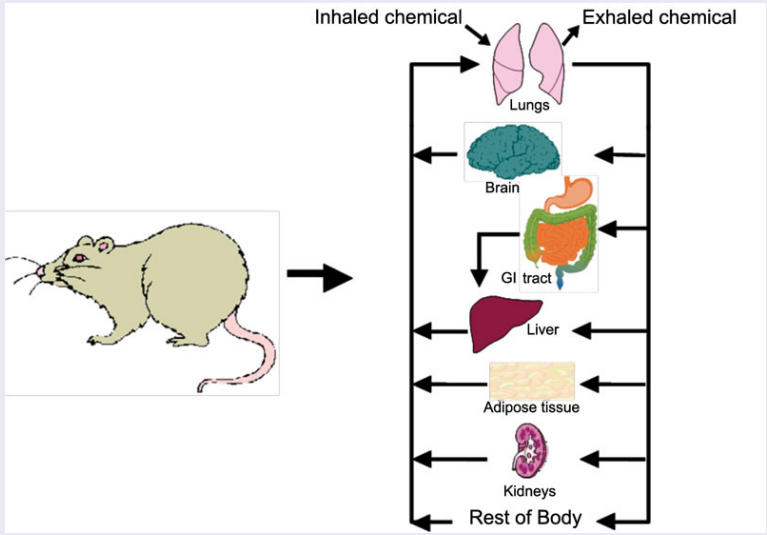
What is PBPK modelling?

PK-Compartment Model



Aim: describing the covariates of variability in drug concentrations ⇒ "What if?"

PBPK-Compartment Model

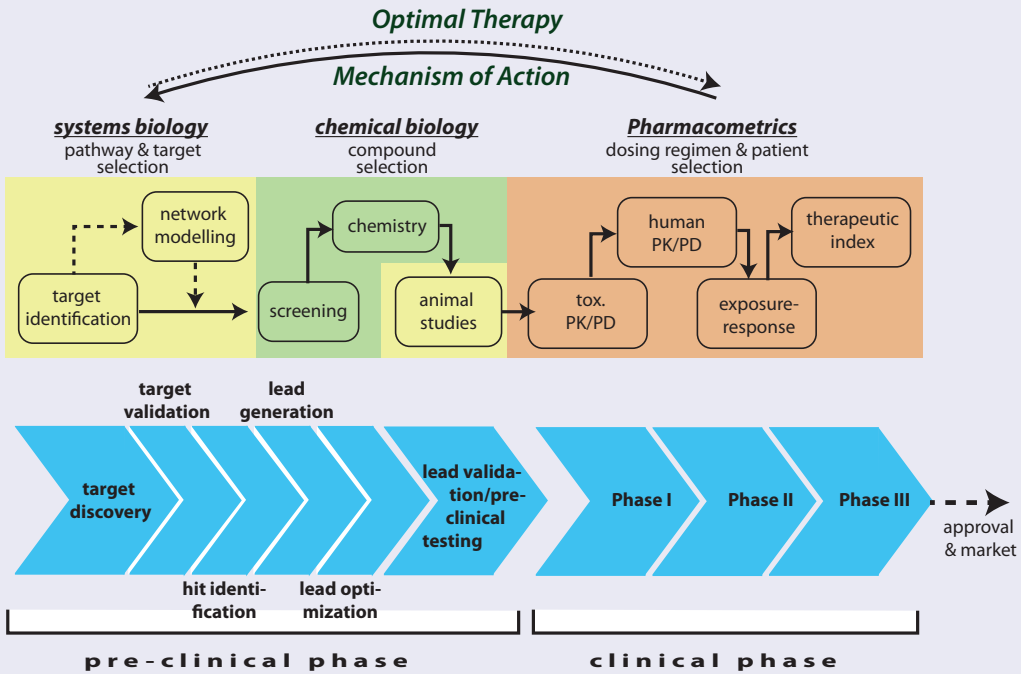


Aim: estimating concentration-time profiles ⇒ "What was?"

Where are we and why using it?

- Drug development:
  - toxicological risk assessment
  - pharmaceutical ingredient development
  - drug-drug-interaction
- Individual/optimal therapy
- Pharmacogenomics
- toxicological guidelines

Workflow Drug-Development



How is the general workflow (ADMET)?

