

Title: Constraining Methods In Estimating Three Compartment Pharmacokinetic Parameters

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Objectives: To evaluate and compare various constraining methods in estimating three compartment pharmacokinetic (PK) parameters

Methods: All simulation and estimation were performed using NONMEM VI beta [1]. A 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 doses (MD)) and sampling schemes (17 observations per subject (rich) vs. 6 observations per subject (sparse)). Under the 4 scenarios, observations were simulated for 100 individuals and 100 such data sets were created. 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 in parameter estimates which was assessed as a mean estimation error (mee, %) ($ee = (\text{estimated} - \text{true})/\text{true} \times 100$).

Results: The most common reason for unsuccessful termination was reported as an IIV parameter estimate near zero. As expected, sparser samples yielded less stability (Table III). The mee's for IIV in V3 and Q2 were not calculated nor compared as their error structures could have been modified due to different parameterizations and the true values are unknown. Most fixed effects parameters were estimated with good accuracy (lmeel < 10 %) but accuracy in some random effects parameters was not acceptable (>100 %) (Fig.1). 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.1).

Conclusions: It is considered that constraining the relative magnitude of some PK parameters is desirable in estimation in the way that ETA's are not mixed when distinguishing the two parameters is difficult (for example, the first order absorption rate constant and the rate of elimination for one compartment PK without intravenous data); thus it might stabilize the problem. However, having constraints did not seem to be particularly helpful in estimating three compartment PK parameters according to the results of current simulations and evaluations.

Table I. PK Parameters used for simulation

PK Parameters	Mean	IIV (% CV)
CL	3.2	30
V1	100	30
V2	52	30
V3	133.4	30
Q2	26	30
Q3	6.67	30
RUV		15 (% CV)

Table II. Constraining methods

Methods	Description	Implementation
U	Unconstrained	As simulated; no constraints
D	$K_{21} > K_{31}$	$DK_{21} > 0$ (estimated to be positive); $K_{21} = K_{31} + DK_{21}$
F	$K_{21} > K_{31}$	$FK_{21} > 1$ (estimated to be greater than 1); $K_{21} = K_{31} \times FK_{21}$
V	$V_3 > V_2$	$DV_3 > 0$ (estimated to be positive); $V_3 = V_2 + DV_3$
Q	$Q_2 > Q_3$	$DQ_2 > 0$ (estimated to be positive); $Q_2 = Q_3 + DQ_2$

Table III. The rate of successful termination

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

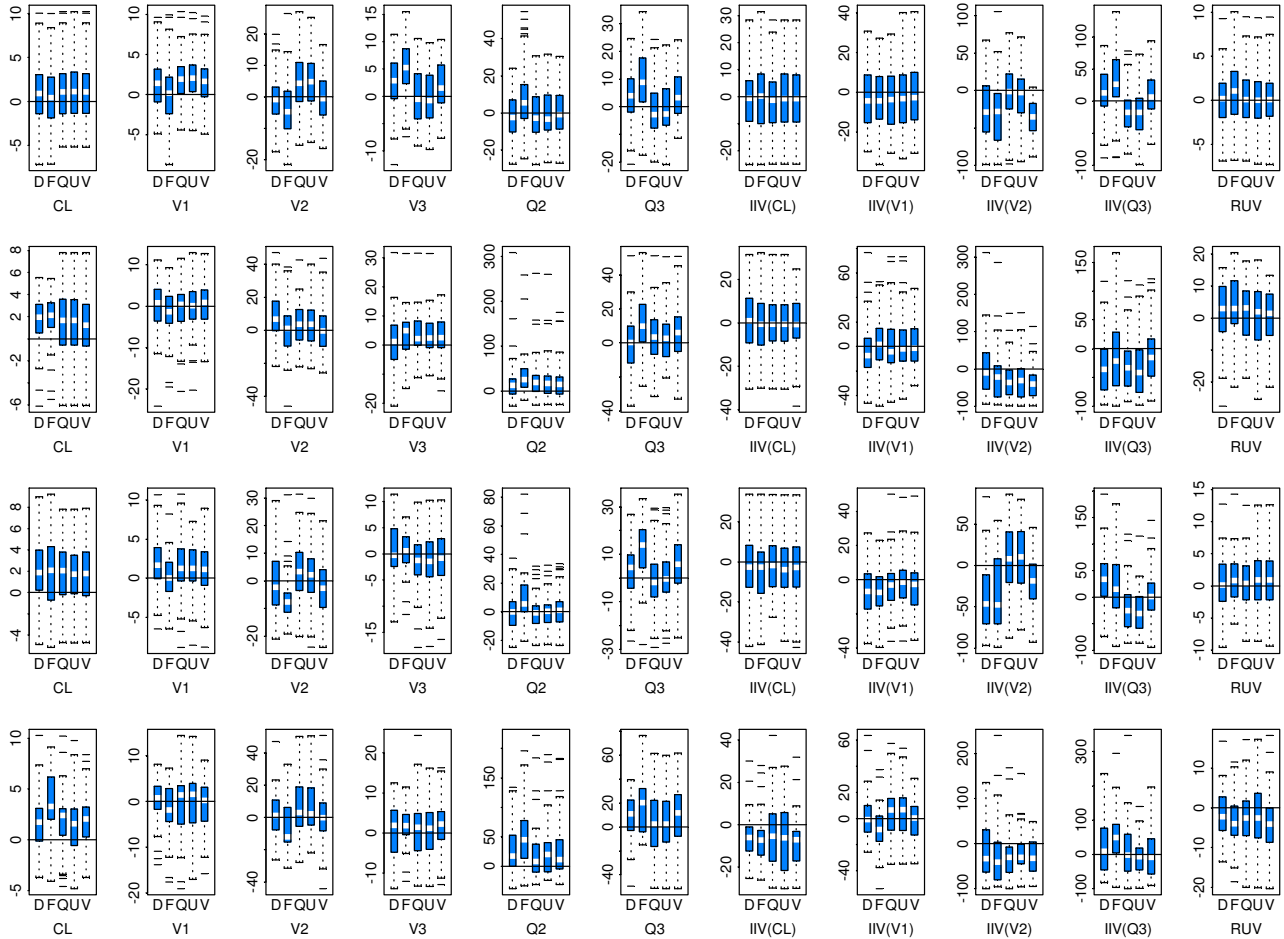


Fig.1. Box split plots of estimation errors in parameter estimates (from upper to lower, SD rich, SD sparse, MD rich, and MD sparse; only results from successful terminations were used for creating the plots)

Abbreviations: CL, clearance; V1 (2, 3), central (peripheral) volume of distribution; Q2 (3), inter-compartmental clearance between central and peripheral 2 (3); CV, coefficient of variation.

References:

[1] S. L. Beal, L. B. Sheiner, and A. J. Boeckmann (Eds). NONMEM Users Guides, ICON Development Solutions, Ellicott City, MD, 1089-2006.