

Structural and practical identifiability of some mPBPK-TMDD models

Lavezzi Silvia Maria (1), Zamuner Stefano (2), De Nicolao Giuseppe (1), Ma Peiming (3), Simeoni Monica (2).
(1) University of Pavia, Pavia, Italy; (2) GlaxoSmithKline, London, United Kingdom; (3) GlaxoSmithKline, Shanghai, China

Background

In model building the study of structural (a priori) and practical (a posteriori) identifiability is a crucial step. **A priori identifiability** is a theoretical property of the model structure; it ensures that model parameters can be uniquely (globally or locally) determined from knowledge of the input-output behaviour assuming perfect experimental data [1]. **A posteriori identifiability** refers to the ability of practically estimating an unknown parameter vector and it is intimately related to the type and amount of experimental data available. A priori identifiability is a necessary but not sufficient condition for a posteriori identifiability [2]. In [3], four mPBPK-TMDD models for monoclonal antibodies with binding occurring in the leaky tissue were presented and compared:

- **Full Model** [4] (Figure 1),
- **Model A**, using a quasi-steady state (qss) approximation on binding process,
- **Model A+B**, using qss approximations on binding process and receptor concentration,
- **Model A+B+C**, including also a qss approximation on free antibody tissue concentration.

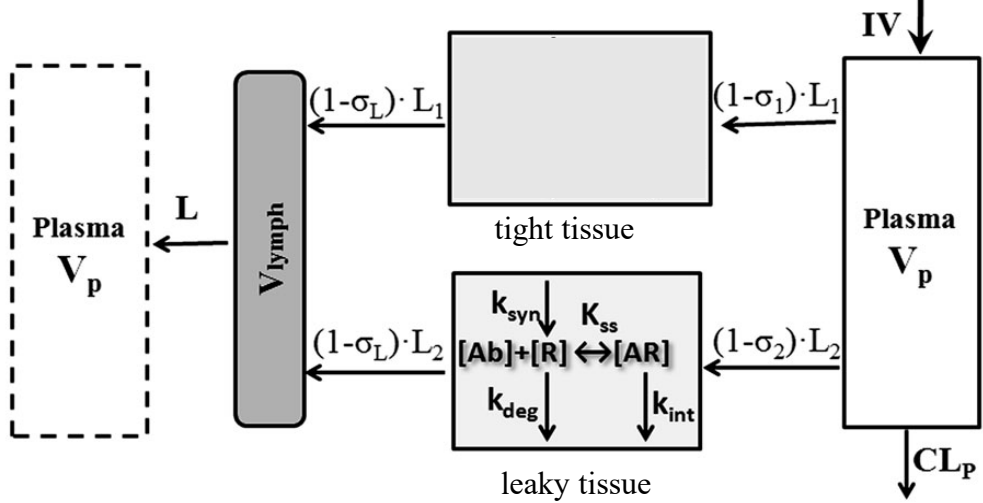


Figure 1: Representation of the Full mPBPK-TMDD Model with binding occurring in leaky tissue. The compartment in the left box represents the venous plasma, but is not applied in the present model [4].

Practical identifiability issues were detected. The present work aims to verify whether such issues originated from the lack of structural identifiability and to better explore practical identifiability via a Monte Carlo (MC) approach.

Methods

Local a priori identifiability analysis: A local a priori identifiability analysis of the models was conducted via the Identifiability Analysis package [1,5]. Prerequisite of this tool is for the model to be rational [3]. Although the approximated models are not rational, Model A and A+B could be rationalized by adding a dummy state; the same did not hold for Model A+B+C, hence its a priori identifiability could not be studied.

System input: i.v. bolus of 1, or 5 mg/kg.

Measurable system output:

- i. drug concentration in plasma, or
- ii. drug concentration both in plasma and in binding tissue, or
- iii. drug concentration in plasma together with target concentration in binding tissue.

