Parameter Estimates of Population Models: Comparison of NONMEM Versions and Estimation Methods

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PAGE 2008, June 18-20, Marseille, France

RESULTS

Nonmem V versus Nonmem VI: NM V and NM VI delivered very similar results. The only case with large differences led to identification of the NM VI bug (fixed in the current version)

FOI versus FO: FOI and FO delivered similar results except cases (7, 25, and 27) of high intra-patient variability where FOI provided slightly better estimates of intra-patient variability.

FOI versus FOCEI: FOCEI was superior to both FO and FOI (although there were cases when FO and FOI were sufficient).

FOCEI versus LNUMI: FOCEI was very similar to LNUMI except Model 10-11 where THETA parameter (distribution of the dose fraction between fast and slow components of absorption) was better estimated by the LENUIM method, and Model 66 where OMEGA parameter was better estimated by the LNUM method.

FOCE versus FOCEI (for models with non-transformed dependent variables): INTER option was necessary to obtain unbiased estimates when residual variability was very high (> 30%).

Models with original versus log-transformed dependent variables: Similar to the INTER option, log-transformation allowed to obtain unbiased estimates even when the residual variability was very high (40% or higher). For data sets with small to medium (30% or lower) residual error, models with and without log-transformation delivered very similar results. There was one model with dense sampling (Figure 2) where log-transformation slightly increased bias.

SPRED models: Nonmem V and VI and all applicable estimation method delivered identical results.

CPU time: Nonmem VI was similar (FO and LNUM) or faster (FOCE, FOCEI, LNON) than Nonmem V (Figure 2).

CONCLUSIONS

- For converged models, NM V and NM VI parameter estimates and minimum objective function values were nearly identical or very similar.
- Models with exponential residual error presented in the log-transformed variables performed similar to the ones fitted in original variables with INTER option.
- For problems with residual variability exceeding 40%, use of INTER option or log-transformation was necessary to obtain unbiased estimates of inter- and intra-subject variability. FOCEI performed superior to FOI and similar to LNUMI. For the examples considered in this work, FOCEI proved itself as the method of choice for population modeling of continuous data.


Objectives: To investigate performance of estimation methods with the specific objective to compare:

- NM V versus NM VI;
- FOI versus FO;
- FOI versus FOCEI;
- FOI versus LNUMI;

- (v) models implemented in the original versus log-transformed variables.

Methods: The following population models were investigated: 5 PK-PD, Emax (distribution of the dose fraction between fast and slow components of absorption) was better estimated by the LNUM method, and Model 66 where OMEGA parameter was better estimated by the LNUM method.

FOCE versus FOCEI (for models with non-transformed dependent variables): INTER option was necessary to obtain unbiased estimates when residual variability was very high (> 30%).

Models with original versus log-transformed dependent variables: Similar to the INTER option, log-transformation allowed to obtain unbiased estimates even when the residual variability was very high (40% or higher). For data sets with small to medium (30% or lower) residual error, models with and without log-transformation delivered very similar results. There was one model with dense sampling (Figure 2) where log-transformation slightly increased bias.

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