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

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PAGE 2008, June 18-20, Marseille, France

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 population models were investigated: 5 PK-PD EMAX or linear; 4 PK with dense sampling; 6 PK with sparse sampling. Data sets and true parameter values reflected the real data but dependent variables were simulated. Each PK model was presented in both original and log-transformed variables. The simulated data were fitted 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 were on average 20-50% longer than NM VI run times, while the run times of NM V and NM VI for LNUM were comparable. FOCE methods were about 10 times slower that FO and 2 times faster 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.

Conclusions: 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 modeling of continuous data.

OBJECTIVES

- To compare the performance (convergence, speed) and parameter estimates (bias) of Nonmem V and Nonmem VI on a variety of population PK models using FO, FOCE, FOCEI, LNUM and LNON estimation methods;
- To compare the performance of the new FOI method versus FO and FOCEI in order to understand whether "CE" or "I" part is responsible for the improvement of the fit observed in FOCEI when compared to FO;
- To compare the performance of the new LNUMI method versus FOCEI;
- To compare the performance of the models with and without log-transformation of the dependent variable.

METHODS

- Fifteen data sets were simulated using the final population PK and PK-PD models and real datasets;
- Each data set was analyzed using Nonmem V (FO, FOCE, FOCEI, LNUM, LNON) and Nonmem VI (FO, FOI, FOCE, FOCEI, LNUM, LNUMI, LNON) estimation methods ;
- When applicable, each model was simulated and analyzed in both the original and log-transformed dependent variables.
- CPU Time, convergence, and bias relative to the true values were compared.

Table 1. Description of Models

Model Number	Model Description	Log-DV	Number of				
			Patients	Samples	Thetas	Omegas	Sigmas
0	Emax PK-PD, $PRED	no	2500	6	4	3	1
1	Linear PK-PD $PRED	no	5000	5	14	2	1
9	Emax (Hill) PK-PD $PRED	no	10	30	5	1	1
16	Poisson PK-PD $PRED	no	130	3	8	1	-
6	Indirect response Emax PK-PD, $DES ADVAN6	no	100	5	4	2	1
2, 3[a]	2 comp, IV, ADVAN3	yes	40	15	9	3	1 (30%)
4, 5[a]	4 comp, IV, ADVAN7	yes	10	20	9	4	2 (20%)
19, 20[a]		yes	10	20	9	4	2 (50%)
7, 8[a]	1 comp, oral, ADVAN2	yes	200	7	16	3	1 (50%)
10, 11[a]	2 comp, oral, lag, ADVAN4	yes	130	6	8	3	1 (30%)
12, 13[a]	3 comp, IV, ADVAN11	yes	1400	5	13	3	1 (25%)
14,15[a]	3 comp, IV, ADVAN11	yes	200	15	6	2	1 (20%)
17,18[a]	6 comp $DES ADVAN6	yes	36	50	17	6	2 (20%)
21,22[a]	1 comp, oral, ADVAN2	yes	200	6	4	3	2 (50%)
23, 24[a]	1 comp, oral, ADVAN2	yes	700	4	6	3	1 (40%)
25,26[a]	2 comp, oral and IV, Michaelis Menten elimination	yes	150	19	13	5	1 (20%)
27,28[a]		yes	150	19	13	5	1 (50%)

[a] Model used a log-transformed dependent variable

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 LNUMI method, and Model #6 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 (# 2) where log-transformation slightly increased bias.

$PRED models (# 0, 1, 9, and 16): 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)

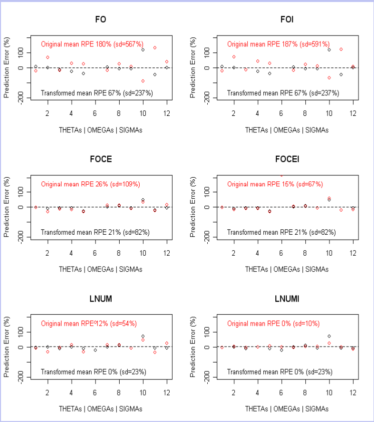

Figure 1. Bias of NM VI estimation methods for Models 10 (in the original variables, red) and 11 (the same model in the log-transformed variables, black)

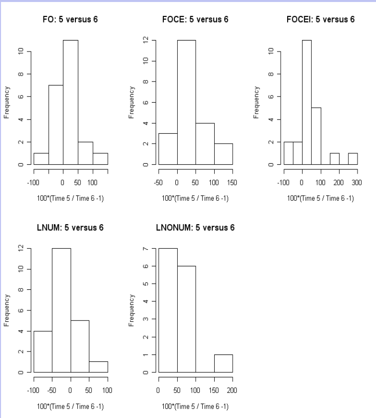

Figure 2. CPU time for Nonmem V versus Nonmem VI (computer load was not accounted for, therefore, the results should be treated as a rough estimate rather than precise evaluation of the performance).

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.