

Quantification of model misspecification of population PK models by a machine learning postprocessing correction of the residual variability.

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Introduction

In Population Pharmacokinetics (PopPK) one of the main sources of residual unexplained variability (RUV) is model misspecification. Efforts have been made to address this issue [1-3]. In this work we address the problem of model misspecification, by modelling RUV by Machine learning (ML) methods in a postprocessing step after conventional model building. The practical purpose of the method is two-fold: (a) the generation of realistic virtual patients (VP) and (b) the quantification of the extent of model misspecification, by introducing an appropriate metric, to be used as an additional diagnostic of model quality.

Methods

The first step of the proposed methodology consists of the following:

- Develop the mixed effects mathematical model.
- Compute the individual residual error $IRES = DV - IPRED$
- Train the machine learning model to the IRES to obtain $IRES_{ML}$.
- Perform the correction of the model predictions based on the modeled residual error $DV_{sim} = IPRED + IRES_{ML}$.

For the second step of the methodology, we assume that the portion of the IRES explained by the ML algorithm offers a magnitude of model misspecification of the original model. Therefore, a goodness of fit metric was computed between the “observed” IRES and $IRES_{ML}$ to quantify this magnitude. The metric appropriate for the purpose was chosen to be, the R^2 , of the IRES vs $IRES_{ML}$, i.e.:

$$R2ML = 1 - \frac{\sum_{i=1}^N (IRES_i - IRES_{ML,i})^2}{\sum_{i=1}^N (IRES_i - \overline{IRES})^2}$$

The methodology was tested on the following scenarios:

- A Ropinirole dataset with two proposed models (optimal and poor) to test the ability of the method to perform corrections.
- Ropinirole, Busulfan and MMF datasets to study the behavior of R2ML.
- A synthetic example of two 2-CMT data - one with a mild and one with a stronger biphasic shape - fitted to 1-CMT model to demonstrate two levels of model misspecification.

Results

❖ In the ropinirole case, with the optimal PopPK model (model 1) the application of the ML methodology significantly improved the individual predictions as seen in figure (1). For the poor model (model 2) the improvement was greater as seen in figure (2). This shows that for the more misspecified model, the ML algorithm can achieve more pronounced corrections to the predictions. IRES vs time plots for both models were created using the corrected predictions and the trends and bias which were present in the initial models, were corrected. VPCs were also improved.

