

Interpretability is coming:

Using a minimal PBPK model in a population analysis



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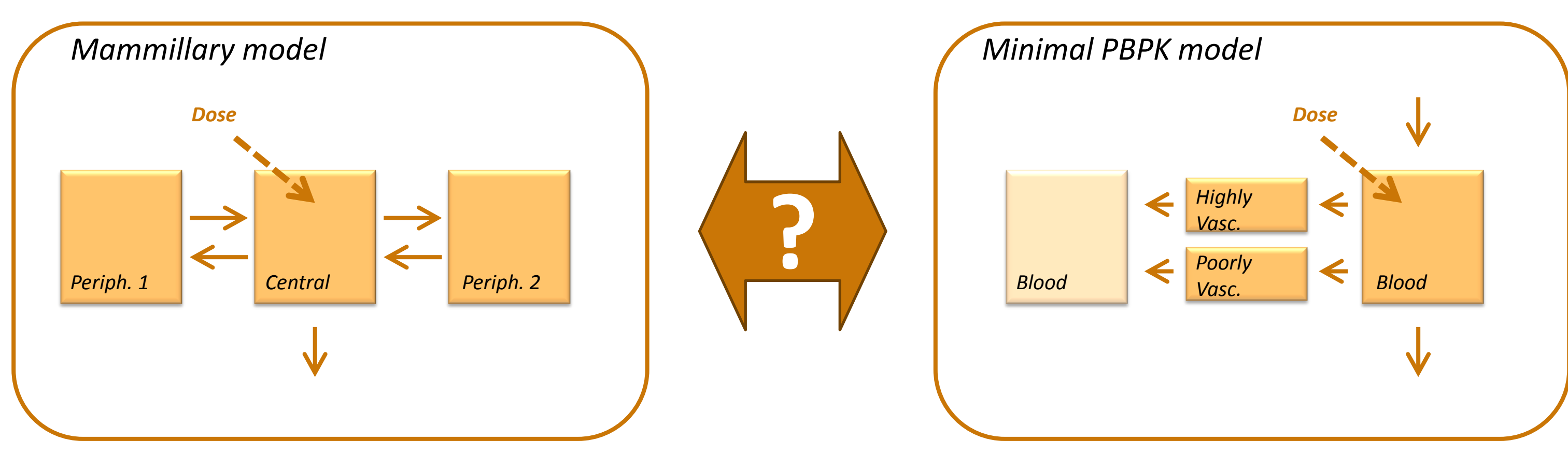


