Close window

Parameter Estimates of Population Models: Comparison of Nonmem Versions and Estimation Methods	
Leonid Gibiansky	
QuantPharm LLC, North Potomac, Maryland, US	Leonid Gibiansky
Poster: Methodology- Algorithms	

Abbreviations: FO: First Order; CE: Conditional Estimation, I: INTER, L: LAPLACIAN; NUM: NUMERICAL, NON: NONUMERICAL; OF: objective function; NM V: Nonmem 5.1.1; NM VI: Nonmem 6.1.2.

Objectives: To investigate performance of estimation methods with the specific objective to compare: (i) NM V versus NM VI; (ii) FO versus FOI; (iii) FOI versus FOCEI; (iv) FOCEI versus LNUMI; (v) models implemented in the original versus log-transformed variables.

Methods: The following models were investigated: 5 PK-PD E_{MAX} or linear; 4 PK with dense sampling; 6 PK with sparse sampling. Data set and true parameter values reflected the real data but dependent variable was simulated. Each PK model was presented in both original and log-transformed variables. Simulated data were fit using Nonmem V (FO, FOCE, FOCEI, LNUM, LNON) and Nonmem VI (FO, FOI, FOCE, FOCEI, LNUM, LNUMI, LNON) estimation methods. Results were compared between methods and with the true parameter values. Windows XP with g77 FORTRAN compiler was used for all model runs.

Results: (i) NM V and VI delivered very similar results with the exception of one problem that revealed a bug in the NM VI code. After the bug was fixed, discrepancy disappeared. For converged models, OF were nearly identical except 2 LNON models where NM VI OF was lower by 6 and 8 points, respectively. NM V run times for FO, FOCE, FOCEI and LNON methods was on average, 20-50% longer than NM VI run times, while the run times of NM V and NM VI for LNUM were, on average, comparable. FOCE methods were about 10 times slower that FO and 2 times quicker than L; (ii) FO and FOI parameter estimates were similar for all problems with residual error CV < 40%; (iii) FOCEI was superior to FOI; (iv) FOCEI and LNUMI were similar in all but one cases where one of the parameters was more precisely estimated using LNUMI; (v) models in the original variables with INTER option performed similarly to models in log-transformed variables. For models with residual variability exceeding 40%, INTER option or log-transformation was necessary to obtain unbiased estimates of inter- and intra-subject variability.

Conclusion: For converged models, NM V and NM VI parameter estimates and OF values were 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 modelling of continuous data.

Return to the Publications Page

Return to the main page