Monte Carlo a posteriori identifiability analysis: The steps of MC a posteriori identifiability analysis were (Figure 2):

- Simulation from the Full Model of 100 datasets per each output choice (i., ii. and iii.), adding the residual error and using a realistic sampling schedule
- Fitting the four mPBPK-TMDD models on all the simulated datasets, with initial parameter values equal to the true ones with a perturbation of +/- 15%
- Examination of the distribution of parameter estimates via: boxplots, density plots, and computation of outliers, sample variance, confidence intervals, bias, MSE and RMSE. Furthermore, the parameters were ranked on the basis of the RMSE/(true value) ratio.
- Exploration of fitting quality by plotting: ODEs states vs. time, CWRES (Conditional Weighted Residuals) vs. Time, CWRES vs. plasma drug concentration, Goodness Of Fit (GOF) plots, and Visual Predictive Checks (VPC).

Software: Simulations of datasets were performed in R version 3.1.2, exploiting the deSolve package.

Fittings of the four models on all the simulated datasets were performed with NONMEM 7.3; the creation and the execution of the control stream files were automated via suitably written batch files; the output of such fittings was analysed in R version 3.1.2.

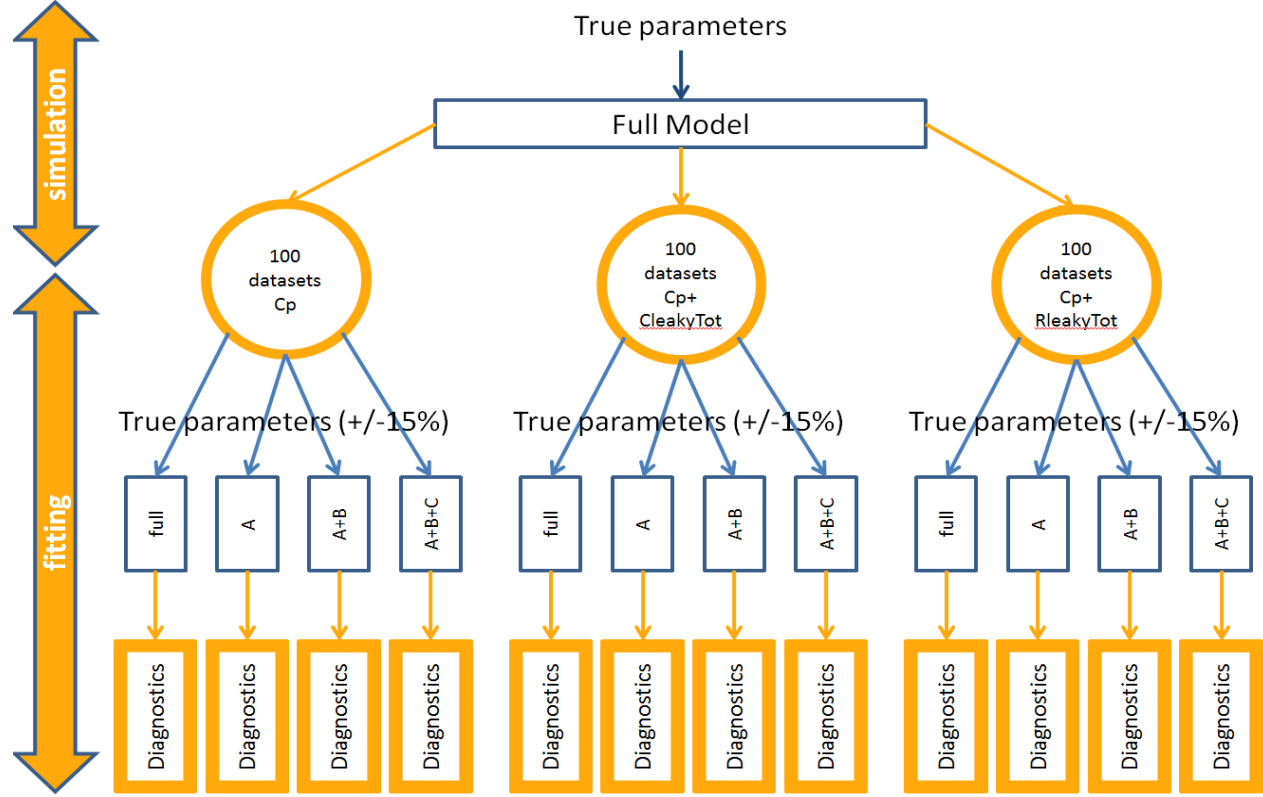


Figure 2: Diagram of the MC a posteriori identifiability analysis. Datasets were simulated with the Full Model and used to identify all the four mPBPK-TMDD models. NONMEM output tables were obtained and analysed.

