Using Population PBPK Modelling to interpret Population PK results exemplified for Levofloxacin in Plasma and Interstitial Fluid

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Objective

Covariate modelling aims at representing the influence of covariates on PK parameters. For example, the levofloxacin plasma data analysis showed that the inclusion of lean body weight (LBW) as a covariate on the peripheral volume decreases the inter-individual variability (IIV) significantly (8%). Is this the expected impact of LBW or is it a surrogate for something else?

Our objective was to study the impact of variations in anatomy & physiology by means of . . .

. . . What are the expectations based on a population (POP) PBPK model?

. . . And how can this expectations be brought in agreement with observed IIV?
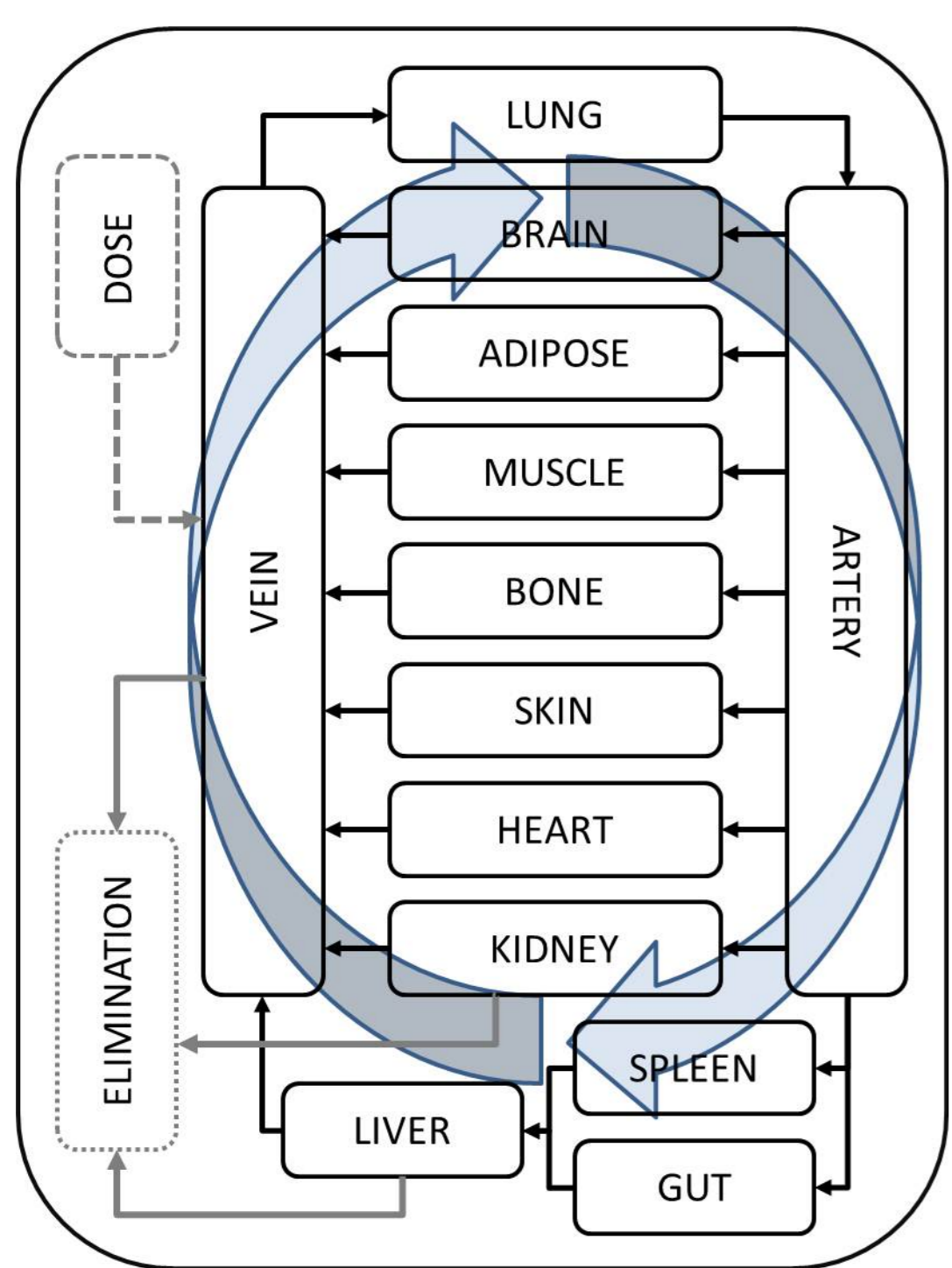
Example:

