Evaluation of the delta-method to efficiently compute probability of target attainment of antibiotics

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Objectives

To assess **therapeutic success or failure** of **antibiotic treatments** pharmacokinetic (PK)/pharmacodynamic (PD) breakpoints are frequently used in **probability of target attainment (PTA) analyses**. For this purpose, commonly time-consuming **Monte-Carlo simulations (MCS)** considering the **interindividual variability (IIV)** in PK are performed. PTA is then calculated as the fraction of scenarios for which the PK/PD breakpoint is attained.

For an empiric **probabilistic dosing module** in the recently developed web-based dosing support software **TDMx** (www.tdmx.eu) [1], MCS was found too slow for convenient usage. Instead, the suitability of the potentially more time-efficient **delta-method (DM)** was to be evaluated to approximate interindividual variability bands around the typical PK profile and resulting PTAs. The comparison between MCS and DM was exemplified with a published PK model for the beta-lactam antibiotic meropenem (MER).

Methods

- A published population PK model of MER [2] was used for evaluation of MCS- and DM-based PTAs. PK covariates were set to their typical values [2], serum creatinine to 0.7 mg/dL, minimal inhibitory concentration (MIC) to 4 mg/L (worst case) and the PK/PD breakpoint for MER to $fT_{>MIC}$ of 40% [2].
- Short (1 h, TID), prolonged (4 h, TID) and continuous infusion (24 h) dosing regimens with total daily doses of 1500, 3000 and 6000 mg were assessed.
- IIV of the fixed-effects PK parameters θ were set to (i) the values of the original publication [2] and (ii) were varied from 20% to 70% CV.
- MCS-based PTAs were calculated based upon 1000 simulations each.
- For DM-based PTAs, the 'apparent' variance of the PK profile $var(f(\theta,t))$ was computed at each time point using the delta method:

$$var(f(\theta,t)) \approx \text{diag} \mid J\{ f(\theta,t) \} * \Omega * J\{ f(\theta,t) \}^T \mid$$

with $f(\theta,t)$ denoting the PK model, J denoting the Jacobian of the PK model w.r.t. θ and the variance-covariance matrix Ω. Variance calculation was performed on log-scale to account for the log-normal distribution of the PK parameters of the PK model [2].

- Based on $var(f(\theta,t))$, prediction intervals up to the 95th (in 1.25 steps) were derived for PTA calculation.
- Both methods were compared with respect to correlation and required CPU time in 'R' (version 3.1.1, [3]).

Results

- For MCS, the variability of the PTA was 0.014 (SD) at n=1000 replicates. DM-based PTA is inherently not variable.
- The simulated PK profiles as well as the resulting PTA of different dosing regimens for the original IIV parameters [2] using MCS and DM are displayed in Fig. 1 and 2. Variability was in good agreement during infusion, but tended to be overestimated by DM in the elimination phase. Yet, resulting PTA was similar for MCS and DM.

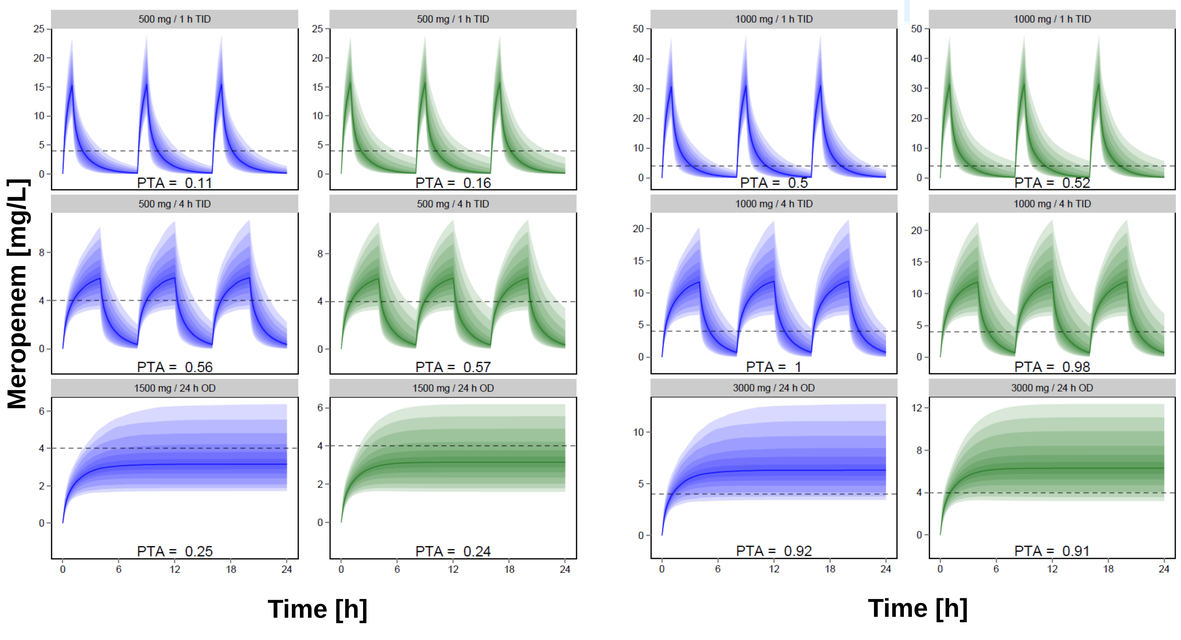

Fig. 1: Prediction of typical PK and uncertainty of a subpopulation receiving total daily doses of 1500 mg (left) and 3000 mg (right) using **MCS** or **DM**. Typical prediction (solid line), prediction interval up to 95th (shaded area), MIC (dashed line)and PTA (number).

