Pharmacokinetic models for drug and metabolites including first pass effects

A priori and a posteriori identifiability analysis

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Background

Joint pharmacokinetic (PK) modelling of a parent drug and its metabolites is fundamental to evaluate absorption, distribution, metabolization, and elimination of all analytes. Metabolites may be formed during first pass through the liver and be pharmacologically active or lead to toxicity episodes. Here, a priori and a posteriori identifiability analyses on three published joint drug-metabolites PK models [1,2] are presented.

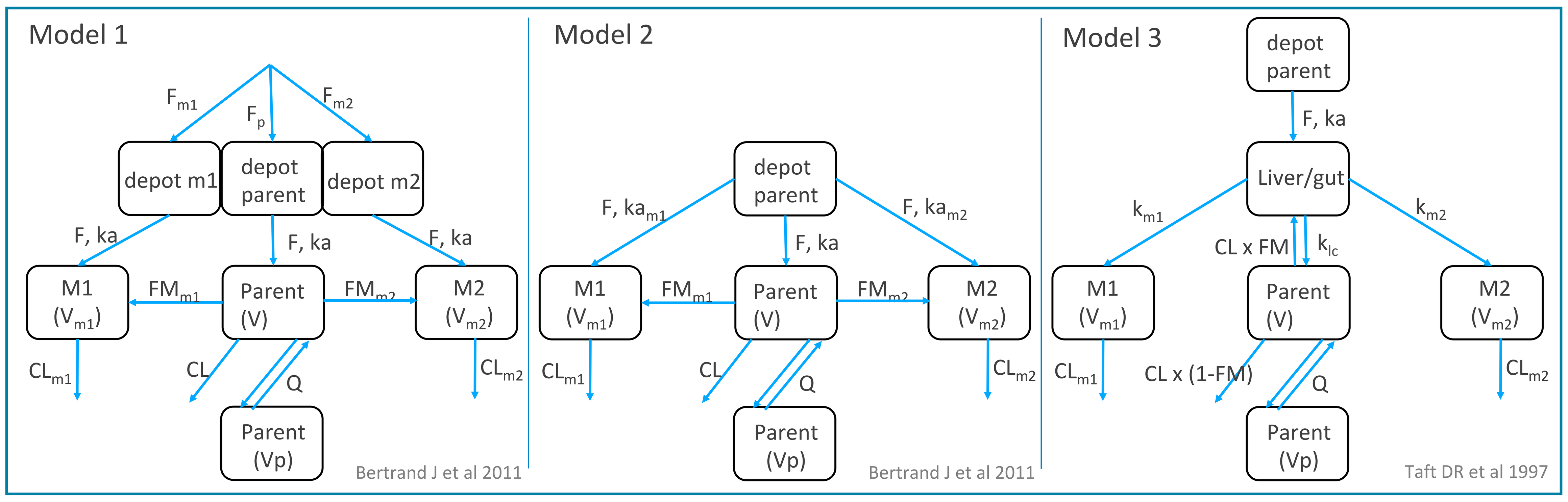
Methods

The evaluated models are presented in **Figure 1**.

A priori identifiability: This property was explored (similarly to [3]) via DAISY [4], assuming the drug is given intravenously (IV) and orally, and parent responses to both IV and oral administration are available, while two metabolites are measured after oral administration only.

A posteriori identifiability: A priori non-identifiable parameters were fixed, and a bootstrap analysis was performed in NONMEM 7.4.3 (FOCE method), generating 500 bootstrap datasets from a re-scaled dataset of a real case study involving two metabolites.

Figure 1.



Results

A priori identifiability: None of the models (**Figure 1**) were a priori identifiable. For all models, analytes volumes and clearances were co-dependent, as well as fractions of analyte absorbed and absorption rate (see **Table 1**).

Therefore, a priori identifiability was met after fixing metabolites volumes (or clearances), one parameter for parent drug distribution/elimination, and one parameter for drug absorption.

Table 1.