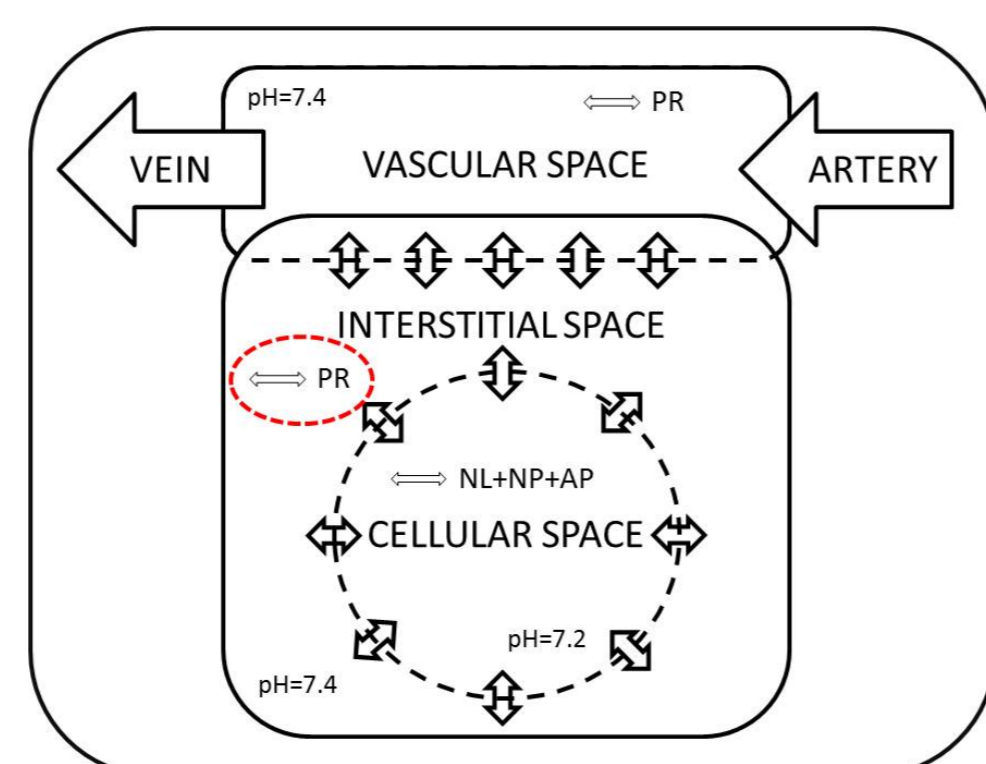**Expectations from POP PBPK:** LBW is a covariate on V_{per}

Results from POP PK analysis: Inclusion of LBW as covariate on V_{per} resulted in:

decreased IIV	covariate is included **consistent with expectations**
increased IIV	covariate is not included **however, contrary to expectations**

Whole Body PBPK Model

- Flow-limited **3** (sub-) compartment organ model
- Combinend tissue-to-blood partition coefficient ($K_{tis:blo}$) model of Rodgers & Rowland 2006 [5] for zwitterions

- **3** routes of (linear) elimination: renal, hepatic, rest
- total blood clearance: **9.5 l/h** (**80%** renal, **5%** hepatic → **15%** remaining) [1]
- Ionisation **pKa(basic) = 5.7**, **pKa(acidic) = 7.9** [2]
- Lipophilicity: **log $P_{oct:wat}$ = −0.48** [2]
- Linear protein binding (primary to albumin): $fu_p = 1/(1 + K_a \cdot C_{alb})$, $K_a = 4.49 \cdot 10^2$ M^{-1} [1,3]
- Blood-to-plasma partition coefficient: $K_{blo:pla} = 1$ (Ofloxacin [4])

Anatomy & Physiology

To build a population PBPK model we introduce IIV only on observable patients characteristics and transform this IIV via proofed relationships to IIV on the PBPK model parameters.