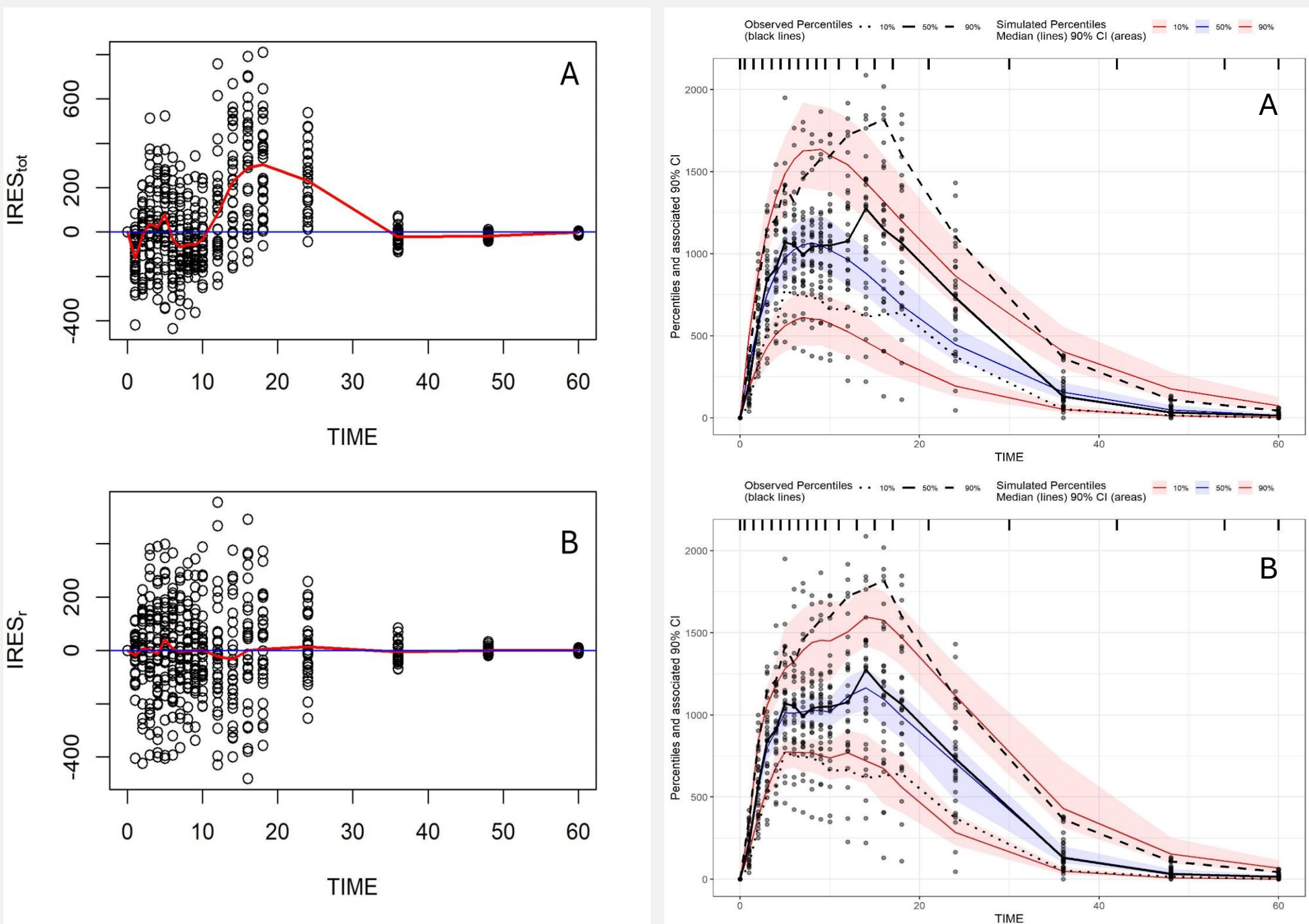


Figure 2. Corrected(B) and Uncorrected(A) diagnostic plots for model 2.

❖ The individual profiles of virtual patients for the two ropinirole models looked more realistic and more similar to the corresponding real, observed profiles after the correction, compared to the uncorrected profiles as seen in figure (3). Regarding the study of the quantification metric R2ML, the more misspecified models indeed have a higher R2ML than the less misspecified ones. The R2ML for the synthetic example shows that the 1-CMT clearly performs better for the mild model than the strong biphasic one, as expected, whereas the poor ropinirole model also has a higher R2ML than the

optimal one. The R2ML for the not misspecified busulfan model is close to 0 whereas for the MMF where some misspecification was present, R2ML is moderate, as seen in Table (2).

Table 2. Effective Doses and Maximum activities for all ages.

Model	R2ML (%)
Ropinirole (Poor)	41
Ropinirole (Optimal)	22
Busulfan	0.08
MMF	30
1CMT (Mild)	25
1CMT (Strong)	47