- Specifying the Structure of the PBPK Model:

  ADM target tissue(s) of interest → explicitly modeled

  A drug administration

  D transport process

  M metabolic process

- Specifying the PBPK Model Parameters
  - Chemical-independent & -specific parameters:

    ADM Physiological Parameters

    D Partition Coefficients

- Computational Implementation

(T) Validation of the Model

The Poulin Theil Model Implementation

Prediction of Pharmacokinetics prior to In Vivo studies. II. Generic Physiologically Based Pharmacokinetic Models of Drug Disposition

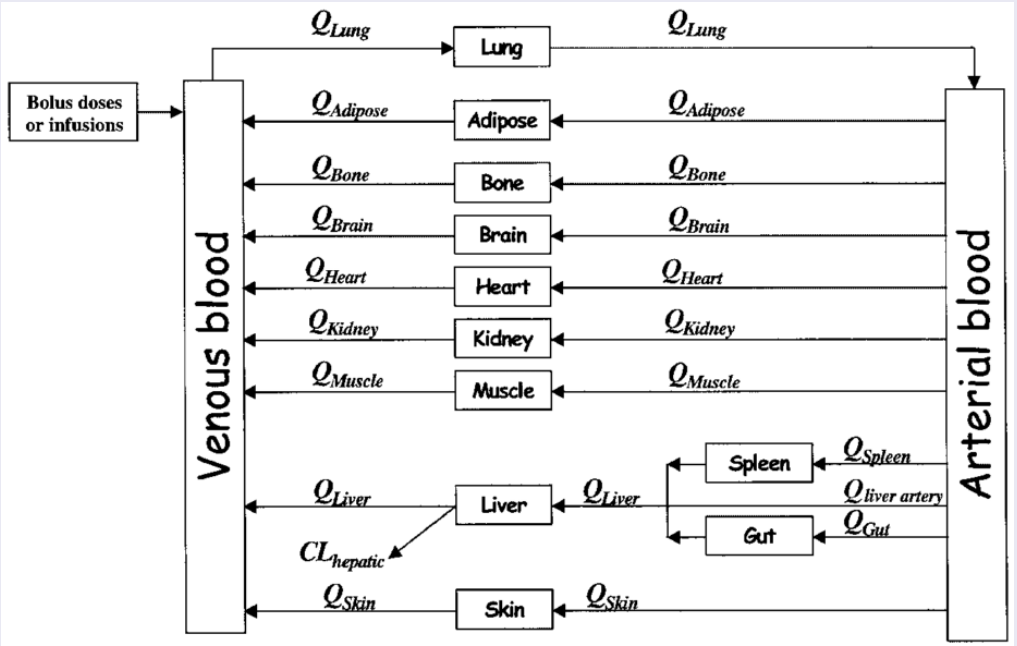
Patrick Poulin & Frank-Peter Theil

- Generic PBPK model for mechanistic evaluations of pharmacokinetics
- used in pharmaceutical industry $\rightarrow$ improve selection & optimization of new drug candidates
- only in vitro & in silico input data $\leftrightarrow$ conventional PBPK models

Core Assumptions of the Model

- A i.v. dosis
- D Distribution over membrane is aimed to be fast/instantaneous
- M over liver (enzymes)

Generic PBPK Model



Implementation of the Poulin Theil Model

General workflow

- Specifying the Structure of the PBPK Model:

ADM target tissue(s) of interest → explicitly modeled

A drug administration

D transport process

M metabolic process

- Specifying the PBPK Model Parameters
  - Chemical-independent & -specific parameters:

