Effect of dataset characteristics on estimation method performance: a TMDD model example

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Introduction

•Expectation maximisation (EM) algorithms included in NONMEM version 7.0 and above have shown increased numerical stability and reduced parameter bias in comparison to the traditional gradient based algorithms, FO and FOCE, in a selection of models [REF1, REF2].

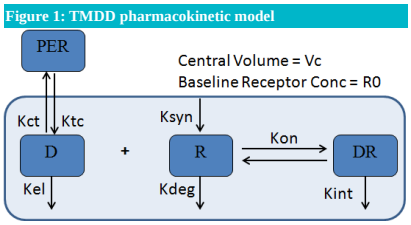
•The aim of this work is to compare the performance of the FOCE and importance sampling EM estimation methods in relation to different dataset characteristics.

•The target mediated drug disposition (TMDD) model [REF3] was chosen as the data descriptor.

Methods

•The model application by Ng and colleagues [REF4] was selected as a reference.

Figure 1: TMDD pharmacokinetic model



Param	Units	Pop Med	CV(%)
Kel	1/day	0.078	21.4
Kct	1/day	0.649	15.9
Ktc	1/day	0.874	24.9
Vc	1/(L kg)	0.0417	3.3
Kdeg	1/day	0.694	5.5
Kon	1/(nM day)	0.753	16.1
Koff	1/day	14.6	18.5
Kint	1/day	3.93	7.3
R0	nM	54.9	6.7

•All model parameters were taken to be log-normally distributed across the population.
•Eight phase 1-like datasets were simulated, differing in the residual variability, number of dose levels, and sampling density (Table 1, Figure 2).

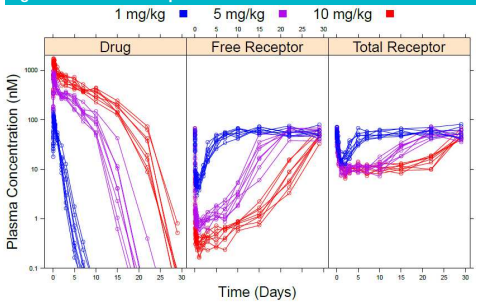
Table 1. Dataset characteristics

Dataset	Residual (%)	Dose Levels (mg/kg)	Sampling Density
1	15	1, 5, 10	Rich
2	30	1, 5, 10	Rich
3	15	1, 5	Rich
4	15	1, 5, 10	Sparse
5	30	1, 5	Rich
6	30	1, 5, 10	Sparse
7	15	1, 5	Sparse
8	30	1, 5	Sparse

•Each dose level consists of 8 subjects.
•The rich / sparse sampling densities involved 18 / 10 samples being taken over the 1 month study period.

Decreasing data quality

Figure 2. Time course profiles for dataset 1



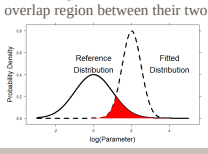
•The TMDD model was successfully fitted to each of the eight datasets using the FOCE, IMP and IMPMAP estimation methods of NONMEM v7.3.
•Convergence using the IMP and IMPMAP methods was preceded by a short ITS estimation procedure to quickly locate the maximum likelihood region, and followed by a high sample EONLY step for a more accurate assessment of the objective function [REF2].

```
$ESTIMATION METHOD=ITS INTERACTION NITER=10 ATOL=3 NOABORT
$ESTIMATION METHOD=IMPMAP INTERACTION ISAMPLE=1000 NITER=1000 CTYPE=3 CINTERVAL=3
CITER=10 CALPHA=0.05
$ESTIMATION METHOD=IMPMAP INTERACTION EONLY=1 ISAMPLE=10000 NITER=30 RANMETHOD=3S1
```

•Any variance terms estimated to be less than 1E-5 were fixed at 0.0025 (CV of 5%) and the model fitting procedure repeated.
•Model comparisons were made by considering objective function convergence and by the population median and between-subject variability in each model parameter.
•For this purpose the population median, and the 5th and 95th percentiles across the population, were normalised relative to the reference values according to:

$$\psi_{norm} = \frac{\psi - \psi_{med}^{ref}}{\psi_{95}^{ref} - \psi_{5}^{ref}}$$

