CONSTRAINING METHODS IN ESTIMATING THREE-COMPARTMENT PHARMACOKINETIC PARAMETERS

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BACKGROUND

- In pharmacokinetic (PK) data analyses, it is desirable to constrain the relative magnitude of some PK parameters. For example of one-compartment PK with first-order absorption and elimination, the absorption rate constant (ka) is usually assumed to be greater than the elimination rate constant (k) in order to avoid the flip-flop in kinetics (in case intravenous data are unavailable).
- For two-compartment PK with first-order absorption, constraining is not as simple as in one-compartment PK but ka is often constrained to be greater than α, the constant characterizing the distribution phase.
- A further complication is when more than one peripheral compartment exist. Consider the simplest three-compartment PK model where elimination occurs from the central compartment 1 which is reversibly connected to a “shallow” and a “deep” peripheral compartment, compartments 2 and 3, respectively (Fig. 1) [1].

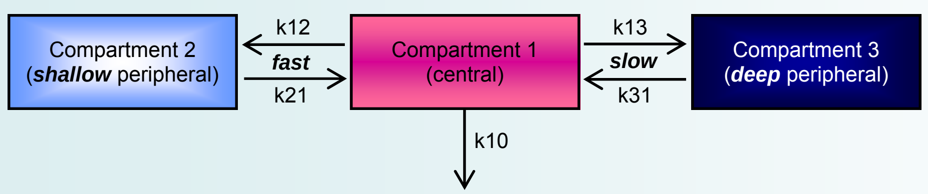

Fig. 1. Schematic representation of a three-compartment model

- Since k31 is the exit rate constant from the “deep” peripheral compartment, it will be smaller than k21, the exit rate constant from the “shallow” peripheral compartment (i.e., k21>k31). Or it is considered that the equilibrium between compartments 1 and 2 will be faster than the one between 1 and 3 (i.e., Q2 > Q3). Alternatively, V3 is assumed to be larger than V2 and this is what PKBugs [2] adopted (Abbreviations are defined in Table I).
- In individual PK analyses, constraining is simply a matter of interpretation and it has no effect on fitting itself. However, in population PK analyses, the variability among the individuals is simultaneously estimated along with the population mean parameters. Therefore, if the relative magnitude between the parameters prone to flip-flop is not defined a priori, extra care should be taken in interpreting the population parameter estimates. Furthermore, the estimates of inter-individual variability can be inflated due to the “mixing” between those parameters in population and this might destabilize the estimation procedure.

PURPOSE

To evaluate and compare various constraining methods in estimating three compartment PK parameters

METHODS

All simulation and estimation were performed using NONMEM VI beta [3]. The three-compartment PK parameters and variabilities used for simulation are provided in Table I. The exponential error model and the proportional error model were used for inter-individual variability (IIV) and residual unexplained variability (RUV), respectively.
Simulation designs were varied by dosing regimens (single dose (SD) vs. multiple (15) doses (MD)) and sampling schemes (17 observations per subject (rich) vs. 6 observations per subject (sparse)). Under these four scenarios, observations were simulated for 100 individuals and 100 such data sets were created.

Table I. PK Parameters used for Simulation

PK Parameters	Mean	IIV (% CV)
Clearance (CL)	3.2	30
Central volume of distribution (V1)	100	30
Shallow peripheral volume of distribution (V2)	52	30
Deep peripheral volume of distribution (V3)	133.4	30
Inter-compartmental clearance between 1 and 2 (Q2)	26	30
Inter-compartmental clearance between 1 and 3 (Q3)	6.67	30
RUV	15 (% coefficient of variation, CV)	

METHODS *continued*

Estimation method was conditional with interaction and five different constraining strategies (Table II) were applied. The performance of each method was evaluated in terms of the successful termination rate (%) and the bias and precision of parameter estimates which were assessed as a mean estimation error (mee, %) and root mean squared estimation error (rmse), respectively (ee = (estimated – true)/true ×100).