ADM Physiological Parameters

D Partition Coefficients

- Computational Implementation

(T) Validation of the Model

Model Framework

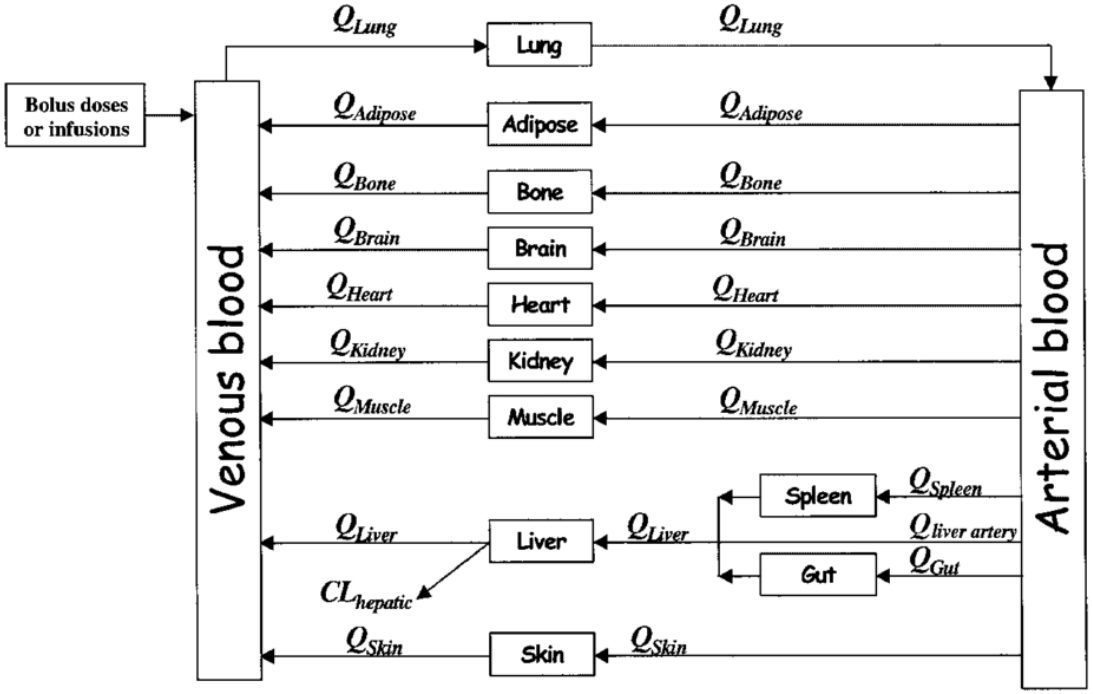
Specifying the Structure of the PBPK Model:

ADM target tissue(s) of interest: Stoichiometric matrix

A drug administration: bolus dosis

D transport process

M metabolic process



General workflow

- Specifying the Structure of the PBPK Model:
  - ADM target tissue(s) of interest → explicitly modeled
    - A drug administration
    - D transport process
    - M metabolic process
- Specifying the PBPK Model Parameters
  - Chemical-independent & -specific parameters:
    - ADM Physiological Parameters
      - D Partition Coefficients
- Computational Implementation

(T) Validation of the Model

Mass Balance Differential Equations of Drug Disposition

D non-eliminating Tissue (Adipose, Bone, Brain, Heart, Kidney, Muscle, Skin):

- $dC_t/dt = [(Q_t * (C_{ab} - C_{vbt}))/V_t]$
- $C_{vbt} = C_t/(P_{t:p}/B{:}P)$
- $\Rightarrow$
- Arterial Blood $\xrightarrow{Q_t}$ Tissue
- Tissue $\xrightarrow{B:P * Q_t / P_{t:p}}$ Venous Blood

Mass Balance Differential Equations of Drug Disposition

D non-eliminating Tissue (Adipose, Bone, Brain, Heart, Kidney, Muscle, Skin):

- $dC_t/dt = [(Q_t * (C_{ab} - C_{vbt}))/V_t]$
- $C_{vbt} = C_t/(P_{t:p}/B{:}P)$
- $\Rightarrow$
- Arterial Blood $\xrightarrow{Q_t}$ Tissue
- Tissue $\xrightarrow{B:P * Q_t/P_{t:p}}$ Venous Blood

Mass Balance Differential Equations of Drug Disposition

DM eliminating Tissue (Liver):