For the population PBPK model we use the following parametrisation and IIV transformations:

- reference tissue volumes, blood flows, cardiac output . . . : ICRP Report 2002 [6]
  - ▷ Parameterset stratified by race, sex & age
  - ▷ IIV on tissue blood flows & volumes by scaling with lean body weight:
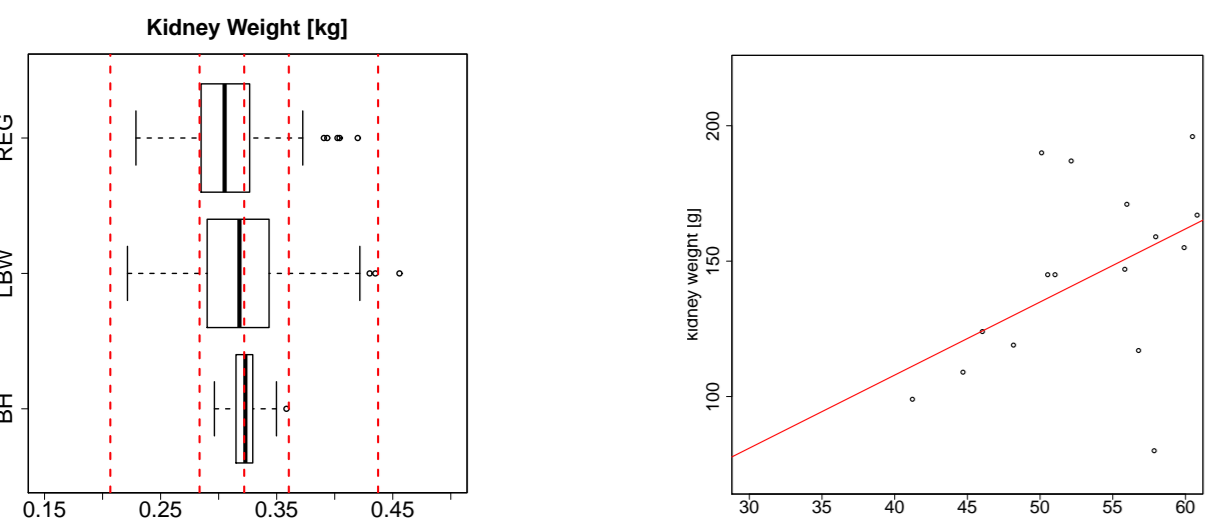
- ▶ Left: different scaling approaches - lean body weight scaling shows good performance reproducing magnitude of IIV (also for other organs, experimental data from [7])
- ▶ Right: model does not necessarily account for individualised patient variations in organ weight (lack of published data for other organs, kidney data from [8])

- Tissue compositions, e.g. interstitial & cellular volumes, lipid concentrations, . . . : Poulin & Theil 2009 [9]
- Serum albumin concentration → fraction unbound
- Heart rate (HR) → cardiac output
- Creatine clearance (CLCR) → renal blood clearance
- Hematocrit + fraction unbound → blood-to-plasma partition coefficient (⇒ IIV on $K_{tis:blo}$)

The population PBPK model predictions are based on a virtual populations with equal population characteristics as the underlying patient population taking into account correlations between characteristics.

Dataset

- Levofloxacin plasma, interstitial fluid muscle and adipose concentrations from 5 clinical trials determined with micro-/retrodialysate principle [10,11,12]
- Only one gender (male)
- Only subjects where height and weight is reported

	unit	patient pop. mean	patient pop. CV [%]	virtual pop. mean	virtual pop. CV[%]
N	[-]	15	-	1000	-
age	[years]	59	18	adult	-
weight	[kg]	76	15	76	14
height	[m]	1.75	4	1.75	4
heart rate	[beats/min]	74	15	75	16
hematocrit	[%]	37	15	39	14
albumin	[mg/l]	35	36	35	30
CLCR	[ml/min]	79	25	76	25

(Range: e.g. CLCR 46-112 in patient- vs. 43-144 in virtual population)

Predicted vs. Fitted

	unit	Mechanistic pred. mean	Mechanistic pred. CV [%]	POP PK mean	POP PK CV [%]
V_{cen}	[l]	19.3	9.2	19.2	51.8
V_{per}	[l]	85.5	12	81.3	21.4
Q	[l/h]	126.2	21	82.5	29.1
CL	[l/h]	9.9	23	8.5	26

- Mechanistic predictions are derived via lumping [13] the POP PBPK model
- POP PK results are derived via fitting a 2 compartment model to the plasma data with NONMEM® 7.12