Results (cont.)

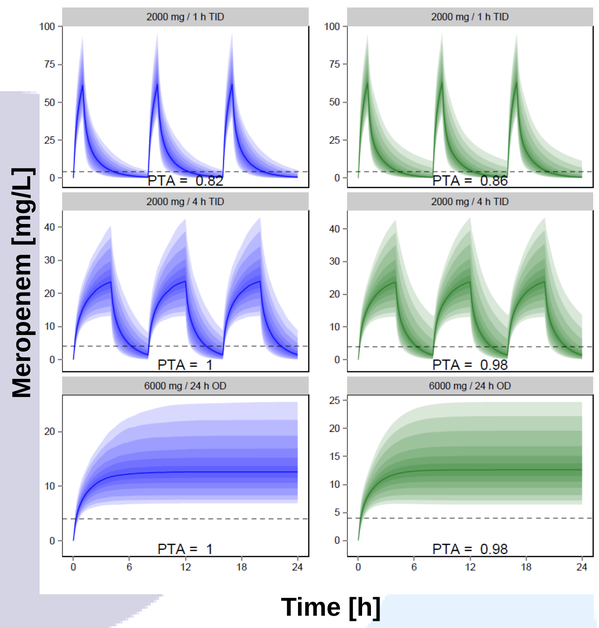

Fig. 2: See Fig. 1, total dose: 6000 mg.

- Differences between MCS-based and DM-based PTAs ranged from -0.05 and 0.03 (mean: -0.004) and were independent of the set interindividual PK variability of the PK model (Fig. 4).
- **CPU time** was ca. **1.3 sec. for DM** and ca. **48 sec. for MCS** for computation of a single dosing scenario.

- For the scenarios in which the IIV was varied from 20% to 70% CV for all PK parameters, PTA's from MCS and DM correlated well, as indicated by the comparison between both methods in Fig. 3.

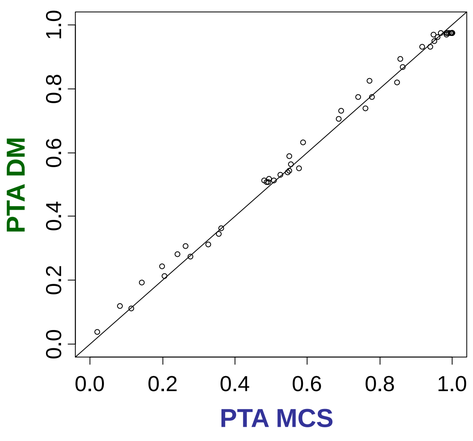

Fig. 3: Correlation of DM and MCS; Line of identity is indicated by the solid black line.

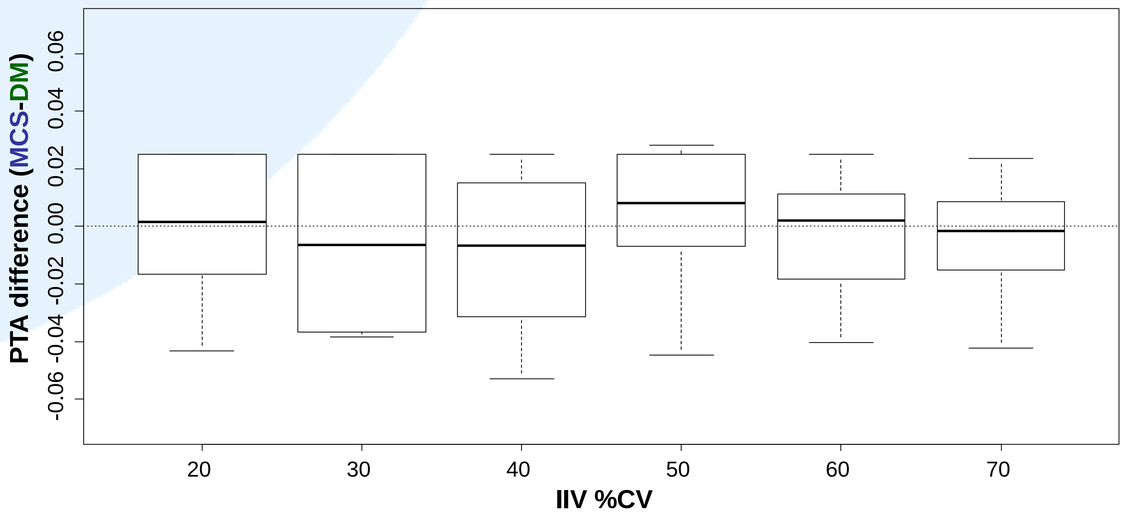

Fig. 4: Boxplot illustrating absolute differences in PTA, stratified by IIV in %CV of the PK parameters.

Conclusion

- The **DM** was successfully applied to **calculate interindividual variability** of a population PK model to perform **PTA analyses** of **antibiotics**.
- **DM**-based computation of PTAs was in **high agreement** with the conventionally used **MCS**-based approach thereby **reducing** the required **CPU time by factor >35**.
- The DM-based algorithm for PTA calculation was hence integrated in **TDMx** (see **booth #11**) facilitating **rapid empiric dosing decisions** prior to initialising antibiotic treatment.

References

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