Table II. Constraining Methods

Methods	Description	Implementation
U	Unconstrained	As simulated; no constraints
D	K21 > K31	DK21 > 0 (constrained to be positive); K21 = K31 + DK21
F	K21 > K31	FK21 > 1 (constrained to be greater than one); K21 = K31 × FK21
Q	Q2 > Q3	DQ2 > 0 (constrained to be positive); Q2 = Q3 + DQ2
V	V3 > V2	DV3 > 0 (constrained to be positive); V3 = V2 + DV3

RESULTS

Most fixed effects parameters were estimated with good accuracy (|mee| < 10 %) but accuracy in some random effects parameters was not acceptable (>100 %) (Fig. 2). The performances of different constraining methods (including no constraints) were comparable to each other and any trends were not observed for both stability (Table III) and the bias in parameter estimates (Fig. 2). However, in terms of precision, method V seems to be better than any other method and method F gave rise to the most imprecise estimates (Fig. 3).

Table III. Rate (%) of Successful Termination

Scenario \ Methods	U	D	F	Q	V
SD rich	65	70	77	62	70
SD sparse	49	40	33	45	52
MD rich	56	51	29	63	69
MD sparse	29	24	24	35	29

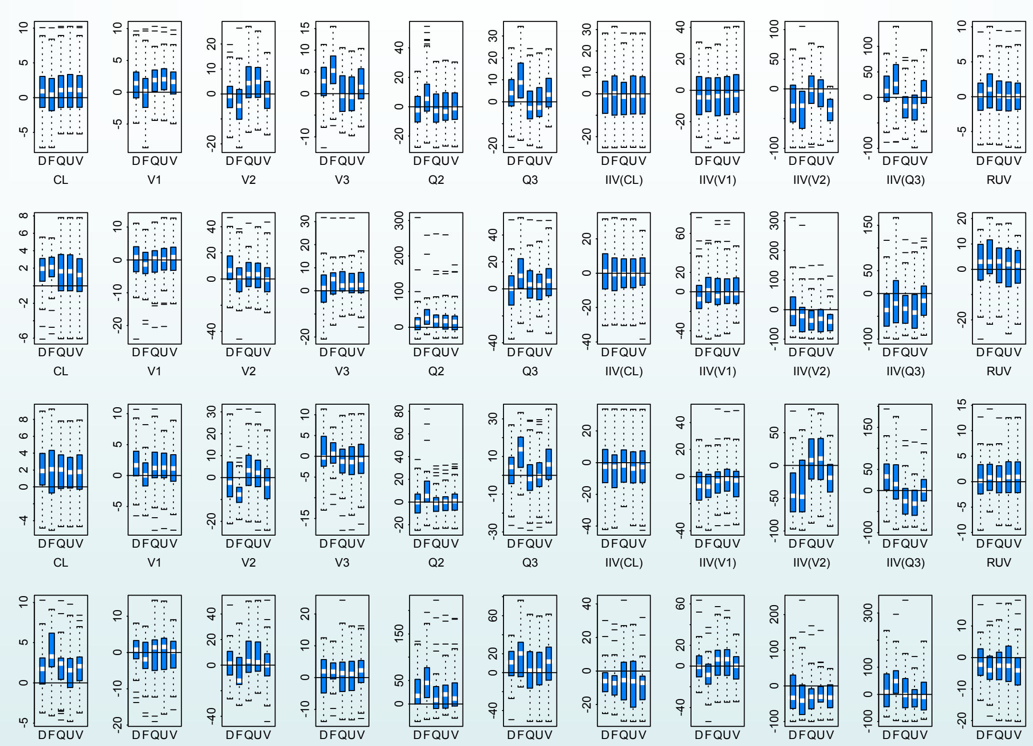

Fig. 2. Box split plots of estimation errors in parameter estimates
(from upper to lower, SD rich, SD sparse, MD rich, and MD sparse; only results from successful terminations were used for creating the plots)

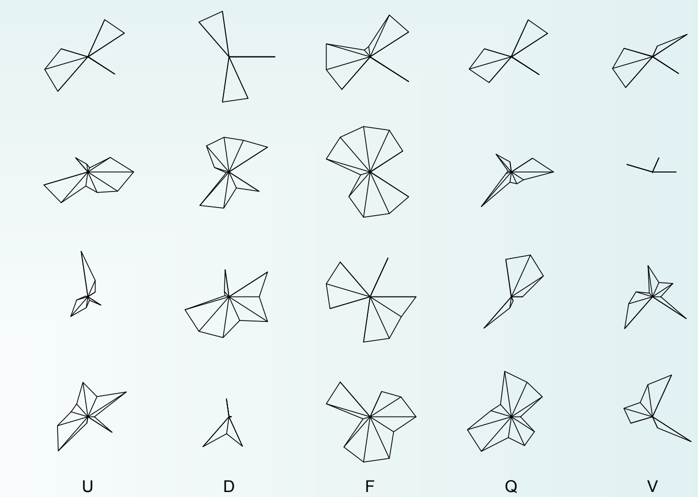

Fig. 3. Star plots of root mean squared estimation error in parameter estimates

(from upper to lower, SD rich, SD sparse, MD rich, and MD sparse; each radius represents PK parameters as shown in Fig. 2;
the columns of the data matrix were scaled independently so that the maximum value in each column is 1 and the minimum is 0)