Results

Structural identifiability

As already mentioned, Model A+B+C could not be fully rationalized and hence no results on its local a priori identifiability are available. Hence, the study of this property was carried out only for the other three models. Full Model and Model A were found to be a priori identifiable for every output choice (i,ii,iii). Model A+B turned out to be a priori identifiable only with the output choice iii. (see Table 1); in cases i. and ii. kdeg and kss are the non-identifiable parameters.

Execution of the Identifiability Analysis package function required one/two seconds.

Model \ Output	Output		
	Cp	Cp + Cleakytot	Cp + Rleakytot
Full Model	✓	✓	✓
Model A	✓	✓	✓
Model A+B	✗	✗	✓
Model A+B+C	—	—	—

Table 1: Summary of the results of the local a priori identifiability analysis. The green tick marks indicate that the model with the specified output choice is locally a priori identifiable, while the red crosses indicate the opposite; the straight black lines indicate that the assessment was not possible.

Practical identifiability

As for MC analysis, the time required for NONMEM 7.3 to fit a “100 runs set” ranged from about 1 minute to about 13 minutes, depending on the fitted model and the number of outputs considered.

- Taking as an example the scenario with the Full Model and plasma drug concentration as output measure, it can be observed that the parameters with the maximum CVs% are the ones linked to the processes of binding, degradation and internalization of the complex. In Figure 3 the distributions of the parameters estimates for this scenario are reported.

