Real data experience of NONMEM 7.2 estimation methods with TMDD models

Tarjinder Sahota[1], Enrica Mezzalana[2], Alienor Berges[1], Duncan Richards[3], Alex Macdonald[1], Daren Austin[1], Stefano Zamuner[1]

1. Clinical Pharmacology Modelling and Simulation, GSK, UK
2. Department of Computer Engineering and Systems Science, University of Pavia, Pavia, Italy
3. Academic DPU, GSK, UK

GlaxoSmithKline

Introduction

Target-mediated drug disposition (TMDD) models are increasingly used to describe drug-target interactions. In practice, however, their use can come with long running times and convergence problems in NONMEM. Gibiansky et al., have previously used simulated data to investigate the accuracy and parallel processing efficiency of TMDD models with NONMEM 7.2.0 estimation methods[1]. They found all methods except BAYES gave accurate parameter estimates, accurate standard error estimates, and high (>85%) parallel processing efficiency.

Here we detail our clinical modelling experience of using FOCE and IMP with parallelisation. This consists of two separate TMDD modelling exercises. We evaluate the estimation methods for stability and parallel processing efficiency.

Methods

Compound A: CPHPC is a small molecule targeting serum amyloid P component (SAP), a soluble target. CPHPC was administered to patients, and plasma CPHPC and SAP samples were collected from baseline (day -1) to follow up (day 28).
Limitations of data:
•Only total concentrations (free + bound fractions of CPHPC-SAP) in plasma were available.
•Limited SAP recovery information was available.

Compound B: Otelixizumab, a monoclonal antibody which is directed against human CD3ε on T lymphocytes [2]. Free drug in serum and free, bound and total receptors on T cells (both CD4+ and CD8+) were measured using immunoassay and flow cytometry, respectively.
Limitations of data:
• More than 70% of free drug concentrations were below the limitation of quantification (BLQ).

Model development
Initial estimation in NONMEM 7.2 for both compounds was FOCE INTER. When convergence did not succeed the FOCE OFV deviance was calculated and IMP was used.
OFV deviance
FOCE OFV deviance was be found by computing the difference between the following OFVs:

```
$EST METHOD=1 INTER MAXEVAL=0
$EST METHOD=IMP EONLY=1 ISAMPLE=20000
```

Parallel processing efficiency
Parallel processing efficiency was calculated using: Efficiency =100% x (time of single CPU run)/ (p x time of p-CPU run). p was 4 for compound A, and 2 for compound B. 100% efficiency corresponds to a linear speedup.