Introduction

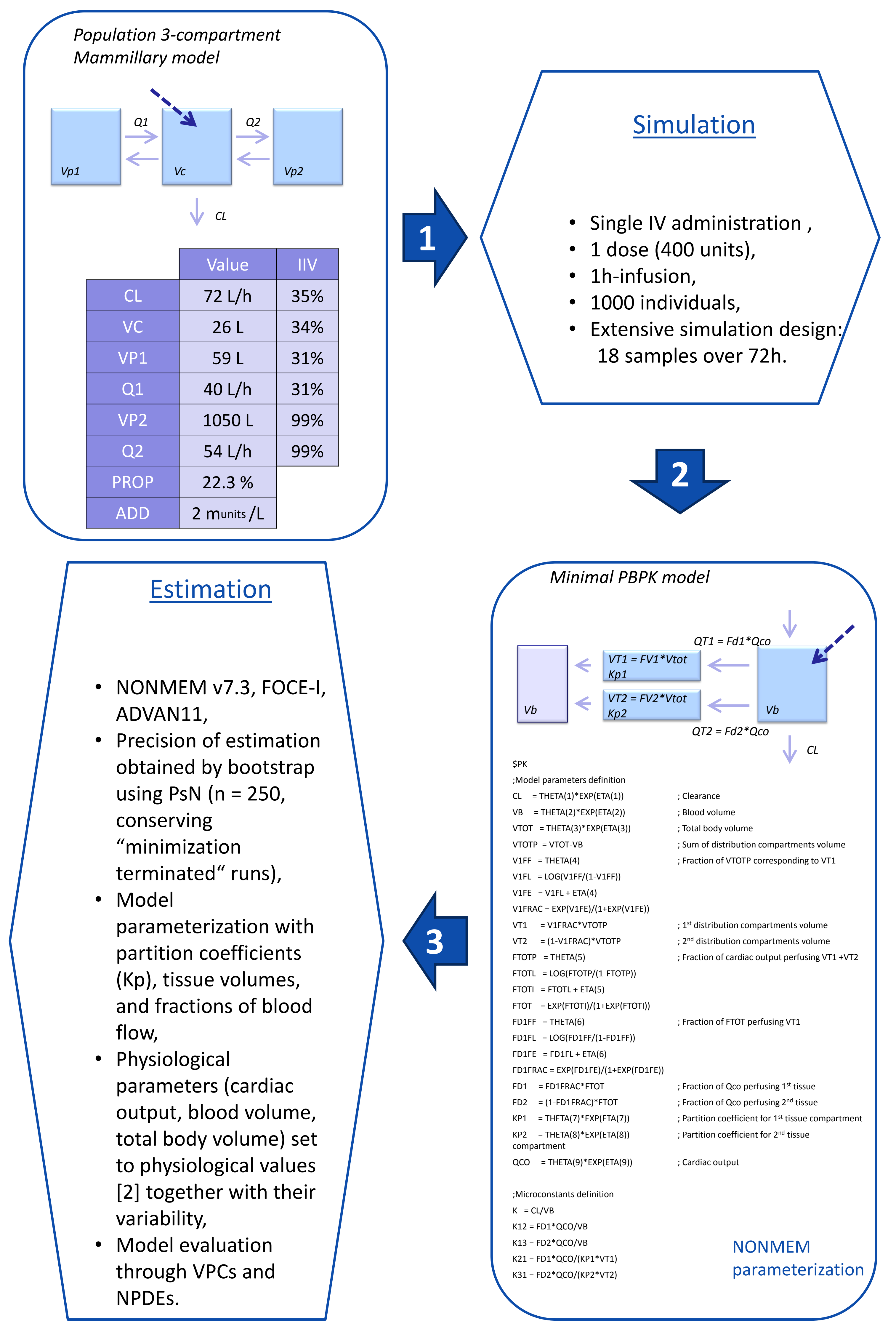
The classical mammillary compartmental models in population analyses are becoming more and more complex, integrating physiological or pharmacological features (enterohepatic recycling, multiple absorption sites...). Yet, the interpretation of peripheral compartments parameters is not straightforward. In parallel, minimal PBPK models [1-3] are proposed as a simplification of full PBPK models, allowing the estimation of interpretable parameters.

Objectives

To use a minimal PBPK model in a population analysis, for fitting simulations performed using a 3-compartment mammillary PK model



