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HANDLING INTER-OCCASION VARIABILITY IN MODEL IMPLEMENTATION FOR BAYESIAN FORECASTING: A COMPARISON OF METHODS AND METRICS.

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Introduction

When implementing a PK model into a Bayesian forecasting (BF) program for therapeutic drug monitoring (TDM), the implantation of inter-occasion variability (IOV) can greatly impact on the predictions. A number of approaches exist to handle IOV, which include ignoring IOV, weighting functions, or variations of accounting for IOV during Bayesian estimation. In this study, we aimed to compare five methods for handling IOV using different metrics in simulations and in a real dataset example.

Methods

Simulations were performed using a 1-compartment population PK model (CL: 5 L/h, V: 20 L, interindividual variabilities (variance) IIV_{CL}: 0.1, IIV_V: 0.1, varying IOV_{CL}: 0.0-0.1, proportional unexplained residual variability (RUV_{prop}) 10 %CV) with a rich (8 samples over 8-hourly dosing) and a sparse sampling design (2 samples at 1 h and 7 h post dose) in 1000 subjects. A real dataset (423 patients, 2422 PK samples) and the resultant 2 compartmental PK model [1] was also utilised.

Forecasting of occasion 6 PK observations for every individual using data from occasions 1-5 (simulation study) or of occasion 3 PK observations from occasions 1-2 data (real data) was assessed. Simulations, estimations and forecasting was performed in NONMEM® 7.4.1. The model implementation methods tested were:

(i) 'True' model with IIV and IOV, quantifying η_{IIV} and η_{IOV}'s, but using only η_{IIV} for forecasting [2]
(ii) IIV + IOV: adding ω^2_{IOV} to ω^2_{IIV} together
(iii) IIV-only 1: re-estimation of a model without IOV, using the new parameters for forecasting
(iv) IIV-only 2: setting ω^2_{IOV} to zero
(v) IIV-only 3: weighting down samples from past occasions by doubling RUV of these

The metrics to evaluate forecasting were:

A rBias/rRMSE calculated based on the individual predicted (IPRED) vs. observed concentration (DV) at the forecasted dosing occasion, and
B rBias/rRMSE calculated based on the estimated individual PK parameter (EBE without η_{IOV}) versus the true parameter (simulation study) or the individual PK parameter determined from the final published model (real data).

Results

The simulation study showed that increasing IOV increased rBias/rRMSE in all metrics (Fig. 1 and 2). Metrics A displayed a positive bias in all scenarios with method (v) being least biased, followed by (i), (iii), and (ii)≈(iv).

For metrics B, individual CL and V determined by method (i) showed to be least biased, followed by (iii), (iv), (ii), and (v). Similar results were obtained with the sparse simulation data (Fig. 2)

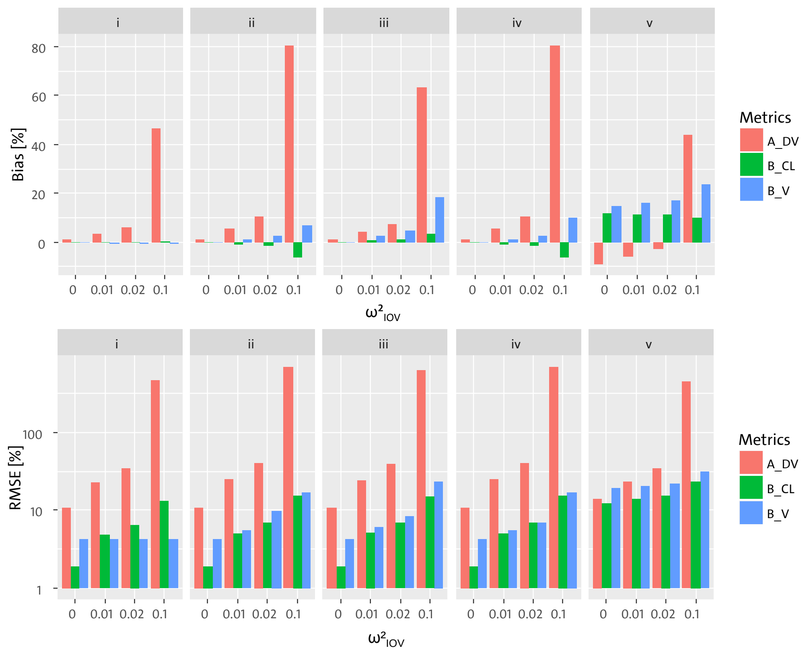

Figure 1: Bias (upper panel) and RMSE (lower panel, log-scale) of IOV handling methods (i)-(v) evaluated by IPRED-DV based metrics A and EBE-based metrics B for the simulation study with the **rich design**.

