Bias and Precision of Parameter Estimates: Comparison of Nonmem 7 Estimation Methods and PFIM 3.2 Predictions on the Example of QSS Approximation of the Two-Target TMDD Model

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OBJECTIVES

- 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

- QSS approximation of the Two-Target TMDD equations [1] was used to simulate a rich population PK-PD data set for a drug that binds to soluble (S) and membrane-bound(M) targets.
- The dataset included 3250 unbound drug and 3305 total S-target concentrations from 224 subjects; rich sampling; IV doses 100-600 nmol; SC doses 1000 nmol.
- PFIM 3.2 optimal design software [2] was used to predict expected precision of the parameter estimates.
- 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.
- All models used ADVAN13, TOL=9, INTER, NSIG=3, SIGL=9 ($EST), and SIGL=12 ($COV). 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.
- 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.

REFERENCES

[1] Gibiansky L, Gibiansky E, TMDD Model for Drugs that Bind Soluble and Membrane-Bound Targets: Can Quasi-Steady-State Approximation Estimate Unobservable Membrane-Bound Target Occupancy?, PAGE 19 (2010) Abstract 1941 [www.page-meeting.org/?abstract=1941]

[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

RESULTS

- All estimation methods except IMP (that diverged) provided parameter estimates (Table 1).
- Population and individual predictions were very similar for all methods .
- 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.

Table 1. Parameters of the True QSS Model and Parameter Estimates (%RSE) [%Bias] Obtained by Various Nonmem 7 Estimation Methods

FOCEI covariance step failed with default options, and MATRIX=S option was used; SAEM RSE were obtained using IMP with EONLY=1, NITER=25, ISAMPLE=3000. Units: volume – liters, time – days, amount – nmol.

Param	True (PFIM)	FOCEI	FOCEI MU-model	SAEM	IMPMAP	BAYES NBURN=10000	BAYES NBURN= 20000
CL	0.3 (3)	0.327 (4) [9]	0.307 (4) [2]	0.305 (3) [2]	0.231 (2) [23]	0.334 (2) [11]	0.35 (2) [17]
V_c	3.0 (2)	3.03 (2) [1]	3.05 (2) [2]	3.01 (4) [0]	2.98 (2) [1]	3 (2) [0]	2.99 (2) [0]
Q	0.2 (4)	0.18 (5) [10]	0.193 (5) [4]	0.187 (12) [7]	0.209 (5) [4]	0.172 (3) [14]	0.164 (4) [18]
V_p	3.0 (4)	2.68 (6) [11]	2.85 (7) [5]	2.63 (14) [12]	2.72 (5) [9]	2.38 (3) [21]	2.13 (3) [29]
F_{SC}	0.7 (1)	0.684 (2) [2]	0.68 (2) [3]	0.673 (3) [4]	0.619 (3) [12]	0.682 (2) [3]	0.689 (2) [2]
k_a	0.5 (3)	0.5 (3) [0]	0.509 (3) [2]	0.517 (3) [3]	0.572 (3) [14]	0.503 (3) [1]	0.497 (3) [1]
V^M_{max}	1.5 (9)	1.22 (12) [19]	1.51 (11) [1]	1.52 (6) [1]	2.97 (2) [98]	1.16 (7) [23]	1.04 (10) [31]
K^M_{SS}	3.0 (9)	2.9 (12) [3]	3.28 (12) [9]	3.86 (0) [29]	8.49 (4) [183]	3.31 (10) [10]	3.76 (12) [25]
R^S_{max}	0.1 (2)	0.107 (3) [7]	0.108 (2) [8]	0.106 (9) [6]	0.104 (2) [4]	0.109 (2) [9]	0.108 (2) [8]
K^S_{SS}	0.015 (2)	0.0156 (2) [4]	0.0159 (2) [6]	0.0154 (12) [3]	0.0151 (3) [1]	0.0159 (2) [6]	0.016 (2) [7]
k^S_{deg}	10.0 (2)	9.9 (2) [1]	9.52 (3) [5]	9.89 (11) [1]	10.2 (2) [2]	9.58 (3) [4]	9.57 (3) [4]
k^S_{int}	0.05 (2)	0.0509 (3) [2]	0.049 (3) [2]	0.0495 (7) [1]	0.0538 (2) [8]	0.048 (3) [4]	0.0476 (3) [5]
ω^2_{CL}	0.04 (14)	0.0341 (13) [15]	0.0343 (18) [14]	0.0338 (522) [16]	0.0624 (22) [56]	0.0295 (14) [26]	0.0276 (16) [31]
ω^2_{Vc}	0.04 (14)	0.04 (15) [0]	0.0386 (16) [3]	0.0401 (116) [0]	0.0407 (19) [2]	0.0421 (14) [5]	0.0432 (15) [8]
ω^2_{Q}	0.04 (18)	0.0655 (22) [64]	0.0644 (20) [61]	0.0836 (19) [109]	0.13 (12) [225]	0.11 (16) [175]	0.151 (18) [278]
ω^2_{Vp}	0.04 (20)	0.0575 (16) [44]	0.0526 (17) [31]	0.0513 (142) [28]	0.0646 (37) [62]	0.0538 (22) [34]	0.0516 (24) [29]
ω^2_{FSC}	0 (-)	0 (Fixed)	0.0050 (76) [-]	0.00344 (6660) [-]	0.0107 (139) [-]	0.0143 (32) [-]	0.0141 (29) [-]
ω^2_{ka}	0.04 (29)	0.036 (30) [10]	0.0396 (30) [1]	0.0406 (525) [1]	0.0477 (59) [19]	0.056 (23) [40]	0.0521 (27) [30]
ω^2_{VMmax}	0.04 (45)	0.047 (34) [18]	0.0271 (69) [32]	0.0333 (554) [17]	0.0157 (50) [61]	0.0496 (36) [24]	0.0705 (37) [76]
ω^2_{KMss}	0 (-)	0 (Fixed)	0.0034 (1380) [-]	0 (4760) [-]	0.0354 (61) [-]	0.112 (48) [-]	0.146 (36) [-]
ω^2_{RSmax}	0.04 (12)	0.0471 (10) [18]	0.0384 (12) [4]	0.0397 (73) [1]	0.047 (15) [18]	0.0401 (13) [0]	0.0406 (12) [1]
ω^2_{KSss}	0 (-)	0 (Fixed)	0.00618 (62) [-]	0.0030 (1860) [-]	0.0162 (20) [-]	0.0128 (29) [-]	0.0121 (30) [-]
ω^2_{KSdeg}	0.04 (15)	0.0022 (39) [95]	0.0458 (17) [15]	0.0474 (37) [18]	0.0266 (18) [34]	0.0494 (14) [23]	0.0496 (14) [24]
ω^2_{KSint}	0.04 (23)	0.072 (14) [80]	0.0494 (19) [23]	0.054 (106) [35]	0.041 (19) [2]	0.0554 (22) [38]	0.0541 (20) [35]
σ^2_{drug}	0.0225 (2)	0.0223 (4) [1]	0.0215 (4) [4]	0.0215 (18) [4]	0.0245 (6) [9]	0.0213 (4) [5]	0.0213 (4) [5]
σ^2_{target}	0.04 (2)	0.0417 (3) [4]	0.0374 (3) [6]	0.0374 (6) [6]	0.0417 (3) [4]	0.0369 (3) [8]	0.037 (3) [8]
CPU time		40 hours	52.5 hours	81 hours	82 hours	23.5 hours	39 hours