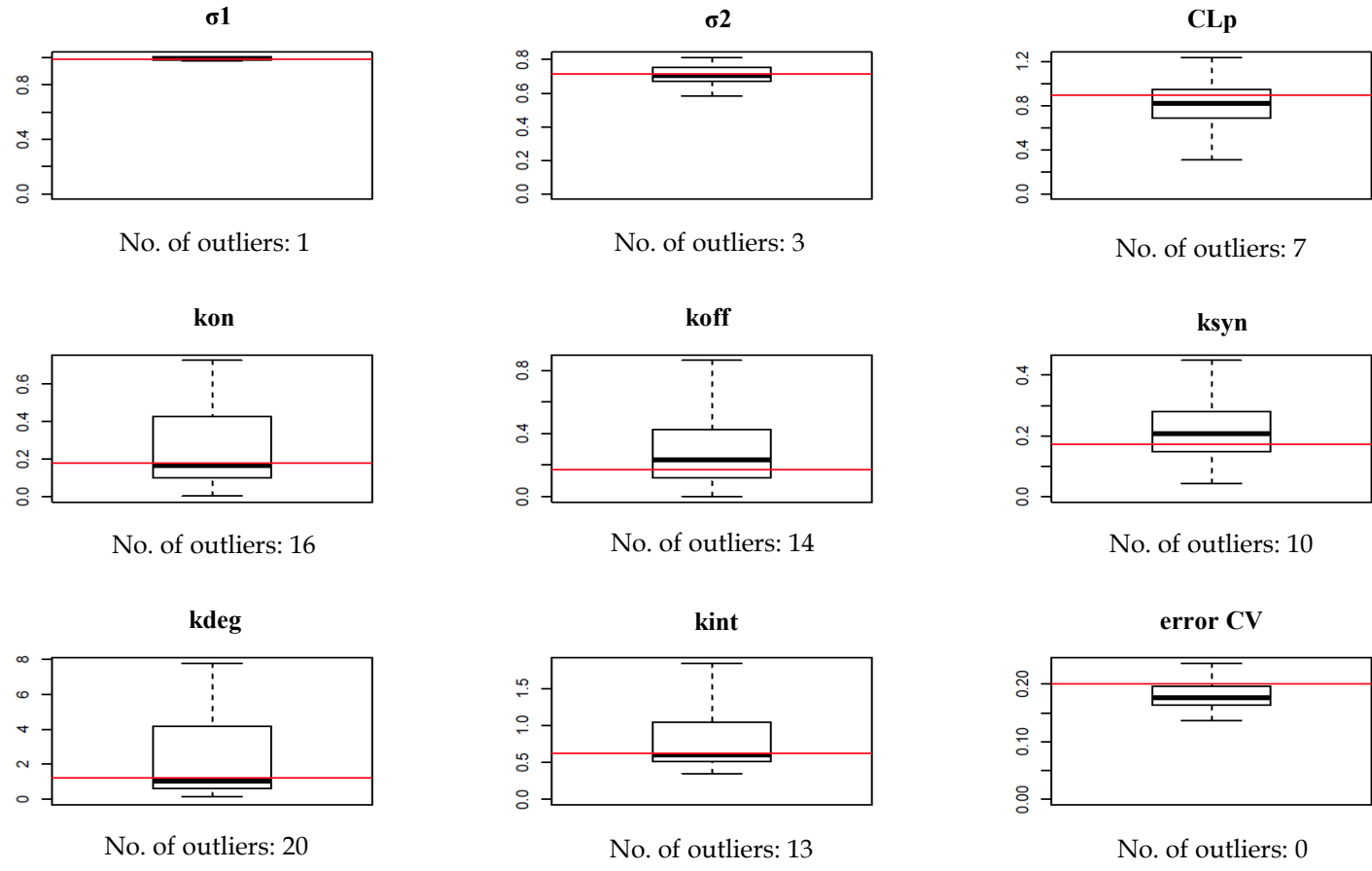


Figure 3: Boxplots representing the distributions of parameters estimates obtained identifying the Full Model on plasma drug concentration data. The number of outliers is indicated.

- The ranking of the parameters based on the RMSE/(true value) ratio allowed the quantification of the sensitivity of parameter estimates to noise in the data: it is worth noticing that the “worst” parameters are, for the Full Model, kon and koff (rank around 120-125%), and for the other three models, in most scenarios, kdeg and kss (with rank often exceeding 130%).
- A classification of the different scenarios based on the maximum CV% obtained for the estimates is presented in Table 2.

Scenario	Max CV%	Scenario	Max CV%
Model A+B / Cp & Cleakytot	39.767	Full model / Cp & Rleakytot	93.443
Model A+B+C / Cp & Cleakytot	65.281	Full model / Cp & Cleakytot	97.072
Model A / Cp & Rleakytot	65.665	Model A+B / Cp	100.042
Model A+B / Cp & Rleakytot	71.445	Full model / Cp	107.261
Model A+B+C / Cp & Rleakytot	72.755	Model A / Cp & Cleakytot	160.555
Model A+B+C / Cp	93.204	Model A / Cp	184.312

Table 2: Classification of the evaluated scenarios: the four mPBPK-TMDD models fitted on the three types of dataset. For each case, the maximum value for CV% obtained for the parameters’ estimates is reported.

- As for CWRES and GOF plots, they did not show significant trends in any scenario.
- Despite the great variability in parameter estimates, in every scenario the VPCs show that the fitted curves agree well with the noise-free measurable outputs considered. These plots were produced by overlaying the noise-free simulated data to the percentiles of the noise-free fitted curves obtained in each “100 runs set”. An example is reported in Figure 4, for the “worst” scenario (see Table 2), with Model A and plasma drug concentration as output measure.

