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Bias and Precision of Parameter Estimates: Comparison of Nonmem 7 Estimation Methods and PFIM 3.2 Predictions on the Example of Quasi-Steady-State Approximation of the Two-Target Target-Mediated Drug Disposition Model

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Poster: Methodology- Algorithms

Purpose: To compare performance of Nonmem 7 FOCEI, IMP, IMPMAP, SAEM, and BAYES methods on the simulated example of a complex pharmacokinetic system with rich sampling, and to compare precision of Nonmem parameter estimates with those predicted by PFIM 3.2 optimal design software.

Methods: The Target-Mediated Drug Disposition (TMDD) equations and the Quasi-Steady-State (QSS) approximation of these equations were extended [1] to describe drugs that can bind to multiple targets. This system was used to simulate a population data set for a monoclonal antibody that binds to both soluble (S) and membrane-bound (M) targets (3250 unbound drug and 3305 total S-target concentrations from 224 subjects; rich sampling; IV doses 100-600 nmol; SC doses 1000 nmol). It was assumed that the unbound drug concentrations and the total S-target concentrations are measured while the M-target is not observable. The true model (started from various initial conditions) was used to fit the simulated data using FOCEI, SAEM, BAYES, IMP, and IMPMAP methods as implemented in Nonmem 7.1.0. All models were MU-modeled with MUs being linear functions of THETAs; FOCEI model was also run without MU-modeling transformation. PFIM 3.2 optimal design software [2] was used to predict precision of the parameter estimates. The parameter estimates and their relative standard errors (RSE) obtained by different Nonmem methods were compared with each other, with the true values, and with PFIM predictions. All models used ADVAN13, TOL=9, INTER, NSIG=3, and SIGL=9. The other used options were: NBURN=15000, NITER=1000, and ISAMPLE=3 for SAEM, NITER=3000 and ISAMPLE=300 for IMP and IMPMAP, and NBURN=10000 or 20000 and NITER=5000 for BAYES.

Results: All estimation methods except IMP (that diverged) provided parameter estimates. Population and individual predictions of all methods were very similar. FOCEI did not converge exceeding the maximum number of function evaluations. $COV step failed with the default options but provided standard error estimates with MATRIX=S. For the fixed-effect parameters, FOCEI with MU-modeling (on the log scale of parameters) provided the best results with the maximum bias of 9%. The FOCEI method on the original parameter scale, SAEM, and BAYES were generally similar with the bias under 10% for all but 2, 2, and 4 fixed-effect parameters, respectively. IMPMAP was not able to estimate parameters of the M-target and generally had larger bias for the other fixed-effect parameters. The variances of the random effects were estimated with the larger bias, but overall, FOCEI and SAEM had the least bias followed by BAYES and IMPMAP. Estimates of RSE for the fixed effects and residual variability were in a good-to-perfect agreement between all Nonmem methods and PFIM predictions. For the variances of the random effects, FOCEI and BAYES provided RSE similar to PFIM while for IMPMAP and SAEM (with the covariance step performed by IMP) RSE estimates were higher than those predicted by PFIM. Surprisingly, for BAYES method increase of NBURN from 10,000 to 20,000 resulted in increase of the bias for most parameters.

Conclusions: For the simulated example of the TMDD model with two targets and rich sampling design, FOCEI, SAEM and BAYES estimation methods of Nonmem 7 performed similarly, both in terms of bias and precision of the parameter estimates. IMP method diverged while IMPMAP parameter estimates were more biased and less precise. FOCEI implemented in log-transformed parameter space overall performed better than all the other estimation methods. PFIM was shown to provide reliable estimates of the expected precision of the parameter estimates.

References:
[1] Gibiansky L, Gibiansky E, Target-Mediated Drug Disposition Model for Drugs That Bind to More than One Target. Submitted to Journal of Pharmacokinetics and Pharmacodynamics, 2010
[2] Bazzoli C, Retout S, Mentré F. Design evaluation and optimisation in multiple response nonlinear mixed effect models: PFIM 3.0. Computer Methods and Programs in Biomedicine, 2009

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