Modeling Inter-Individual Variability in PBPK Models and Deriving Mechanistic Covariate Models for PopPK

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Introduction

Motivation: A population (Pop) pharmacokinetic (PK) model consists of a structural, stochastic (e.g. inter-individual-variability (IIV), residual model) & covariate model (functional relationship between covariates and PK parameter). Different modeling, estimation & validating techniques in data analysis can lead to different results and conclusion for the same data: A mechanistic access is preferable.

Objective:

- Introduce physiological inter-individual variability (IIV) in PBPK models using key-covariates like BH,BW,LBW,etc.
- Derive a covariate model in context of a classical Pop PK analysis via lumping [3] to get better mechanistic understanding of IIV regarding underlying physiology

Variability in Physiology

- Reference (Ref) PBPK: 13-CMT Whole-Body PBPK model, stratification to age & sex
- IIV: Scaling of reference tissue values (volumes & blood flows) with covariate depending scaling factor:

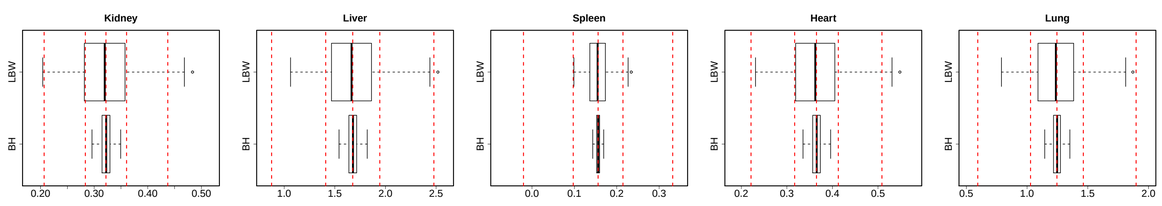
$$V_{tis} = SV_{tis}(Cov) \cdot V_{tis,ref}(age, sex) \qquad Q_{co} = SQ_{co}(Cov) \cdot Q_{co,ref}(age, sex)$$
$$Q_{tis} = SQ_{co}(Cov) \cdot Q_{tis,ref}(age, sex) \qquad CL = SQ_{co}(Cov) \cdot CL_{ref}(age, sex)$$

  with covariates Cov=BW, BH, BMI, LBW, BSA, ...
- Tissue-to-blood-partition-coefficient $K_{tis,i} = K_{tis,ref}(age, sex)$ constant

LBW-Approach:

- $SV_{bra} = 1$ (constant brain volume within population)
- $SV_{ski} = BSA/BSA_{ref}$
- $SV_{adi} = (BW - LBW)/(BW_{ref} - LBW_{ref})$ $(\Leftrightarrow V_{adi} = BW - LBW)$
- $SV_{tis,i} = (LBW - V_{ski} - V_{bra})/(LBW_{ref} - V_{ski,ref} - V_{bra,ref})$ for remaining tissues (constant fraction of tissue volume regarding remaining body mass)
- $SQ_{co} = SV_{hea}$ (detailed derivation in upcoming paper)

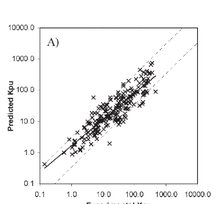
Comparison: (Quartiles and Whiskers) Data generated via LBW-, allometric scalling BH-approach ($SV_{tis} = (BH/BH_{ref})^{3/4}$) and experimental data from autopsy study [1] (red dashed line)