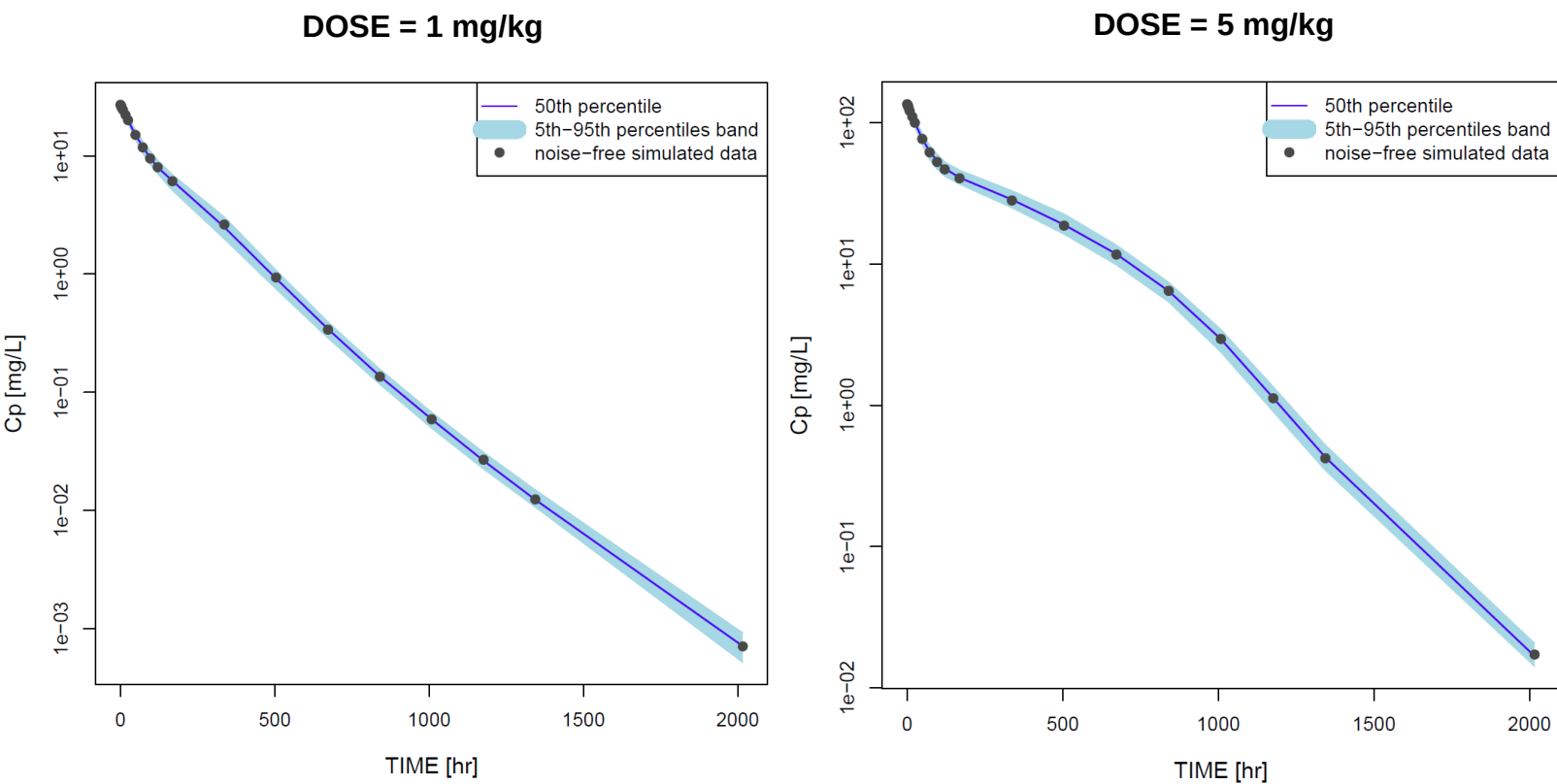


Figure 4: Example of VPCs for the scenario Model A + Cp as output measure. The black dots represent noise-free data, the blue line represent the median of the 100 identified noise-free profiles, while the light blue band represents 5th-95th percentiles.

Conclusions

A priori and a posteriori identifiability of four mPBPK-TMDD models [3] were investigated. For the Full Model and Model A, it was found that practical identifiability issues previously detected are not due to a lack of structural identifiability. The Monte Carlo analysis confirms that all four models have practical identifiability issues. Further development may concern the potential benefits ensuing from adopting optimal design methods.

References

[1] *An Efficient Method for Structural Identifiability Analysis of Large Dynamic Systems*. J. Karlsson, M. Anguelova, M. Jirstrand. 16th IFAC Symposium on System Identification, 16 (1), 941-946, 2012.
[2] *Structural Identifiability of Systems Biology Models: A Critical Comparison of Methods*. O.-T. Chis, J.R. Banga, E. Balsa-Canto. PLoS ONE, 6 (11), 1-16, 2011.
[3] *Integrating Target Mediated Drug Disposition (TMDD) into a minimal physiologically based modelling framework: evaluation of different quasi-steady-state approximations*. E. Mezzalana, S.M. Lavezzi, S. Zamuner, G. De Nicolao, P. Ma, M. Simeoni. PAGE 24 (2015) Abstr 3598
[4] Cao Y, Jusko WJ (2014) Incorporating target-mediated drug disposition in a minimal physiologically-based pharmacokinetic model for monoclonal antibodies. J Pharmacokinet Pharmacodyn 41(4):375-87.
[5] *Minimal output sets for identifiability*. M. Anguelova, J. Karlsson, M. Jirstrand. Math Biosci, 239, 139-153, 2012