Co-dependent parameters
CLm2 ⇔ Vm2
CLm1 ⇔ Vm1
V ⇔ Q
Vp ⇔ Q
CL ⇔ Q
F ⇔ ka

Table 2.

% of achieved convergence		
Model	Scenario (i) (V_{m1}=V_{m2}=1)	Scenario (ii) (V_{m1}=V_{m2}=V)
Model 1	25%	17%
Model 2	37%	44%
Model 3	61%	48%

A posteriori identifiability: V_{m1}, V_{m2}, F, and Q were fixed. In particular, V_{m1} and V_{m2} were set equal either to 1 (scenario (i)) or to V (scenario (ii)). For both scenarios, % of runs which succeeded to converge are reported in **Table 2**. For all models, estimation issues were rarer in scenario (i) (V_{m1}=V_{m2}=1) compared to scenario (ii) (V_{m1}=V_{m2}=V).

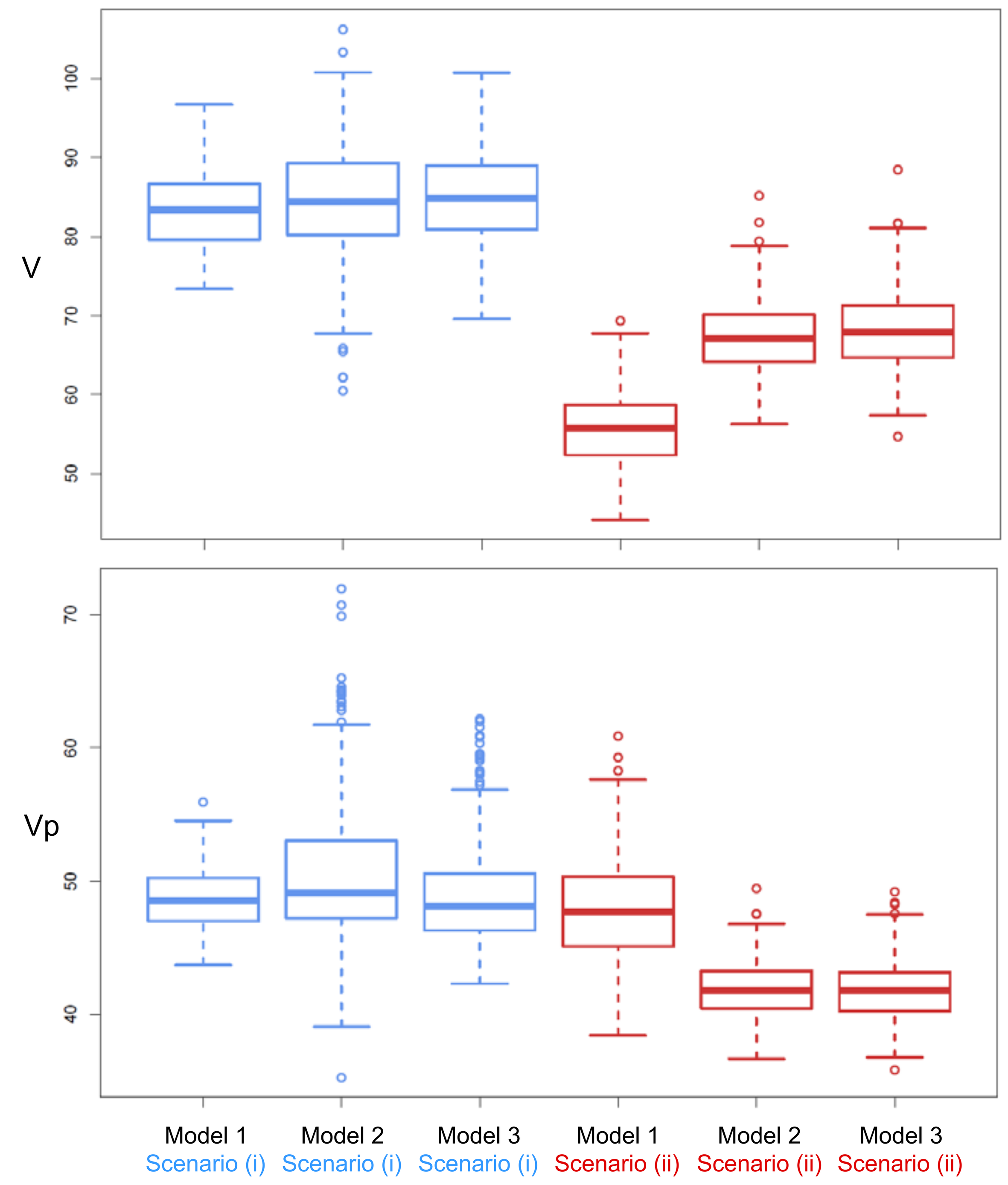
Table 3.

