Improved diagnostic plots require improved statistical tools. Implementation in MONOLIX 4.0

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Background

- Model evaluation is a crucial part of model building. The modeler requires numerical and graphical tools for deciding if the proposed model adequately describes the underlying system.
- Because of the complexity of the pharmacometrics models (mixed effects models, non linearities, covariates, residual errors, BLQ data,…), these tools must be used carefully to avoid misinterpretation due to a poor use.
- Several diagnostic tools (VPC, npde, weighted residuals,…) have been already developed and implemented in different softwares (Xpose, Monolix, …).

Objectives

Improve existing tools for model evaluation

1. *Visual Predictive Checks* (VPC) compares the distribution of the observations with the distribution of simulated data by grouping the data into bins. The binning strategy is crucial to provide a correct summary of these distributions. An automatic binning strategy is extremely useful for the modeler.
2. Because of possible shrinkage, *Empirical Bayes Estimates (EBEs)* based diagnostics may be of limited value for model evaluation. EBEs should be replaced by better suited individual estimates.
3. Presence of *Below the Limit of Quantification* (BLQ) data must be carefully taken into account in graphs to not introduce artifact and bias.

Models and Methods

1. We propose a method that automatically determines the optimal binning (i.e. the number of bins and their limits). The optimal limits of the bins are obtained by optimizing a modified least-squares criteria using a dynamic programming algorithm. The number of bins is selected using a model selection approach.
2. We suggest replacing the EBEs with predicted individual parameters correctly simulated with their conditional distribution. An MCMC procedure is used for this simulation.
3. We suggest replacing these BLQ data by data correctly simulated with their conditional distribution. An acceptance-reject procedure is used for this simulation.

Numerical Experiments

1. An alternative to EBEs for inference

We applied the proposed methodology on the warfarin PK data. Few data were collected during the first hours and most individual absorption rate constants *ka* are shrinked toward the population rate constant (Figure 2-a). Inference on the distribution of *ka* should not be based on the EBEs but on the simulated parameters which are not affected by any possible shrinkage (Figure 2-b).

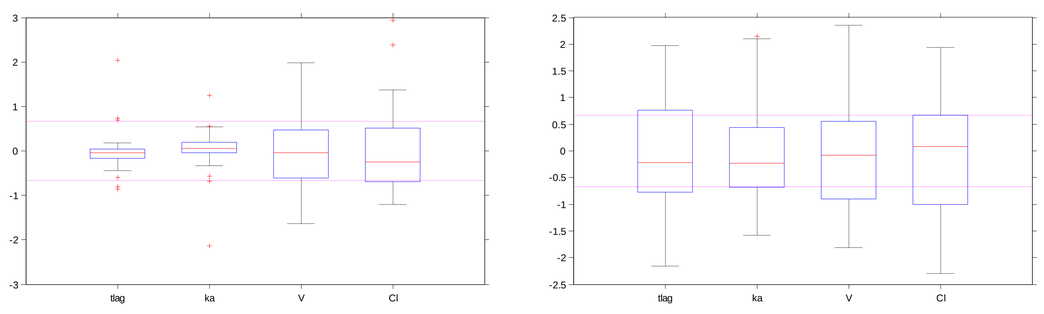

Figure 1: distribution of the standardized random effects ;
(a) random effects estimated by maximizing the conditional distribution (EBEs); (b) random effects simulated with the conditional distribution

2. VPC based on optimal binning

When the data presents clusters of different sizes, equal size binning (similar amount of data in each bin) produces a poor description of the data since a bin overlaps different clusters (Figure 2-a). On the other hand, the proposed method perfectly detects the clusters and the resulting VPC correctly detects a poor absorption model and a miss-specified residual error model(Figure 2-b).

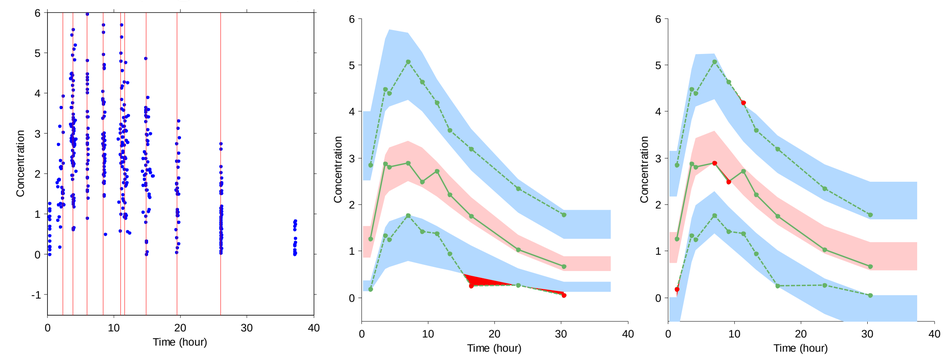

Figure 2-a: Equal size binning (similar amount of data in each bin). The VPC does not allow to distinguish the correct model used for the simulation (middle) from a wrong model (right).