$\Rightarrow$ IIV via BH $<$ IIV via LBW $\leq$ experimental observed IIV

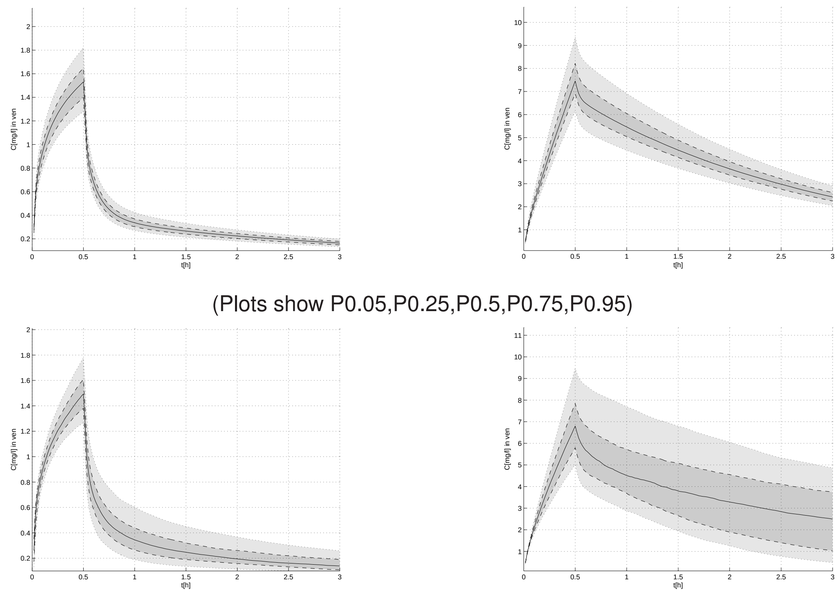
Impact of IIV vs. uncertainty in K_{tis}:

- Example: Lidocaine and Ibuprofen, 30 min. i.v. infusion,
- IIV is simulated via creating a virtual population (n=500) $BH \sim \mathcal{N}(1.71, 0.07)$ and $BMI \sim \log\mathcal{N}(22.8, 3.3)$ (Parameters taken from ICRP [2])
- Uncertainty in K_{tis} modeled with Monte Carlo simulations (n=500) for the reference man, drawing K_{tis} out the interval $[1/3K_{tis,pred}, 3K_{tis,pred}]$:



Rodgers et al. [4,5]: Misspecification of $K_{tis} \in [1/3K_{tis,obs}, 3K_{tis,obs}]$ for all tissues, for about 90% of compounds they tested in rat. (Plot taken from [4])

- Simulated via virt. Pop
- Simulated via uncertainty in K_{tis}



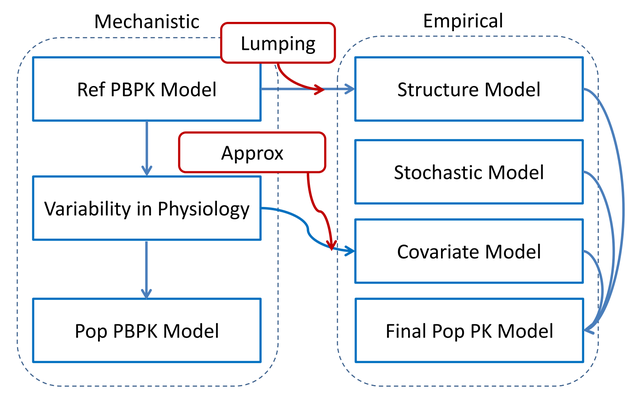
(Plots show P0.05,P0.25,P0.5,P0.75,P0.95)

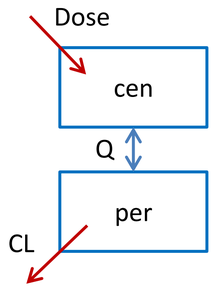
$\Rightarrow$ Impact of uncertainty in partition coefficients can be more pronounced than the impact of variations in BH, LBW, etc. within a population

Mechanistic Covariate Model

Proceeding:

I. Approximation of scaling factors of skin and brain:
$SV_{bra} \approx SV_{ski} \approx LBW/LBW_{ref} \Rightarrow SV_{tis} = LBW/LBW_{ref} =: SV$ for all tissues except adipose
II. Via lumping derivation of a mechanistic covariate model for PK parameter (e.g. 2-CMT model):





- Lumped compartments $cen = \{ven, art, lun\}$, $per = \{rest\}$
- Volumes of distributions $V_{cen,d}$ and $V_{per,d}$:

$$V_{cen,d} = \sum_{tis \in cen} V_{tis} \cdot K_{tis} = \ldots = SV \cdot V_{cen,ref} \cdot K_{cen}$$
$$V_{per,d} = \ldots = SV \cdot V_{rest,ref} \cdot K_{rest} + (BW - LBW) \cdot K_{adi}$$

- Intercompartmental clearance Q and hepatic clearance CL:

$$Q = SV \sum_{tis \in per} Q_{tis,ref} = SV \cdot Q_{per,ref} \qquad CL = SV \cdot CL_{ref}$$