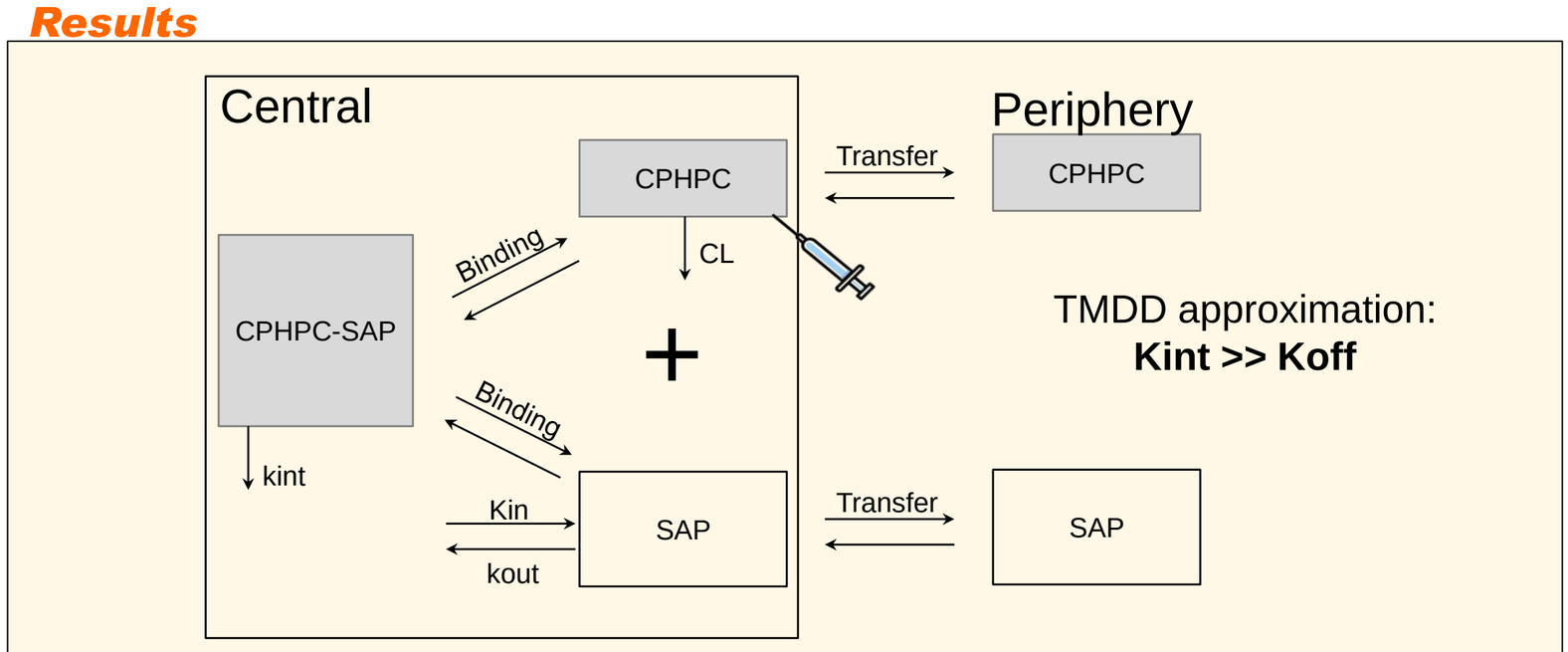
Conclusions

- In datasets with limited sampling schedules, FOCE can be unstable.
- Large deviance in OFV between FOCE and IMP can be an indicator of FOCE approximation bias.
- IMP enables the incorporation of likelihood based BQL handling methods (e.g. M3 and M4) without the characteristic loss of stability seen with FOCE
- Parallel processing efficiency varied between drugs. Differences between estimation method also appeared to be problem dependent.
- **With NONMEM 7, the use of exact likelihood methods (e.g. IMP) with multi-CPU parallelisation is recommended for the development of TMDD models within industrial time constraints.**

References

- [1]Gibiansky, L., et al. (2012) J. PKPD. 39 (1) 17-35
- [2]E. Mezzalana PAGE 2012
- [3]Ahn, J.E, et al (2010) J. PKPD. 35 (4) 401-21

Results

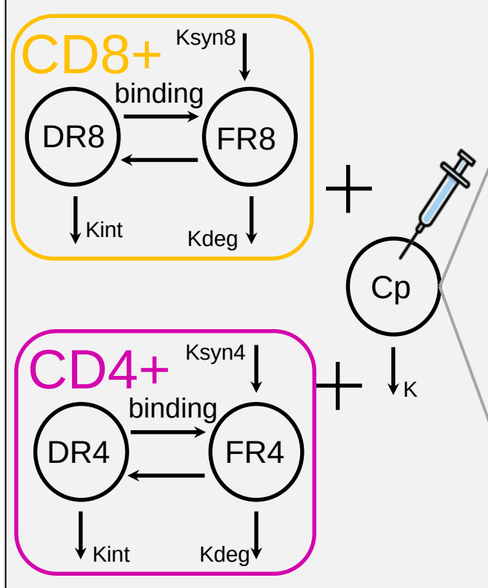


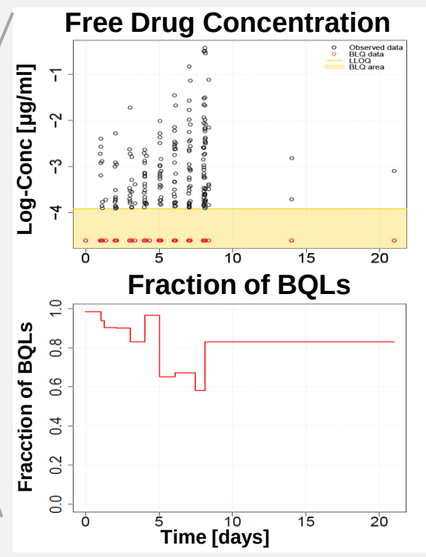
Model development: Compound A

Indirect response model	Base TMDD model	Base TMDD model	**Final TMDD model**
Method: FOCE INTER Estimation: No problems Parallel efficiency: 84%	Method: FOCE INTER **Estimation: Sensitive to initial estimates** Parallel efficiency: 72% OFV deviance: 1884	Method: IMP Estimation: No problems Parallel efficiency: 87%	Method: IMP Estimation: No problems Parallel efficiency: 90%

FOCE OFV deviance can be found by computing the difference between the following OFVs:

```
$EST METHOD=1 INTER MAXEVAL=0
$EST METHOD=IMP EONLY=1 ISAMPLE=20000 NITER=5
```





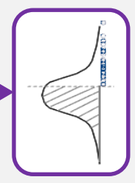
BQL handling methods[3]

M5: BQLs set to LLOQ/2

M3: different likelihoods for continuous or categorical (BQLs) data

BQL observations

$$l(t) = \Phi\left(\frac{LLOQ - f(t)}{g(t)}\right)$$



Probability observation is < LLOQ

Model development: Compound B

Base TMDD model	Base TMDD model	Base TMDD model + M3 BQL method	**Base TMDD model + M3 BQL method**
Method: FOCE INTER BQL method: M5 Estimation: No problems Parallel efficiency: 72%	Method: IMP BQL method: M5 Estimation: No problems Parallel efficiency: 66%	Method: FOCE INTER + LAPLACIAN BQL method: M3 **Estimation :** **No convergence** Parallel efficiency: 94% OFV deviance: **<1**	Method: IMP + LAPLACIAN BQL method: M3 Estimation: No problems Parallel efficiency: 55%