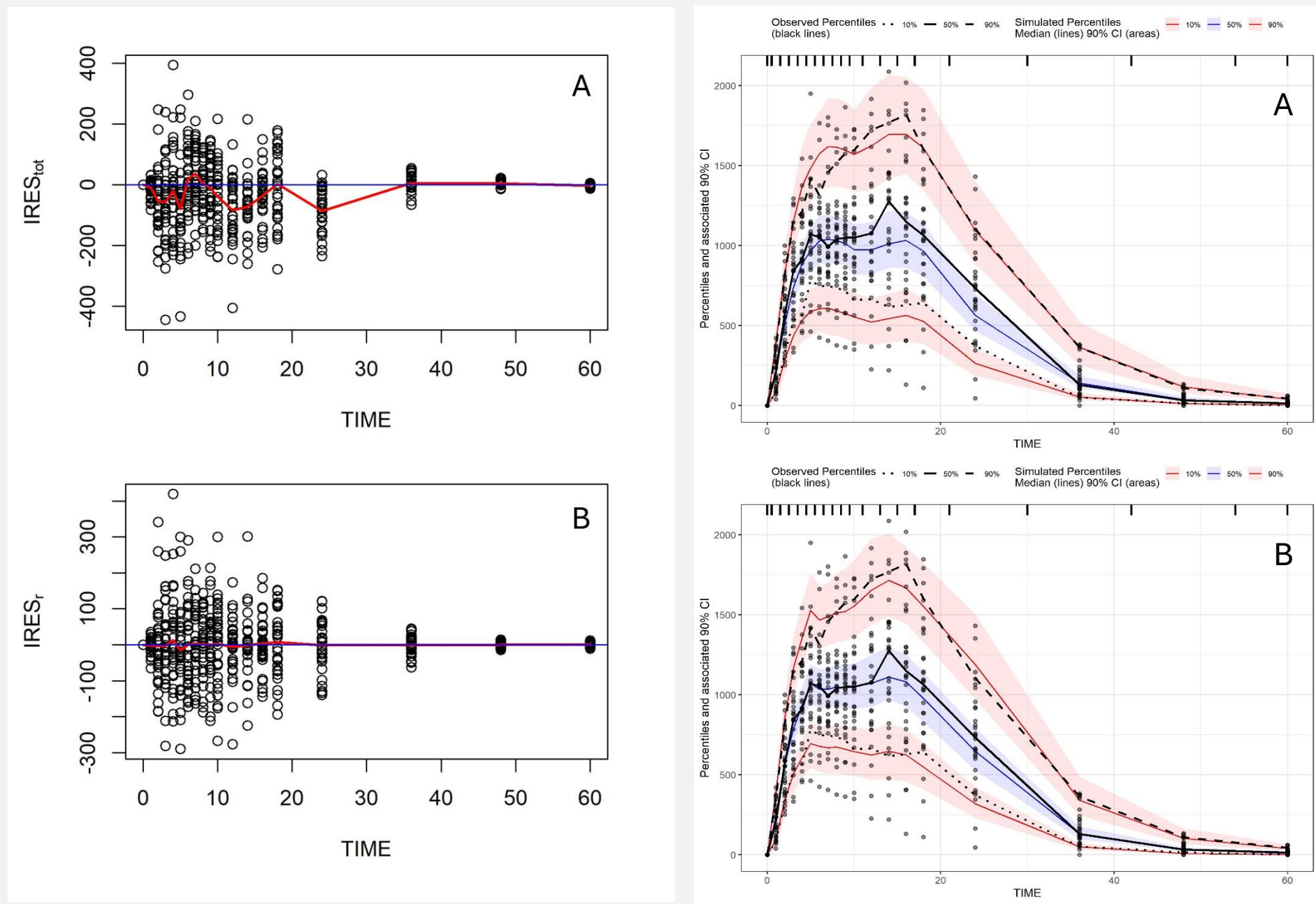


Figure 1. Corrected(B) and Uncorrected(A) diagnostic plots for model 1.