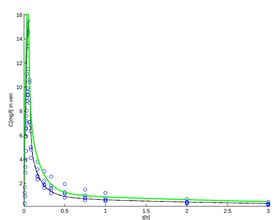
Conclusions:

I. Covariate model takes into account important role of adipose in the PK for many drugs,
II. 1-1 relationship between IIV in physiology and IIV in mechanistic covariate model

Lidocaine Example

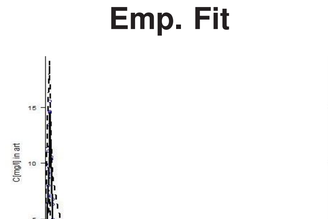
- Tucker et al. data [6]: 5 male subjects, dosing 3 mg/[kg BW], 3 min. i.v. infusion, arterial plasma concentration measured
- Pop PK analysis with lumping strategy [3]: 3-CMT, elimination in **per1** CMT: $cen = \{ven, art, lun\}$, $per1 = \{liv, kid, ...\}$, $per2 = \{ski, adi, bon, mus\}$
- No information about LBW, BMI, BH given $\rightarrow$ no estimation for V_{adi} possible (because of homogeneous population BW is taken as descriptor for physiological IIV)

Mech. Pred.



	Mech. Pred.		Emp. Fit	
	Mean	CoV[%]	Mean	CoV[%]
$V_{cen,d}$	7.46	5.23	14.1	10.5
$V_{per1,d}$	14.44	4.16	44.33	26.82
$V_{per2,d}$	125.21	5.69	71.97	10.53
Q_2	4.64	5.17	2.74	10.58
Q_3	1.92	5.21	1.11	10.81
CL	1.01	4.95	1.53	26.8

Emp. Fit



(Plots show VPC P0.3,P0.5,P0.7, green line lumped prediction)

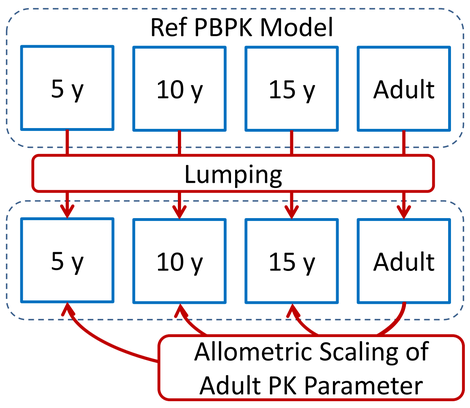
Conclusions:

Differences between mechanistic and empirical methods in population ...

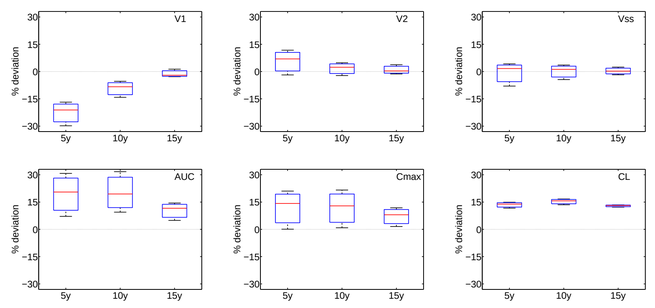
I. ... means could be due to possible misspecification in K_{tis}, e.g.: $K_{cen,pred} = 1.4$, using the experimental data to estimate K_{cen} in the mechanistic model gives $K_{cen} = 2.64$
II. ... IIV could be due to neglected variability in K_{tis}, e.g.: In the mechanistic model there is $Var(V_{cen,d}) \propto Var(SV)$ because $V_{cen,ref}$ and K_{cen} are constants; assume an IIV in K_{tis} which is independent of V_{tis}, using the experimental data we would expect an IIV on K_{cen} of $CoV(K_{cen}) = 7\%$ in the mechanistic model

Children

Comparison: Lumped Ref PBPK models and allometric scaling from adult to child $PK_{child} = a^b \cdot PK_{adult}$ with $a = BW_{child}/BW_{adult}$ and $b = 1$ for tissue volumes, $b = 3/4$ for tissue blood flows



E.g.: For 25 compounds a 2-CMT model is assumed (deviation from Lumped Ref PBPK model):



$\Rightarrow$ Results are in good agreement and theoretically underpin allometric scaling (note: allometric scaling does not respect changing proportions of the largest tissues adipose and muscle over the age classes)

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