- $dC_h/dt = [((Q_{li}\text{-}Q_{gu}\text{-}Q_{sp})*C_{ab}+(Q_{gu}*C_{vbgu}+Q_{sp}*C_{vbsp}+Q_{li}*C_{vbli}))/V_h - [(((Q_{li}\text{-}Q_{gu}\text{-}Q_{sp})*C_{ab}+(Q_{gu}*C_{vbgu}+Q_{sp}*C_{vbsp}))*E_{li})]/V_{li}]$
- $C_{vbt} = C_t/(P_{t:p}/B{:}P)$
- $\Rightarrow$
- Arterial Blood $\xrightarrow{Q_{li}-Q_{gu}-Q_{sp}}$ Liver
- Arterial Blood $\xrightarrow{E*(Q_{li}-Q_{gu}-Q_{sp})}$ Elimination
- Gut $\xrightarrow{B:P*Q_{gu}/P_{gu:p}}$ Liver
- Gut $\xrightarrow{E*(B:P*Q_{gu}/P_{gu:p})}$ Elimination
- Spleen $\xrightarrow{B:P*Q_{sp}/P_{sp:p}}$ Liver
- Spleen $\xrightarrow{E*(B:P*Q_{sp}/P_{sp:p})}$ Elimination
- Liver $\xrightarrow{c_{li}*B:P*Q_{li}/P_{li:p}}$ Venous Blood

Mass Balance Differential Equations of Drug Disposition

DM eliminating Tissue (Liver):

- $dC_h/dt = [((Q_{li}\text{-}Q_{gu}\text{-}Q_{sp})*C_{ab}+(Q_{gu}*C_{vbgu}+Q_{sp}*C_{vbsp}+Q_{li}*C_{vbli}))/V_h - [(((Q_{li}\text{-}Q_{gu}\text{-}Q_{sp})*C_{ab}+(Q_{gu}*C_{vbgu}+Q_{sp}*C_{vbsp}))*E_{li})]/V_{li}]$
- $C_{vbt} = C_t/(P_{t:p}/B{:}P)$
- $\Rightarrow$
- Arterial Blood $\xrightarrow{Q_{li}-Q_{gu}-Q_{sp}}$ Liver
- Arterial Blood $\xrightarrow{E*(Q_{li}-Q_{gu}-Q_{sp})}$ Elimination
- Gut $\xrightarrow{B{:}P*Q_{gu}/P_{gu:p}}$ Liver
- Gut $\xrightarrow{E*(B{:}P*Q_{gu}/P_{gu:p})}$ Elimination
- Spleen $\xrightarrow{B{:}P*Q_{sp}/P_{sp:p}}$ Liver
- Spleen $\xrightarrow{E*(B{:}P*Q_{sp}/P_{sp:p})}$ Elimination
- Liver $\xrightarrow{c_{li}*B{:}P*Q_{li}/P_{li:p}}$ Venous Blood

Parameters from Clinical Data/Prediction

	Physiological Data		Predicted Tissue:Plasma Ratio ($P_{t:p}$)		
Tissues	B-F Rates (Q_t)	Vol. (V_t)	Diazepam	Ethoxybenzamide	Propranolol
Adipose	0.07	0.076	12.09	0.61	0.18
Bone	0.122	0.04148	6.03	0.53	6.90
Brain	0.2	0.0057	11.82	0.99	13.54
Gut	0.131	0.027	7.20	0.82	8.22
Heart	0.049	0.0033	3.87	0.77	4.38
Kidney	0.141	0.0073	4.59	0.79	5.18
Liver	0.175	0.0366	4.99	0.74	5.67
Lung	1	0.005	5.62	0.82	6.46
Muscle	0.278	0.404	2.89	0.72	3.20
Skin	0.058	0.19	6.32	0.72	7.22
Spleen	0.02	0.002	2.65	0.73	2.98
Art.l blood	-	0.0272	-	-	-
Ven. blood	-	0.0544	-	-	-
Extr. ratio	-	-	0.851	0.082	0.985

General workflow

- Specifying the Structure of the PBPK Model:
  - ADM target tissue(s) of interest → explicitly modeled
    - A drug administration
    - D transport process
    - M metabolic process
- Specifying the PBPK Model Parameters
  - Chemical-independent & -specific parameters:
    - ADM Physiological Parameters
      - D Partition Coefficients
- Computational Implementation

(T) Validation of the Model

Computational Implementation

+ Reaction = Source-Compartment * Mass-Balance-Equation
+ simulation time
+ dose = (initial values + dose in dosing compartment)/Volume

---

$\Rightarrow$ run ODE-Solver(Reaction, SimTime, dose)

