Precision of Parameter Estimates: Covariance ($COV) Step versus Bootstrap Procedure

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Objectives: To compare parameter estimates (PE), standard errors (SE) and 95% confidence intervals (CI) on PE obtained by bootstrap procedure and NONMEM $COV step (see definitions in Table 1).

Methods: Investigation included 13 pharmacokinetic and pharmacodynamic models identified on real datasets: 5 linear compartmental and 5 E_{MAX} models, 1 proportional odds, 1 time-to-event, and 1 Poisson model for count data (Table 2). Overall, the models included 126 THETA parameters, 31 OMEGA parameters and 9 SIGMA parameters. First, NONMEM V was used to fit the models using either First Order Conditional Estimation method with eta-epsilon Interaction (FOCEI) or LAPLACIAN method with LIKELIHOOD option. All models converged and provided PE, SE, and eigenvalues of the correlation matrix (EV). Separate runs with MATRIX=S and R options were used to compute SE and EV and compare them with SE and EV obtained by the default option (these $COV options can be used if the run with the default option cannot be completed). Then, 1000 bootstrap datasets stratified by covariates of interest were created for each model, and PE were obtained for each of these datasets. Results (irrespectively of convergence) were used to obtain 95% CI on PE. Medians and standard deviations of bootstrap parameter distributions were treated as bootstrap PE and SE. Correlation matrix of the bootstrap PE was estimated, and it's eigenvalues computed for each model. Finally, results of $COV step and bootstrap procedures (PE, SE, CI and EV) for all models together were compared visually and by computing correlation coefficients.

Results: Results indicate surprisingly good agreement of PE, SE, CI and EV (Figure 1 – Figure 3) obtained by the two procedures: correlation coefficients exceed 0.98. Correlation coefficients for CI normalized by PE exceed 0.82 for all but two models (Table 3). Two exceptions can be explained by a very shallow objective function profile and parameter correlations (Figure 4 and Figure 5). Agreement was even better for the well-estimated parameters (those with relative standard error RSE=100*SE/PE not exceeding 20%). Contrary to the expectations, agreement between variance parameters was similar to those for THETA parameters. For SIGMA parameters, nearly perfect agreement was observed. Good agreement of NONMEM and bootstrap CI and EV indicated that NONMEM variance-covariance matrix of the PE was in agreement with the bootstrap distributions of PE.

Conclusions: In the variety of examples with different PK and PD models, NONMEM FOCEI and LAPLACE estimation methods in conjunction with the default option of the $COV step provided excellent approximation of the estimation precision and correlation of PE. This applies not only to the model parameters but also to variances of the intersubject variability and the residual error. Nearly perfect agreement with bootstrap results was observed for the well-estimated parameters with RSE < 20%. MATRIX=S or R options also provided good approximation of the estimation precision.

References: Similar problems were discussed in Dartois C, et al. Evaluation of Uncertainty Parameters Estimated by Different Population PK Software and Methods. J Pharmacokinetic Pharmacodynamic Jan 2007.

Table 1 Definitions of the Main Quantities

Parameter	NONMEM	Bootstrap
PE: Parameter Estimate	Estimate of the parameter provided by the NONMEM final model	Median of the bootstrap parameter estimates (provided by the final model for 1000 bootstrap datasets)
SE: Standard Error	Standard error of the parameter estimate provided by the NONMEM final model $COVARANCE step.	Standard deviation of the bootstrap parameter distribution
95% CI: 95% confidence interval	Assuming normal distribution, computed as PE ± 1.96*SE	Computed as 2.5^{th} and 97.5^{th} percentiles of the bootstrap parameter distribution
EV: eigenvalues of the correlation matrix	Eigenvalues of the correlation matrix provided by NONMEM $COVARIANCE step using PRINT=E option.	Eigenvalues of the correlation matrix of bootstrap parameter distributions.

Table 2 Description of Models

Model			Number of Parameters		
Model	Type	Description	Θ	Ω	Σ
1	PK-PD	E_{MAX}	9	1	2
2	PK	Linear three-compartment oral	12	3	0^a
3	PK	Linear three-compartment oral	13	6	1
4	PK-PD	E_{MAX}	8	2	1
5	PK-PD	E_{MAX}	8	2	1
6	PK-PD	E_{MAX}	9	2	1
7	PK-PD	E_{MAX}	3	1	1
8	PK-PD	Weibull E_{MAX} time-to-event	5	0	0
9	PK	Linear three-compartment IV	16	2	0^a
10	PK-PD	Effect compartment E_{MAX} proportional odds (ordinal data)	8	4	0
11	PK	Linear one-compartment oral	17	4	1
12	PK	Linear two-compartment oral	10	3	1
13	PK-PD	Poisson model (count data)	8	1	0

[a] Combined error described by THETA parameters in log-transformed variables

Figure 1. Correlation of NONMEM and Bootstrap 95% Confidence Intervals

Top Row (log scale): correlation of the upper bounds (right), parameter estimates (middle) and the lower bounds (left).

Middle Row: correlation of the upper bounds normalized by the final parameter estimates (log scale), histogram of the bootstrap parameter estimates normalized by the final parameter estimates and correlation of the lower bounds normalized by the final parameter estimates (log scale).

Bottom row: blow up of the middle row figures.