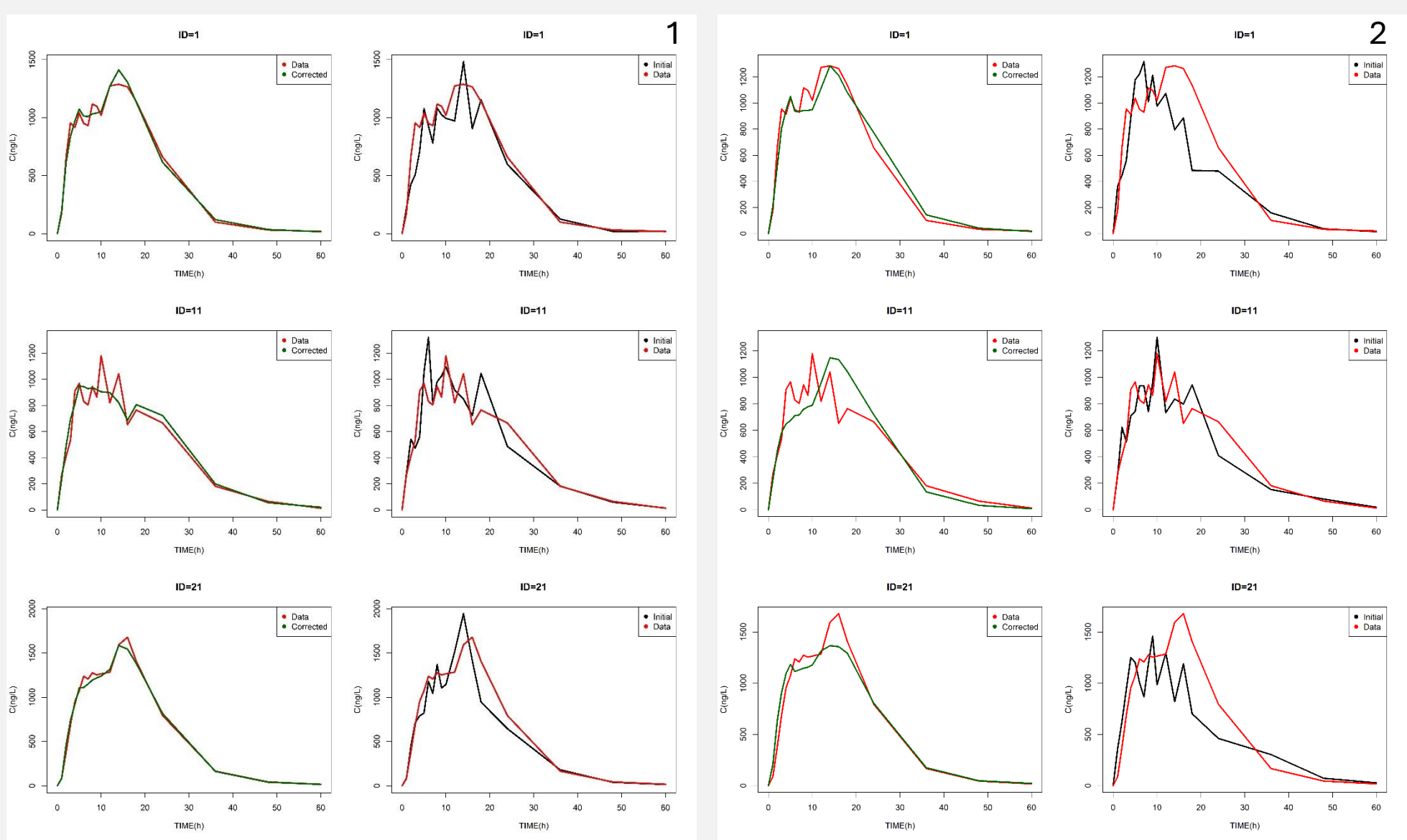


Figure 3. Profiles of the corrected virtual patients compared to the initial ones for models 1 and 2.

Conclusions

- We present a novel application of ML in pharmacometrics to address model misspecification by modelling RUV
- Corrected virtual patients were generated for the Ropinirole Case study which looked much more realistic and in accordance with the data and a numerical index was introduced to quantify model misspecification.
- The new method can be useful for simulation exercises where individual predictions are considered, such as for example for model informed bioequivalence studies [4], while the R2ML is a novel quality measure for models that could have many applications.
- More details can be found in the recent publication [5]

References

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