Mechanistic Interpretation:

$$V_{cen} \approx \underset{\sim\, 0.4\text{ (const.)}}{\theta_{cen}} \cdot \underset{\sim\, 58 \pm CV\, 10\%}{LBW} \cdot \underset{\sim\, 0.8 \pm CV\, 3\%}{(fu_p/K_{blo:pla})}$$

$$V_{per} \approx \left(\underset{\sim\, 18 \pm CV\, 35\%}{[BW - LBW]} \cdot \underset{\sim\, 0.6\text{ (const.)}}{\theta_{adi}} + \underset{\sim\, 58 \pm CV\, 10\%}{LBW} \cdot \underset{\sim\, 1.7\text{ (const.)}}{\theta_{LBW}} \right) \underset{\sim\, 0.8 \pm CV\, 3\%}{(fu_p/K_{blo:pla})}$$

$$Q \approx \underset{\sim\, 0.03\text{ (const.)}}{\theta_Q} \cdot \underset{\sim\, 58 \pm CV\, 10\%}{LBW} \cdot \underset{\sim\, 75 \pm CV16\%}{HR}$$

$$CL \approx \underset{\sim0.1\text{ (const.)}}{\theta_{ren}} \cdot \underset{\sim79 \pm CV\, 25\%}{CLCR} + (\underset{\sim0.02\text{ (const.)}}{\theta_{hep} + \theta_{rest}}) \cdot \underset{\sim\, 58 \pm CV\, 10\%}{LBW}$$

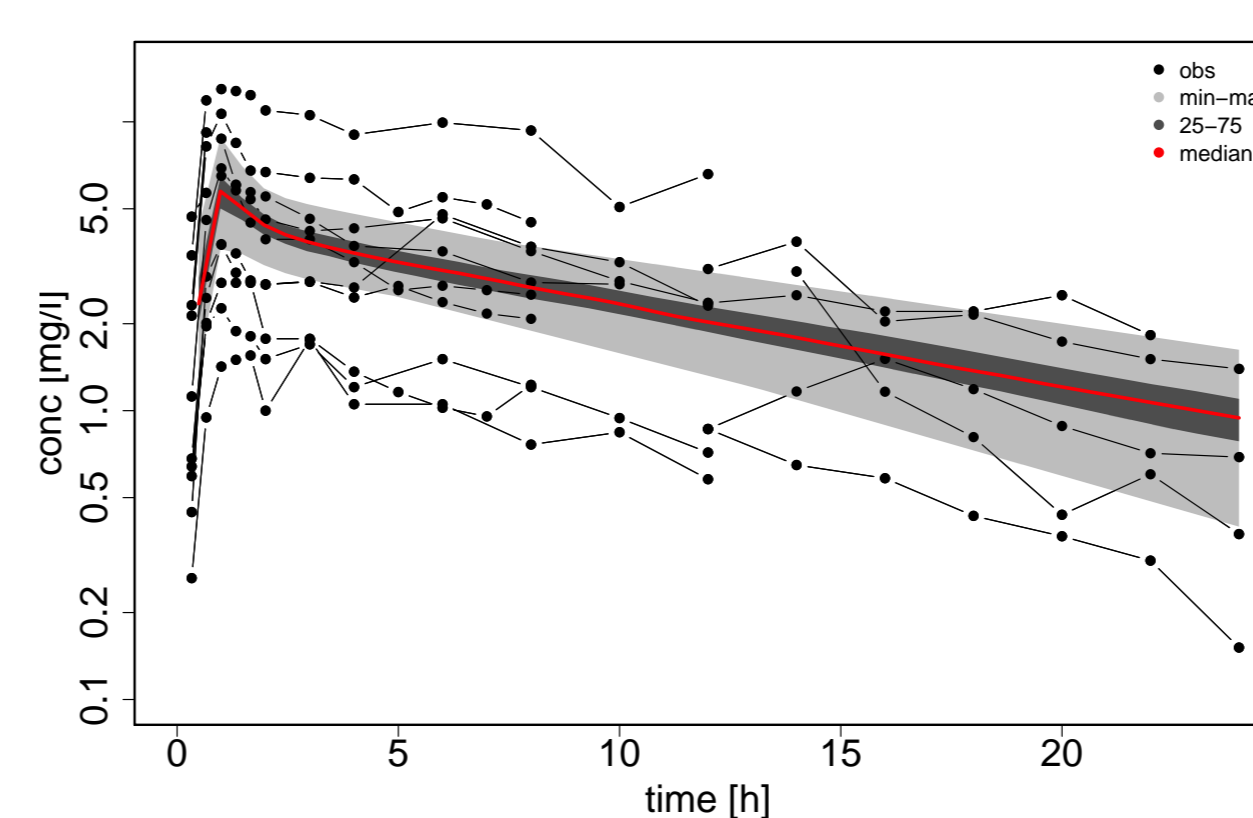⇒ **Distributions of those lumped PK parameters can be derived analytically.**