DISCUSSION

- The mee’s for IIV in V3 and Q2 were not calculated nor compared as their variability structures were modified due to different parameterizations (see the NONMEM codes below) and it requires complex calculation to approximate the true values.

```
;Simulation
 CL=THETA(1)*EXP(ETA(1))
 V1=THETA(2)*EXP(ETA(2))
 V2=THETA(3)*EXP(ETA(3))
 V3=THETA(4)*EXP(ETA(4))
 Q2=THETA(5)*EXP(ETA(5))
 Q3=THETA(6)*EXP(ETA(6))
 K=CL/V1
 K12=Q2/V1
 K21=Q2/V2
 K13=Q3/V1
 K31=Q3/V3
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```
;Estimation (Method D)
 CL=THETA(1)*EXP(ETA(1))
 V1=THETA(2)*EXP(ETA(2))
 V2=THETA(3)*EXP(ETA(3))
 V3=THETA(4)*EXP(ETA(4))
 DK21=THETA(5)*EXP(ETA(5))
 Q3=THETA(6)*EXP(ETA(6))
 K31=Q3/V3
 K21=K31+DK21
 Q2=K21*V2 ;=(Q3/V3+DK21)*V2
```

Note that ETA’s in simulated Q2 and estimated Q2 are no longer comparable!

$$Q2 = \left(\frac{\theta_6 \cdot \exp(\eta_6)}{\theta_4 \cdot \exp(\eta_4)} + \theta_5 \cdot \exp(\eta_5) \right) \cdot \theta_3 \cdot \exp(\eta_3)$$

- However, IIV in Q2 could have been simply approximated in method F due to the exponential error model. This can be an advantage of constraining as a factor of k when Q2 is considered to be log-normally distributed.

$$Q2 = \left(\frac{\theta_6 \cdot \exp(\eta_6)}{\theta_4 \cdot \exp(\eta_4)} \cdot \theta_5 \cdot \exp(\eta_5) \right) \cdot \theta_3 \cdot \exp(\eta_3)$$

$$\ln Q2 = \ln \theta_6 + \eta_6 - \ln \theta_4 - \eta_4 + \ln \theta_5 + \eta_5 + \ln \theta_3 + \eta_3$$

$$\mathrm{Var}(\ln Q2) = \overline{\Omega}_{6,6} - \overline{\Omega}_{4,4} + \overline{\Omega}_{5,5} + \overline{\Omega}_{3,3} \qquad \overline{\Omega}: \text{omega estimate}$$

```
;Estimation (Method F)
 CL=THETA(1)*EXP(ETA(1))
 V1=THETA(2)*EXP(ETA(2))
 V2=THETA(3)*EXP(ETA(3))
 V3=THETA(4)*EXP(ETA(4))
 FK21=THETA(5)*EXP(ETA(5))
 Q3=THETA(6)*EXP(ETA(6))
 K31=Q3/V3
 K21=K31*FK21
 Q2=K21*V2
;Q2=Q3/V3*FK21*V2
```

CONCLUSION

Unlike the common conception that controlling the relative magnitude of some PK parameter is desirable, having constraints did not seem to be particularly helpful in estimating three-compartment PK parameters and any single constraining method evaluated in this study was not found to be best for all the criteria. However, constraining V3 to be greater than V2 seems to give the most accurate and precise parameter estimates overall.

REFERENCES

1. M. Gibaldi and D. Perrier, Pharmacokinetics Volume 1, Marcel Dekker, INC. New York (1975)
2. D. J. Lunn, J. Wakefield, A. Thomas, N. Best, and D. Spiegelhalter, PKBugs User Guide Version 1.1 (1999)
3. S. L. Beal, L. B. Sheiner, and A. J. Boeckmann (Eds.), NONMEM Users Guides, ICON Development Solutions, Ellicott City, MD (1989-2006)