

Estimation of random variance in NONMEM using different approaches

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Introduction

- NONMEM is one of the most preferred tools in to model PK
- The program allows a large degree of freedom when specifying the model
- This freedom allows the user to estimate the variance of random components in different ways

Methods

- A PK data set consisting of 100 subjects was simulated using a 2 compartment model with first order absorption and repeated 100 times₁.
- 3 different estimation methods scenarios were explored:
 1. Changing the variance estimation of inter-individual random effects from random to fixed components,
 2. Changing the variance estimation of random errors from a random to a fixed component and
 3. Changing the variance estimation of random errors from a random to a fixed component with data points below level of quantification using M3 method with lower limit of quantification (LLOQ) at 4 four levels (15 %, 25 %, 35 % and 50 % LLOQ of data set)
- All simulations and estimations were performed using NONMEM V7.3.0 with similar initial estimation method (FOCE).
- The estimated post hoc parameters were compared to the simulated parameters to quantify the absolute relative deviation of the two estimation method in each of the 3 scenarios for every subject.

Results

NONMEM post hoc estimations were found for all data sets. The results in the different scenarios were:

1. The mean deviation was smaller using fixed effects to estimate the variance of IIV random effects except for clearance. The difference ranged from 0.008 % for clearance to 3.4 % for central volume. In scenario
2. The mean deviation was smaller using fixed effects to estimate the variance of random errors. The difference ranged from 0.005 % for clearance to 7.3 % for the central volume. In scenario

The results of the two scenarios are given in table 1.

Table 1: Mean deviation of results for scenario 1 and 2. Numbers indicate relative mean deviation in percent between using variance or fixed components to estimate simulated individual parameters. Positive and negative numbers indicate respectively whether using variance or fixed components had the largest difference to the simulated parameter.

Parameter	Scenario 1 (IIV estimated with ETA or THETA)	Scenario 2 (error estimated with SIGMA or THETA)
KA (mean% [conf])	3.2 [2.8-3.5]	7.0 [6.7-7.3]
CL (mean% [conf])	-0.008 [-0.0017-0.001]	0.005 [-0.003-0.013]
V _c (mean% [conf])	3.4 [3.1-3.8]	7.3 [7.0-7.6]
V _p (mean% [conf])	0.13 [0.06-0.20]	0.35 [0.29-0.40]
Q (mean% [conf])	0.24 [0.17-0.31]	0.60 [0.54-0.67]

3. The mean deviation increased with increasing proportion of LLOQ data points. The mean deviation was smaller using fixed effects to estimate the variance of the random errors.

The results of the different proportion of LLOQ are given in table 2. Inspections of optimization shows similar objective value initially with different gradients for the tested parameters

Table 2: Mean deviation of results for scenario 3.

Numbers indicate relative mean deviation in percent between using variance or fixed components to estimate simulated individual parameters. Positive and negative numbers indicate respectively whether using variance or fixed components had the largest difference to the simulated parameter.

Parameter	LLOQ 15%	LLOQ 25%	LLOQ 35%	LLOQ 50%
KA	10.1 [9.8-10.4]	8.2 [7.8-8.5]	8.4 [8.1-8.7]	3.0 [2.7-3.2]
CL	0.02 [0.004-0.3]	0.03 [0.02-0.05]	0.03 [0.02-0.04]	0.15 [0.11-0.18]
V _c	10.6 [9.8-10.4]	8.4 [8.1-8.8]	8.6 [8.4-8.9]	3.3 [3.0-3.6]
V _p	0.88 [0.79-0.97]	0.65 [5.6-7.3]	0.54 [0.46-0.61]	0.95 [0.75-1.1]
Q	1.16 [1.07-1.24]	0.95 [0.87-1.04]	1.01 [0.94-1.08]	0.46 [0.38-0.54]

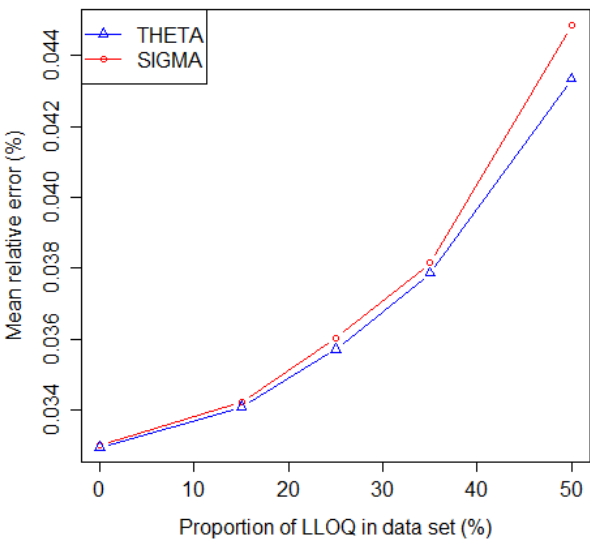


Figure 1: Mean relative error of results for scenario 2 and 3. The mean relative error using variance (SIGMA) or fixed (THETA) components to estimate individual clearance parameter for each of the different proportion of LLOQ in the data set.

Conclusions

- NONMEM seems to have irregular behavior when estimating the variance of random effects as random or fixed components even though likelihood function should be the same.
- This work suggests that random effects in general should be estimated as fixed component unless correlation between parameters is needed. .
- Further analysis on simpler and more complex models with differing initial estimates should be performed in order to further illuminate the degree of irregularity and to guide future modelling approaches in NONMEM.

References

1. R: Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. J Pharmacokinet Pharmacodyn. 2010 Jun;37(3):305-8.