Methods



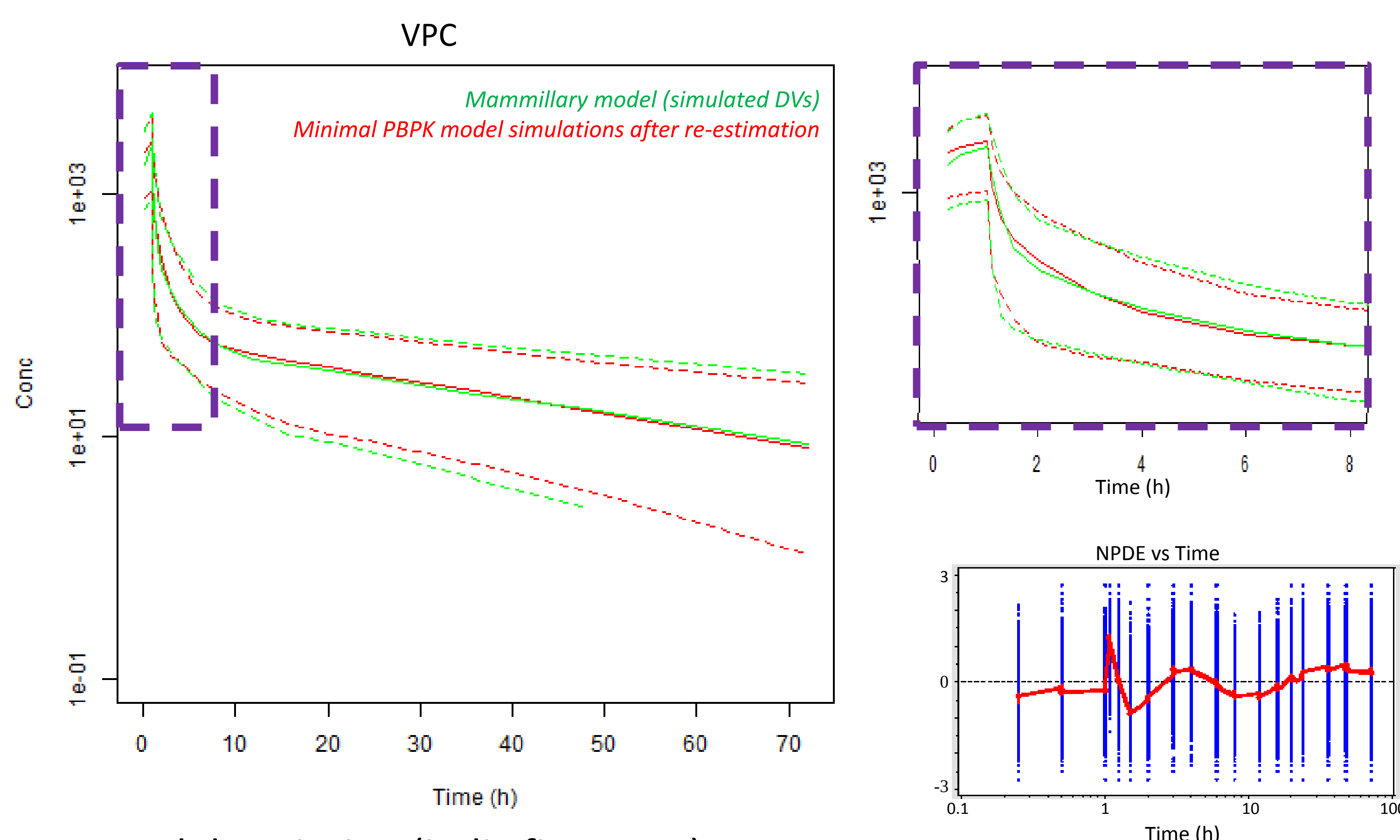
Results

1) Minimal PBPK model evaluation

- Similar clearance as compared to simulation parameters,
- Good overall precision of estimation:
 - Consistent with very extensive simulation design,
 - Suggests no identifiability issues with model or parameterization,
 - Slightly worse on KP1 IIV.
- IIV on every parameter but one:
 - Most of the simulated IIV is captured by the model,
 - Eta distributions are well-balanced, except for VB,
 - Residual error magnitude is bigger however.
- Bootstrap outcome:
 - Successful minimisation: 70%,
 - Covariance step: 0 % (identifiability issue ?),
 - OFV 90% CI: [163388.8, 164868.5] (identifiability issue ?).

	Fixed effect value [90% CI]	IIV (ω²) [90% CI]
CL	72 L/h [71, 73]	0.10 [0.10, 0.11]
VB	5 L (*)	0.20 (*)
VTOT	80 L (*)	0.20 (*)
V1FF	24 % [22, 25]	0.67 [0.63, 0.91]
FTOT	47 % [46, 47]	1.3 [1.1, 1.4]
FD1FRAC	40 % [39, 41]	0.66 [0.59, 0.77]
KP1	65 [62, 72]	0.34 [0.21, 0.59]
KP2	0.86 [0.84, 0.89]	0
QCO	340 L/h (*)	0.2 (*)
PROP	26 % [26, 27]	
ADD	1.8 munits /L [1.7, 2.0]	

(*) = fixed to physiological value during estimation step [2]



- Good description (indiv fits, VPCs)
- Correct NPDEs (?)
- Ok for structural model (slightly misfit of early distribution)
- Ok for structural model Variability is correctly described

2) Pharmacokinetic interpretation

- High affinity in less vascularized tissue, consistently with known drug lipophilicity,
- Distribution of the drug in extensively vascularized tissues is consistent with drug S activity,
- Distribution of drug S in both extensively and poorly vascularized tissues, consistently with the large volume of distribution of the drug ($\sum Kp_i \cdot V_i$),
- Separation of drug-related parameters (Kp_i , Ft_{ot}) and system-related parameters (Q_{t_i} , VT_i).

High Affinity Tissues	KP1	64.6
	VT1	20 L
	QT1	62.9 L/h
Low Affinity Tissues	KP2	0.861
	VT2	61 L
	QT2	95.2 L/h

Conclusions

Minimal PBPK models allows for better parameter interpretation, hypotheses generation, and assumption testing, than classical mammillary distribution models. More thorough covariate investigations are thus possible, especially because of the separation between drug-related parameters and system-related parameters. Though investigations regarding identifiability issues are still ongoing, using these models in popPK analyses of rich data should be promoted.

References:

- [1] Cao Y. et al (2012) “Applications of minimal physiologically-based pharmacokinetic Models”, J Pharmacokinet Pharmacodyn
- [2] Cao Y. et al (2013) “Second-generation minimal physiologically-based pharmacokinetic model for monoclonal antibodies”, J Pharmacokinet Pharmacodyn
- [3] Tsamandouras N. et al “Combining the ‘bottom up’ and ‘top down’ approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data”, Br J Clin Pharmacol, 2015