Range of RSE%			
Model	RSE%	Scenario (i) (V_{m1}=V_{m2}=1)	Scenario (ii) (V_{m1}=V_{m2}=V)
Model 1	30%<RSE%<50%	ω^2_{CL}, $\sigma^2_{add\_m1}$	ω^2_{CL}, ω^2_{CLm1}, ω^2_{Fm2}
	50%<RSE% <100%	ω^2_{Vp}, ω^2_{Fm2}, ω^2_{FM}	ω^2_{Q}, ω^2_{V}, ω^2_{ka}
	RSE%>100%	ω^2Q, ω^2_{CLm2}	ka, ω^2_{Vp}, ω^2_{FM}, $\sigma^2_{add\_m1}$
Model 2	30%<RSE%<50%	–	FM, ω^2_{Vp}, ω^2_{kam2}
	50%<RSE% <100%	ω^2_{CL}, ω^2_{V}, ω^2_{ka}, ω^2_{kam1}	ω^2_{ka}, ω^2_{kam1}
	RSE%>100%	CL_{m2}, ka_{m2}, FM, ω^2_{Q}, ω^2_{Vp}, ω^2_{FMm2}, $\sigma^2_{add\_m1}$	ω^2_{CL}, ω^2_{Q}, ω^2_{FMm2}, ω^2_{FM}, $\sigma^2_{add\_m1}$
Model 3	30%<RSE%<50%	FM, ω^2_{klc}	FM, ω^2_{V}, $\sigma^2_{add\_p}$
	50%<RSE% <100%	ω^2_{km1}, ω^2_{Vp}, ω^2_{CL}, ω^2_{CLm2}, ω^2_{FM}	ω^2_{Vp}, ω^2_{CL}, ω^2_{CLm2}
	RSE%>100%	ω^2_{Q}, $\sigma^2_{add\_m1}$	ω^2_{km1}, ω^2_{Q}, ω^2_{FM}, $\sigma^2_{add\_m1}$

- **Model 1:** In both scenarios, fixed effect and inter-individual variability (IIV) for F_{m2} did not change from their initial estimates; a high IIV on FM_{m2} was estimated. In scenario (ii), also a high IIV on total fraction metabolized (FM) was estimated.
- **Model 2:** In scenario (ii), IIV on FM and FM_{m2} were high on average.
- **Model 3:** In scenario (i), IIV on FM was fairly high (on average) and became higher in scenario (ii).

Precisions for all models and scenarios (percentage relative standard error, RSE%) are detailed in **Table 3**.

Figure 2.



Among common parameters, V and CL_{m1} were on average consistently estimated (i.e. with similar bootstrap medians) across models but not across scenarios (see e.g. V in **Figure 2**, top panel). CL and Vp were consistently estimated across both models and scenarios (see e.g. Vp in **Figure 2**, bottom panel).

Conclusions

- A priori identifiability analysis performed on three PK models for a parent compound and two metabolites including first pass effects demonstrated structural over-parametrization.
- Practical identification issues were highlighted by the bootstrap analysis even after fixing non-identifiable parameters: additional information would be needed to obtain reliable model estimates.
- Despite a posteriori identifiability results are dataset-dependent, it is noteworthy that Model 3 showed the lowest rates of failed runs, and, when successfully estimated, reasonable precisions for the majority of parameters.

REFERENCES

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