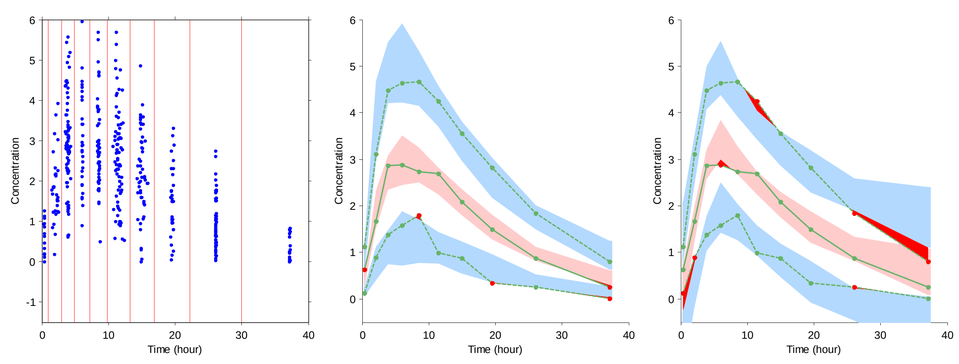

Figure 2-b: Optimal binning (implemented in MONOLIX 4.0).
The VPC clearly allows to distinguish the correct model (middle) from a wrong model (right).

3. Handling BLQ data

We used the theophylline PK data to illustrate the proposed method. Different LOQs were arbitrary introduced in the original data. As expected, the residual computed by replacing the BLQ data with the LOQ present a positive bias (Figure 3-a). On the other hand, no bias is introduced when imputing the BLQ data with simulated data (Figure 3-b).

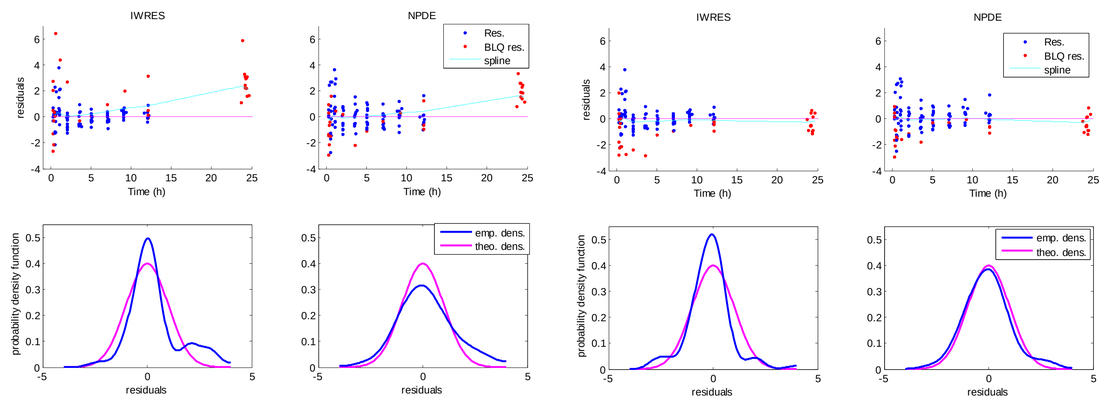

Figure 3: Individual Weighted Residual and NPDE (a) residuals computed by replacing the BLQ data with the LOQ; (b) residuals computed using BLQ data simulated with the conditional distribution $P(y_{BLQ} \mid y_{obs})$

Conclusion

Even if the existing procedures generally used for producing diagnostic plots are satisfactory in standard situations, some improvements appear to be necessary in more difficult situations (sparse data, BLQ data,…). Computational statistics can provide different new valuable tools (simulation procedures, MCMC, optimal segmentation,…) to improve model evaluation.

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[3] Hooker A., Karlsson M., Jonsson Niclas, *Xpose 4*, http://xpose.sourceforge.net
[4] Lavielle M. and the Monolix team *"MONOLIX 3.2 User's Guide"*, http://software.monolix.org, 2010.