Visual Comparison
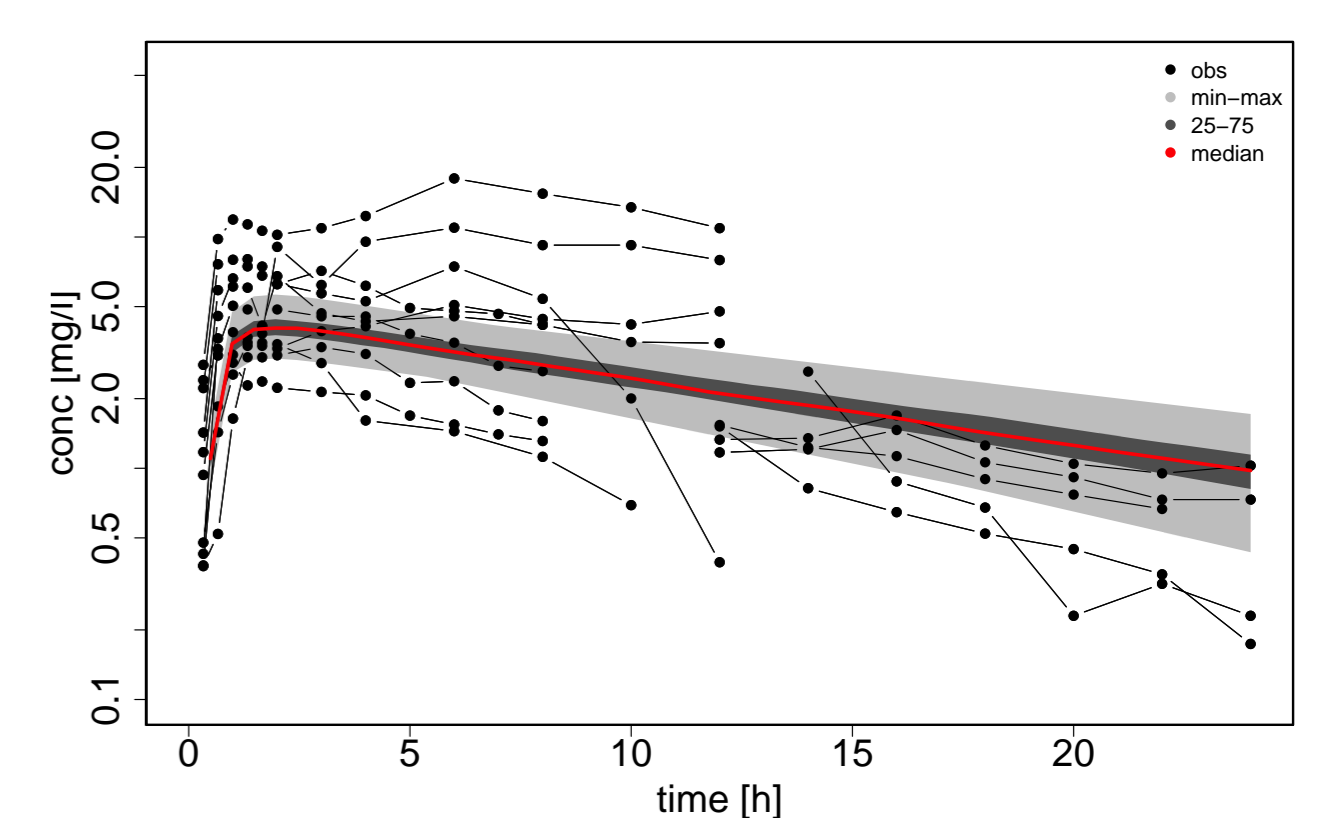
What are the expectations based on a POP PBPK model?
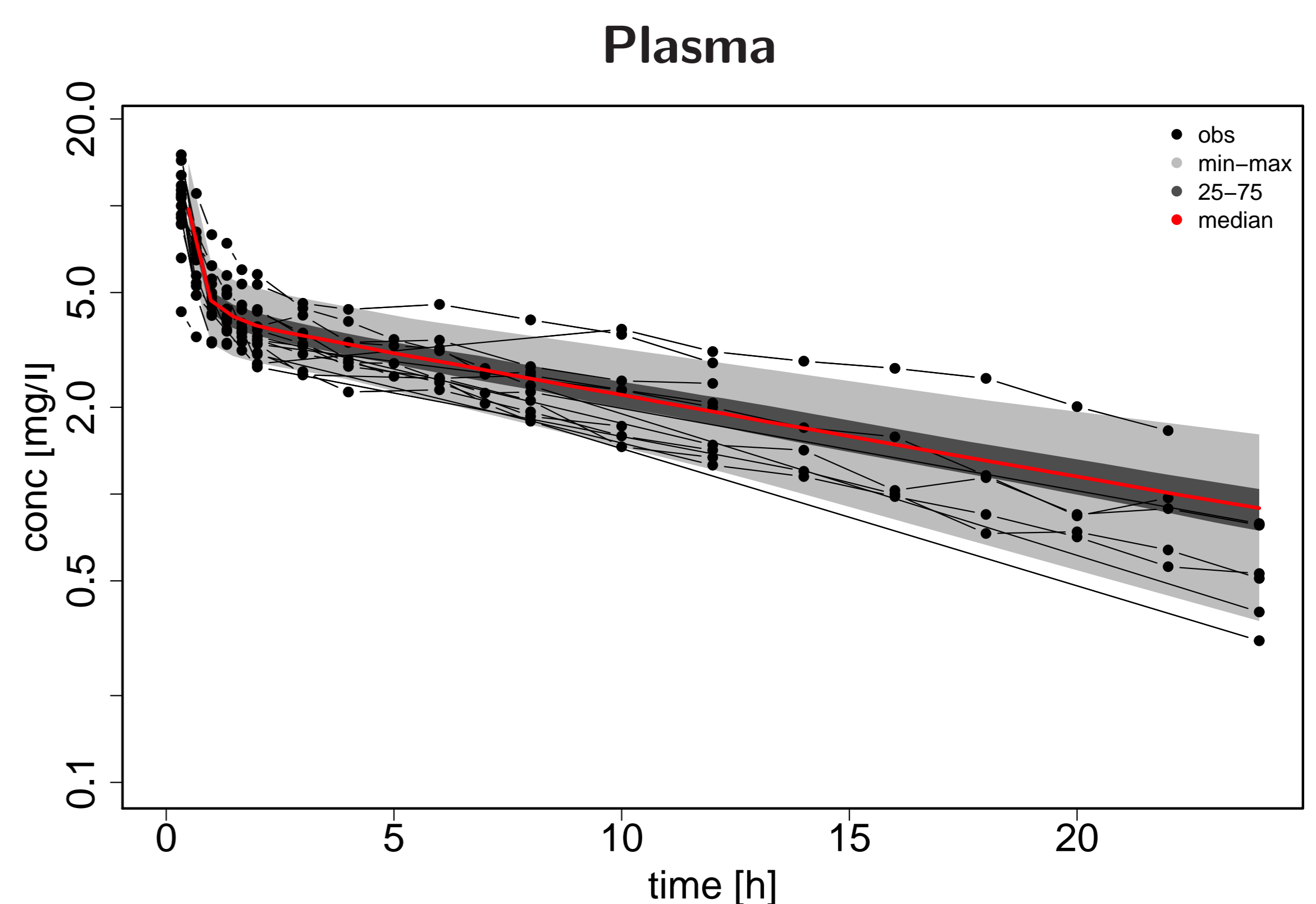
Plasma

- POP PBPK model is able to describe the average plasma kinetic and the variability

Adipose interstitial fluid

Muscle interstitial fluid

- Variability in tissue kinetics larger than expected from IIV included. Possible reasons:
  - ▷ Potential IIV in tissue composition impacting the tissue-to-plasma partition coefficients; this would be in line with literature findings [14].
  - ▷ Observed μD data very sensitive with respect to determination of the recovery rate

How can this expectations be brought in agreement with observed IIV?

- In the mechanistic setting the IIV can be assigned precisely (correlation structure & magnitude) and processes might cancel out
- If "true" model increases IIV- is this desirable?

Conclusion

As expected, anatomical IIV can only explain part of the IIV. Our approach quantified the contribution of the anatomical IIV. Such information is expected to help understanding to what extent a covariate-relationship involving body size descriptors reflects differences in anatomy and to what extent it might reflect a yet unidentified interaction.

References

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