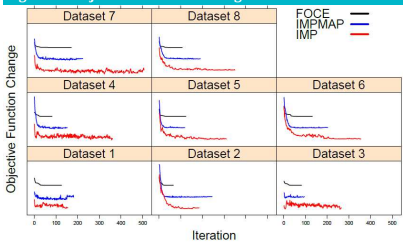
•For each parameter, the similarity between the fitted and reference distribution was measured by the overlap region between their two log-scale between-subject probability densities:



$$\phi = \int_{-\infty}^{+\infty} dx \cdot min\{\mathcal{N}(\mu,\omega^2), \mathcal{N}(\mu_{ref},\omega_{ref}^2)\}$$

Results

Figure 3: Objective Function Change versus Iteration

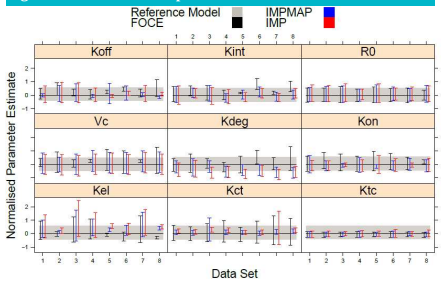


•Number of iterations to convergence are comparable between the FOCE and IMPMAP methods.

•In general, convergence using the IMP estimation method was less stable and required a greater number of iterations.

•In all FOCE model fits the covariance step failed, preventing standard error estimates from being reported.
•The final objective function value for the FOCE method converged to 3 decimal places, making it suitable for use in covariate hypothesis tests.
•For the IMP and IMPMAP methods, the objective function values from the last five EONLY step iterations typically varied over 10 or more units (ISAMPLE=10,000), which in this case makes these methods unsuitable to test covariate significance.

Figure 4: Parameter Comparisons Across Datasets



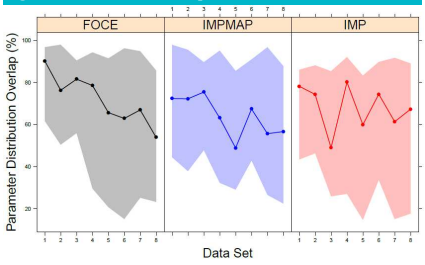
•All 5th, 50th and 95th percentile estimates are normalised (see Methods), and compared on a single lattice plot.

•Grey shaded region is the 5th to 95th percentile region of the reference parameter values.

•The vertical bar end-points are the 5th and 95th percentiles of the estimated parameters.

•Baseline receptor concentrations (R0) were accurately estimated for all datasets and estimation methods.
•The receptor degradation rates (Kdeg) were underestimated by the IMP and IMPMAP methods across all datasets. In contrast, FOCE estimates of Kdeg were superior, but accuracy decreased with dataset quality.
•IMP and IMPMAP methods compared favourably to FOCE for complex internalisation rate (Kint) estimates deduced from the poorer quality datasets 5 to 8.
•All estimation methods performed well at estimating the drug elimination rate (Kel) from the best dataset (dataset 1), but no method accurately characterised this parameter on any of the other inferior datasets 2 to 8.

Figure 4: Distribution Overlap Metric Across Each Dataset



•Parameter fits were characterised by the overlap region (ϕ) with respect to the corresponding reference distribution (see Methods).

•Solid Lines: Median overlap value across all model parameters.

•Shaded Regions: Minimum to Maximum overlap value across all model parameters.

•As one moves from the most data rich (dataset 1) to the most data depleted (dataset 8) scenario, the ability of each estimation method to estimate the population median and between-subject variability in the reference parameters drops off.
•In the data rich scenarios (datasets1 to 4) the FOCE estimation method performed as well, or better, than the IMPMAP and IMP algorithms.
•For the data deficient scenarios (datasets 5 to 8) performance of the FOCE algorithm falls away, with the distribution overlap metric falling as low as 20% for some parameters, and may be considered to be outperformed by the IMPMAP and IMP algorithms.

Conclusions

•When fitting a TMDD model to a PK/PD dataset, the route to convergence was most stable for FOCE and IMPMAP, and least stable for the IMP estimation methods.
•No single estimation method stood out as being superior over the entire range of datasets tested.
•For sufficient data with moderate residual noise (~15%), the FOCE method is most reliable.
•For the data limited scenarios the IMPMAP and IMP methods may be considered favourable over FOCE.

References

[1] Johansson, A. M., et al. Evaluation of bias, precision, robustness, and runtime for estimation methods in NONMEM 7. JPKPD (2014) 41:223-238
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