Results

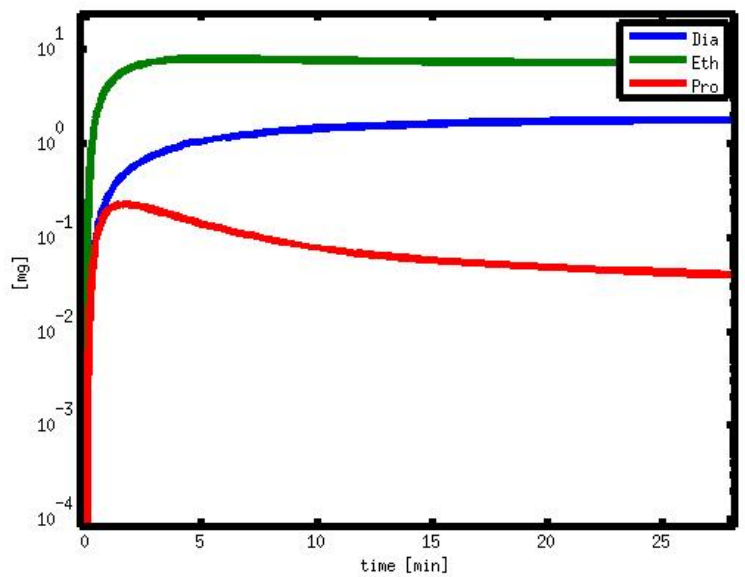
Comparison of different pharmaceutical ingredients

- Diazepam:
  - sophoric/epileptic seizures
  - lipophilic
  - target tissue: brain
- Propranolol:
  - beta-blocker
  - lipophilic
  - target tissue: heart
- Ethoxybenzamide:
  - analgesic
  - neutral/hydrophilic
  - target tissue: brain

Comparison of different pharmaceutical ingredients

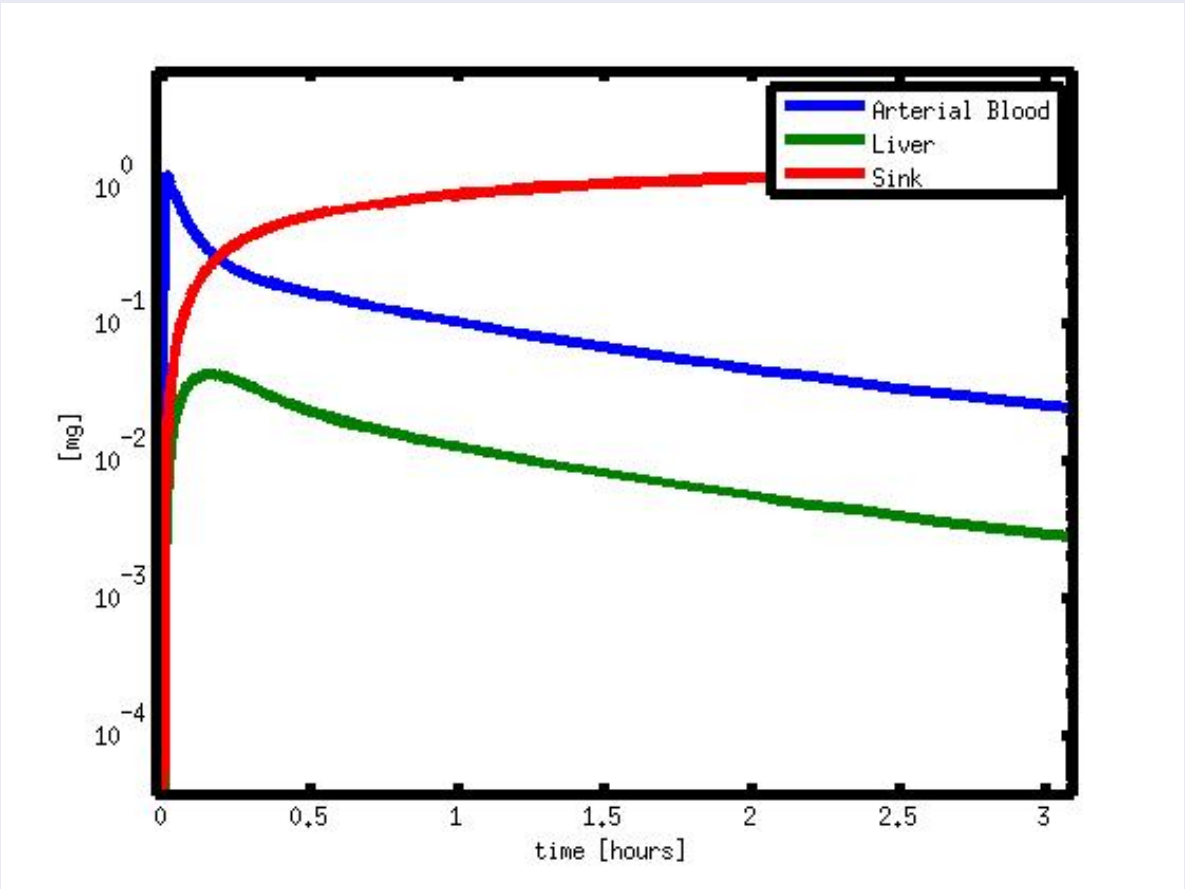
- Diazepam:
  - sophoric/epileptic seizures
  - lipophilic
  - target tissue: brain
- Propranolol:
  - beta-blocker
  - lipophilic
  - target tissue: heart
- Ethoxybenzamide:
  - analgesic
  - neutral/hydrophilic
  - target tissue: brain

