Performance of FOCEI vs SAEM in Simple Population Pharmacokinetic analysis of Rich, Medium and Sparse data

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Introduction:

First order conditional estimation with interaction (FOCEI) is one of the most commonly used estimation methods in nonlinear mixed effects modeling while stochastic approximation expectation maximization (SAEM) is the newer estimation algorithm. This work aimed to evaluate the performance (accuracy, precision, completion rates, and runtimes) of FOCEI and SAEM estimation methods in population pharmacokinetic (PK) analysis using NONMEM® when implemented with a one compartment model across rich, medium and sparse sampling data.

Methods:

A one-compartment model (ADVAN1 TRANS2 and residual variability with proportional model) from previously published results[1] was used for the comparison. Three different scenarios were simulated; rich (8 to 12 samples per subject), medium (4 to 7 samples per subject) and sparse sampling data (1 to 3 samples per subject). In each scenario, 100 datasets (100 subjects/dataset) were simulated. The simulated data below the limit of quantification were removed from the datasets.

Every dataset was separately estimated with FOCEI and SAEM methods using the same initial estimates.

The percentage of relative estimation error (RER) and root mean square error (RMSE) of parameter estimates were calculated to assess the accuracy and precision. The completion rates and runtimes were also compared.

Results and Discussion:

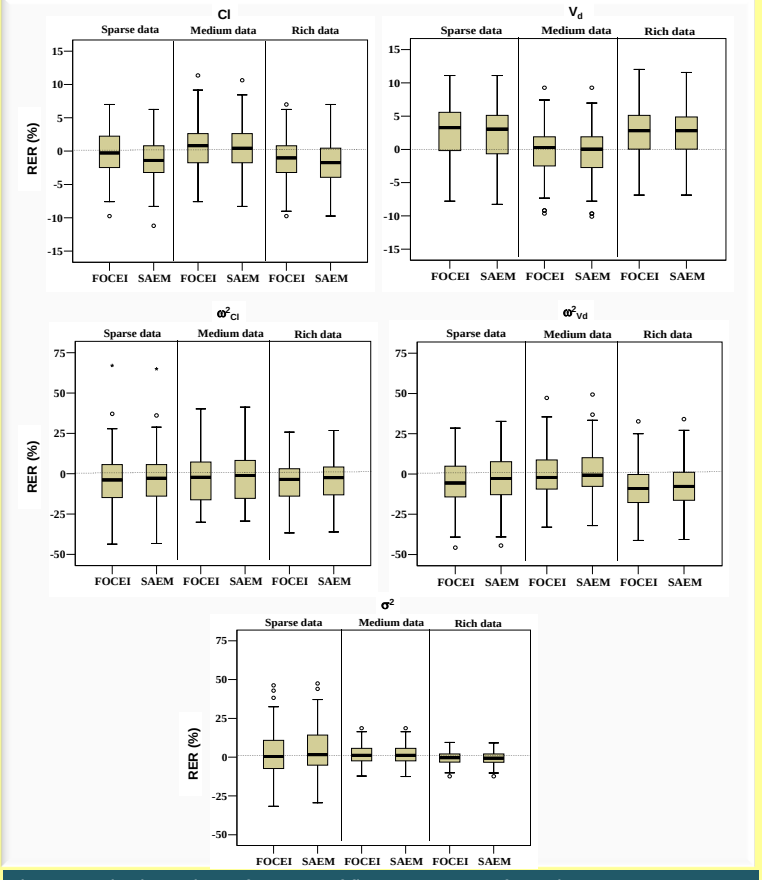

Figure 1: The box-plots of %RER of five parameters from the one-compartment model; Cl: Clearance; V_d: Volume of distribution; ω^2: Inter-individual variability; σ^2: Residual variability.

Results and Discussion:

Table 1: The root mean square errors of parameter estimates from FOCEI and SAEM estimation methods

Root mean square error	Sparse data		Medium data		Rich data	
	FOCEI	SAEM	FOCEI	SAEM	FOCEI	SAEM
Cl (L/h)	0.466	0.493	0.484	0.473	0.478	0.486
V_d (L)	1.016	0.993	0.769	0.784	0.913	0.895
ω^2_{Cl}	0.016	0.016	0.015	0.015	0.014	0.013
ω^2_{Vd}	0.023	0.023	0.022	0.022	0.022	0.021
σ^2	0.001	0.001	0.001	0.001	0.0004	0.0004

Cl: Clearance; V_d: Volume of distribution; ω^2: Inter-individual variability; σ^2: Residual variability.

Table 2: The runtimes of FOCEI and SAEM estimation methods

Median Runtime (mins) (Range)	Estimation methods	
	FOCEI	SAEM
Sparse data	0.18 (0.15 to 0.27)	5.85 (3.58 to 7.15)
Medium data	0.23 (0.20 to 0.33)	8.62 (5.40 to 10.07)
Rich data	0.29 (0.26 to 0.42)	10.70 (9.55 to 13.52)

Across the three scenarios, FOCEI provided the same accurate and precise parameter estimates as SAEM did (Median %RERs ranged from -9.03 to 3.27% and -7.64 to 3.04% for FOCEI and SAEM, respectively. RMSEs ranged from 0.0004 to 1.016 and 0.0004 to 0.993 for FOCEI and SAEM, respectively). Moreover, %RER of random effect parameter estimates were larger than %RER of fixed effect parameter estimates. Gibiansky et al. compared estimation methods available in NONMEM using rich data. They showed that when using the naive option both FOCEI and SAEM provided estimates similarly close to the true values and random effect parameter estimates had more deviation than fixed effect parameters[2], similar to the present study. In addition, FOCEI and SAEM provided the same completion rate of 100%. However, the runtimes were significantly shorter with FOCEI (ranged from 0.15 to 0.42 mins) compared to SAEM (ranged from 3.58 to 13.52 mins), different from the earlier finding which SAEM took shorter times than FOCEI when implemented with complex models.[2]

Conclusion:

In simple population PK analysis, FOCEI could provide accurate and precise PK parameter estimates across rich, medium and sparse data similar to SAEM but with significantly shorter run times.

References:

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2.Gibiansky L, Gibiansky E, Bauer R. Comparison of NONMEM 7.2 estimation methods and parallel processing efficiency on a target-mediated drug disposition model. J Pharmacokinet Pharmacodyn. (2012) 39:17-35.

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