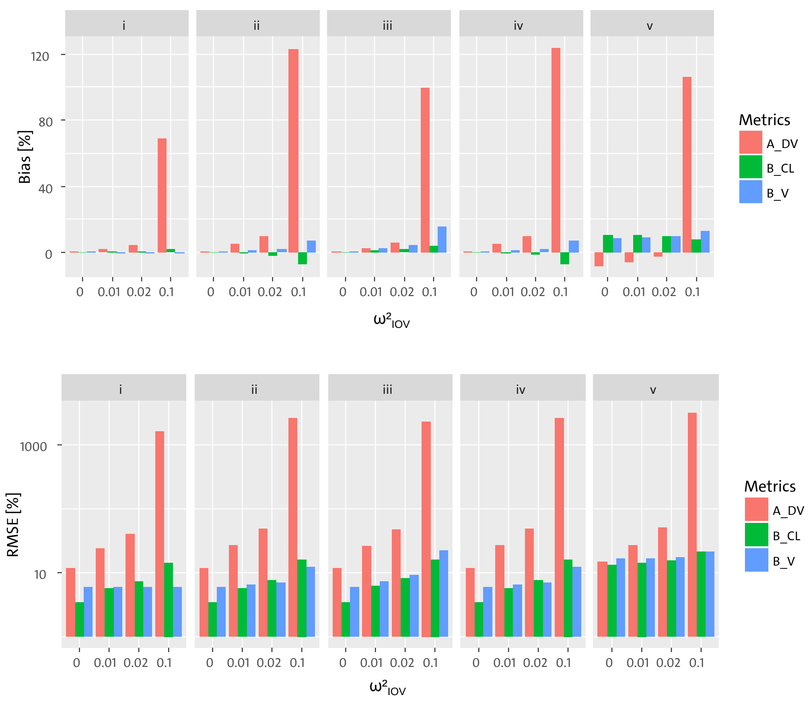

Figure 2: Bias (upper panel) and RMSE (lower panel, log-scale) of IOV handling methods (i)-(v) evaluated by IPRED-DV based metrics A and EBE-based metrics B for the simulation study with the **sparse design**.

Using real data (Fig. 3), metrics A also displayed a positive bias in all scenarios. Method (v) was least biased, followed by (i), (iii), (iv), and (ii).

For metrics B, method (i) showed to be least biased, followed by (ii), (iv), (v) and (iii).

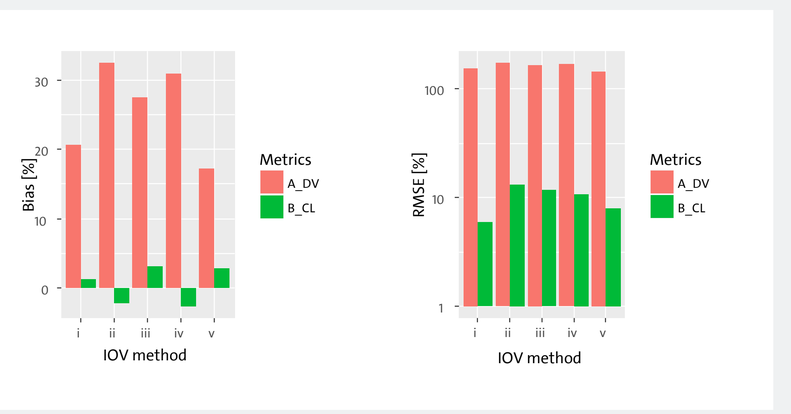

Figure 3: Bias (left) and RMSE (right) of IOV handling methods (i)-(v) evaluated by IPRED-DV based metrics A and EBE-based metrics B for the **real dataset** of gentamicin.

The intrinsic bias observed in metrics A might originate from the 'overlay' of the proportional residual variability with the log-normal distribution of the IOV component (Fig. 4).

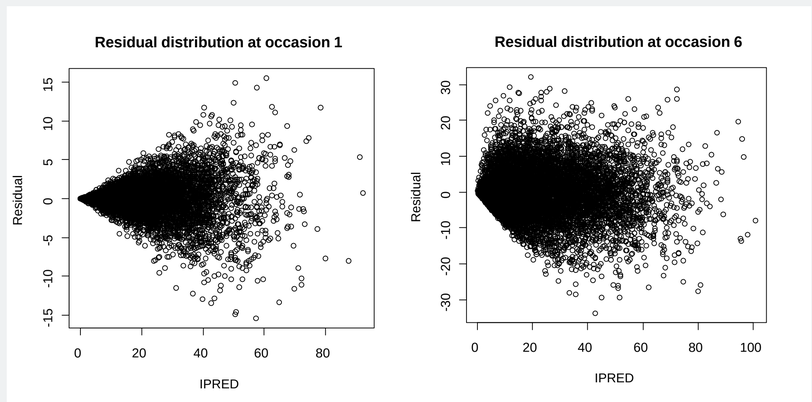

Figure 4: Residual distribution at occasion 1 (DV used to obtain individual PK parameters) and occasion 6 (DV from occasions 1-5 used to determine individual PK parameter, occasion 6 forecasted) obtained in the simulation study with ω^2_{IOV} of 0.1.

Conclusion

Metrics A, although popular and frequently used, was intrinsically biased in presence of IOV and hence should be interpreted with caution. As a consequence, metrics A wrongly suggested the weighting approach (v) to outperform the true model (i) in the simulation study.

Comparisons on the forecasting performance of models on the level of estimated vs. true individual PK parameters, i.e. metrics B might be more meaningful, but susceptible to shrinkage (reason for not showing V in the real clinical dataset). Similar trends in forecasting accuracy were observed in the simulation study and the real dataset, but less marked in the latter.

Overall, method (i) displayed the best forecasting performance. Method (iii), where IOV was not estimated may be preferable over the weighting method (v) in presence of IOV.

Literature
[1] LLANOS-PAEZ ET AL. ANTIMICROB AGENTS CHEMOTHER. 2017;61(8).
[2] ABRANTES ET AL. PAGE 26 ABSTR 7290 (2017).

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