Concentration-Time profile of the Adipose Tissue.



Illustrate mechanisms of a drug and tissues

Concentration-Time profile of Propranolol.



Extrapolation

$\Rightarrow$

- adapt Volumes, Blood-Flow-Rates(Q_t) and Clearance

Extension: Oral Absorption

A extra compartment: e.g. Intake/Absorption (Dose $\xrightarrow{F_{bio} * k_a}$ Venous blood)

Discussion

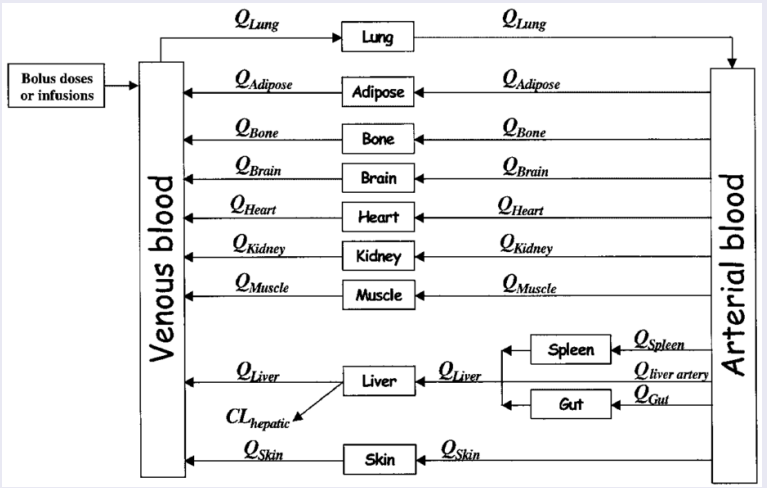
What are they good for?

+ Comparison of different agents & tissues
+ Learn more about mechanisms & ambiguous reactions
+ fast extrapolation & easily extendible
+ coupling to system biology
+ parameters from independent experiments / literature or estimated from in vitro data $\rightarrow$ no need for data from expensive in vivo studies

Core Assumptions of the Model - Review

- A i.v. dosis
- D Distribution over membrane is aimed to be fast/instantaneous
  - unexpected distribution & clearance processes under in vivo conditions (V_{max} & K_m)
  - permeability lowered (e.g. by barriers)
- M metabolism over liver (enzymes)
  - Too simple mechanistic of too complex compartment: metabolic clearance only present in liver → relevant processes not modeled

Generic PBPK Model



Potentials & Limits of PBPK modelling

Potentials

+ efficient screening efforts
+ simulation of concentration profiles under different doses
+ Software packages
+ mismatch of simulation & observation
  → better compound characterization
  → improved compound understanding
+ understanding of processes → improve drug candidate / design better one
+ continuous workflow & model improvement possible

Limits

- Proof of estimated parameters
- Too simple mechanistic of too complex compartment (e.g. Liver)
- Accurate determination of V_{max} & K_m is crucial
- for (simple) input model too complex
- parameter estimation = complex

How informative are those models?

As good as their input!

Thank you for listening!