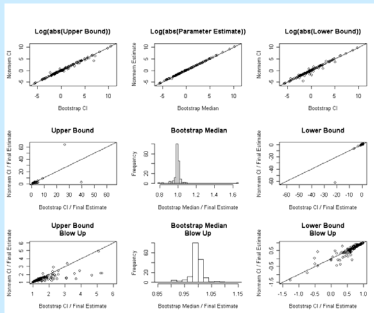


Figure 2. Correlation of NONMEM and bootstrap eigenvalues of the correlation matrix

Eigenvalues of the correlation matrix of the parameter estimates ($COV step PRINT=E option) are plotted versus eigenvalues of the correlation matrix of 1000 bootstrap parameter estimates.

Left column: default options; **Middle column:** MATRIX=S; **Right column:** MATRIX=R. **First Row:** original scale; **Second Row:** log scale

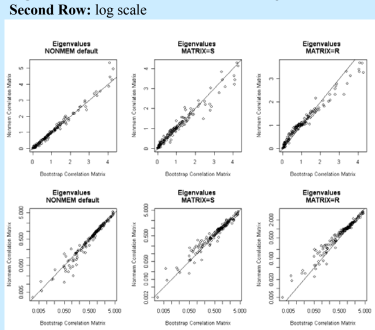


Figure 3. NONMEM and Bootstrap Normalized 95% Confidence Intervals versus Relative Standard Error of the Parameter Estimates (semi-log scale) .

Thin black lines: NONMEM 95%CI (1±1.96 RSE).

Bold black lines: Ratio of bootstrap PE to the final PE.

Points: bootstrap confidence intervals (**black**: THETAs; **green**: OMEGAs; **red**: SIGMAs).

Fist row: (left to right) sequentially closer look on the same dependence. Horizontal dashed line shows range of the next plot. **Second row:** top right plot divided by parameter type (left: THETAs, middle: OMEGAs, and right: SIGMAs)

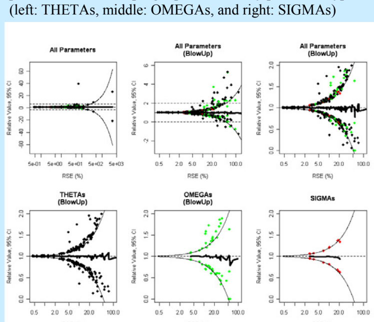


Table 3 Correlation of parameters between NONMEM and bootstrap: overall and for each model

N: number of parameters

CI_{boot} and CI_{NM}: bootstrap and NONMEM 95% confidence intervals

PE_{boot} and PE: bootstrap and NONMEM final parameter estimates

Red: correlation coefficient < 0.8

R^{Upper}= $Cor(CI_{boot}^{Upper}/PE, CI_{NM}^{Upper}/PE)$: correlation coefficients for the normalized upper bound

R^{Lower}= $Cor(CI_{boot}^{Lower}/PE, CI_{NM}^{Lower}/PE)$: correlation coefficients for the normalized lower bound

Parameters	N	R^{Upper}	R^{Lower}	SD of PE_{boot}/PE	Median of PE_{boot}/PE
Model 1	12	0.957	0.953	0.052	0.998
Model 2	15	0.506	0.955	0.011	0.995
Model 3	20	0.836	0.992	0.024	1.000
Model 4	11	0.970	0.970	0.010	1.000
Model 5	11	0.985	0.984	0.004	1.000
Model 6	12	0.847	0.934	0.014	1.000
Model 7	5	0.953	0.943	0.041	0.977
Model 8	5	0.920	0.999	0.016	1.004
Model 9	18	0.941	0.995	0.048	0.997
Model 10	12	0.299	0.530	0.017	1.003
Model 11	22	0.893	0.823	0.055	0.993
Model 12	14	1.000	0.999	0.175	0.999
Model 13	9	0.992	0.997	0.019	1.004

Figure 4 Comparison of NONMEM and bootstrap confidence intervals for Model 2 (linear three-compartment PK model).

Explanation for the large difference: V_2 is poorly defined (mostly steady-state data)

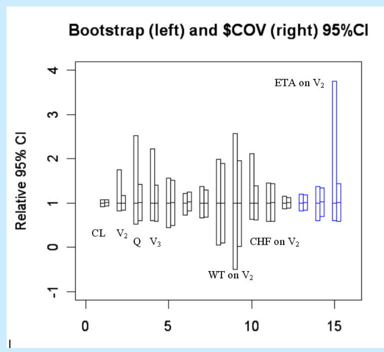
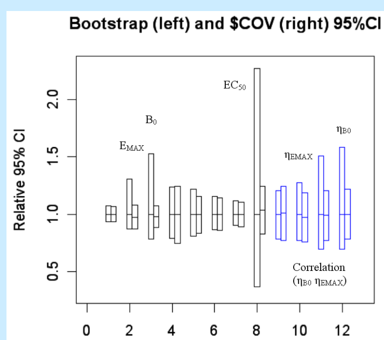


Figure 5 Comparison of NONMEM and bootstrap confidence intervals for Model 10 (proportional odds E_{MAX} PK-PD model).

Explanation for the large difference: strong correlation between PK and PD parameters (intercept B_0, E_{MAX} and EC_{50})



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