Flattening of model priors: A comparative simulation study across multiple compounds

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Background and Objective

MIPD supports clinical decision making using mathematical models and individual drug measurements [1].

MAP estimation is commonly used in MIPD to derive individual model parameters used for simulation [1, 2].

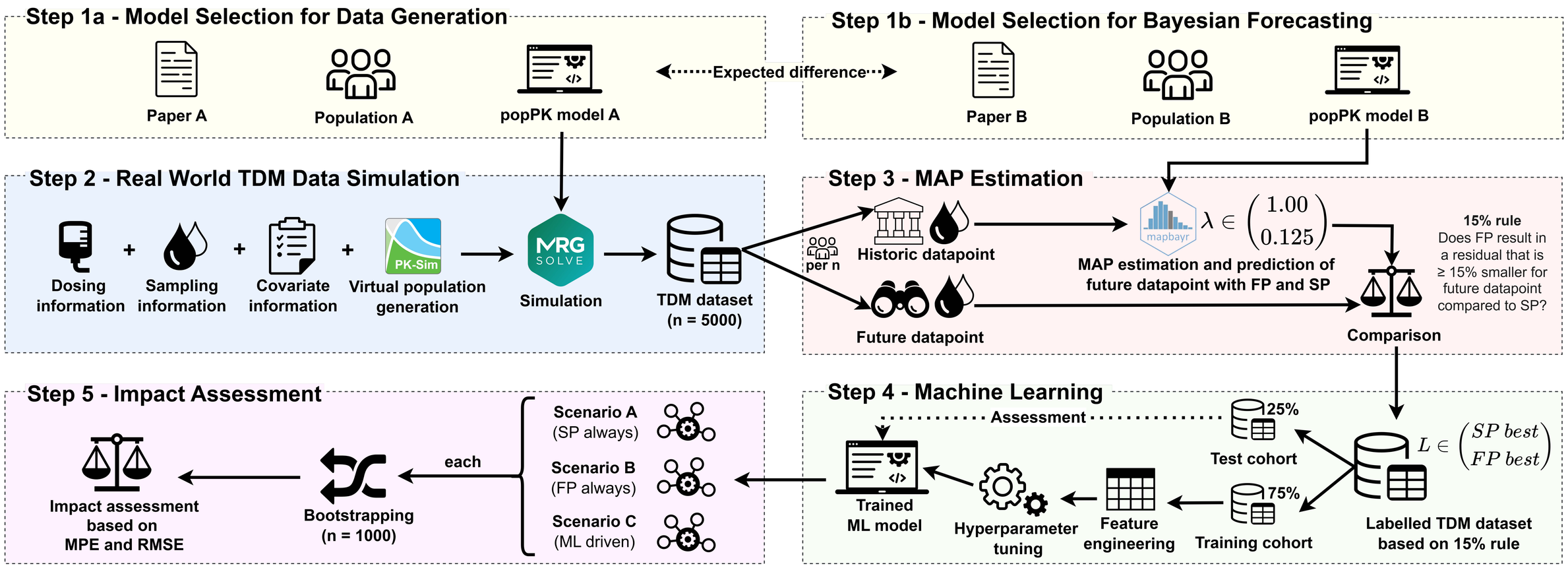
Prior beliefs about the magnitude of IIV and RUV need to be defined, which are typically based on the model.

In real-world settings, however, **deviations** between model and clinical population are expected.

Thus, a novel method [3] of **machine learning-driven flattening of model priors** has been proposed for MIPD of vancomycin.

Objective: Investigate if this method is also increasing the predictive model performance across multiple other compounds [4-11].

Methods



Results

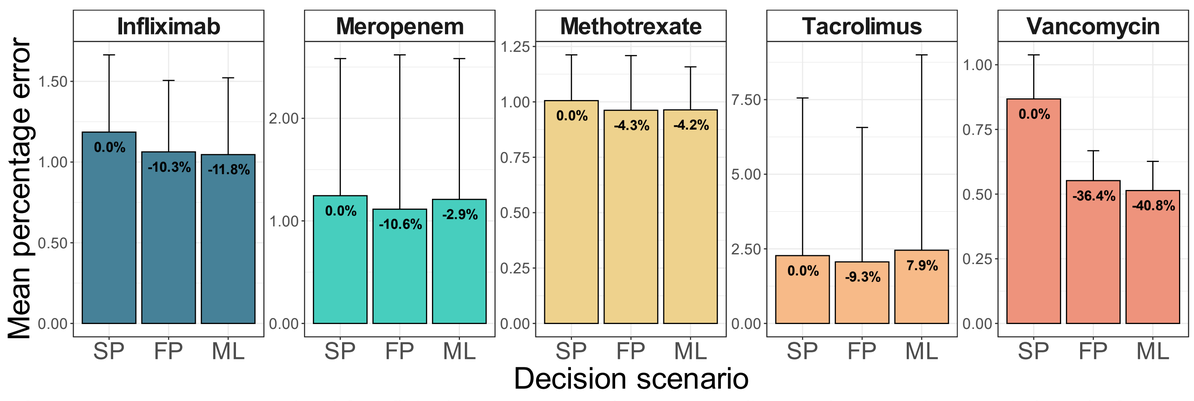


Figure 1 Mean percentage error (MPE) for infliximab, meropenem, methotrexate, tacrolimus, and vancomycin, respectively, under four decision scenarios for future datapoints. Percentages indicate MPE change relative to SP. Error bars represent the upper 95% confidence interval obtained through bootstrapping. Abbreviations: See below.

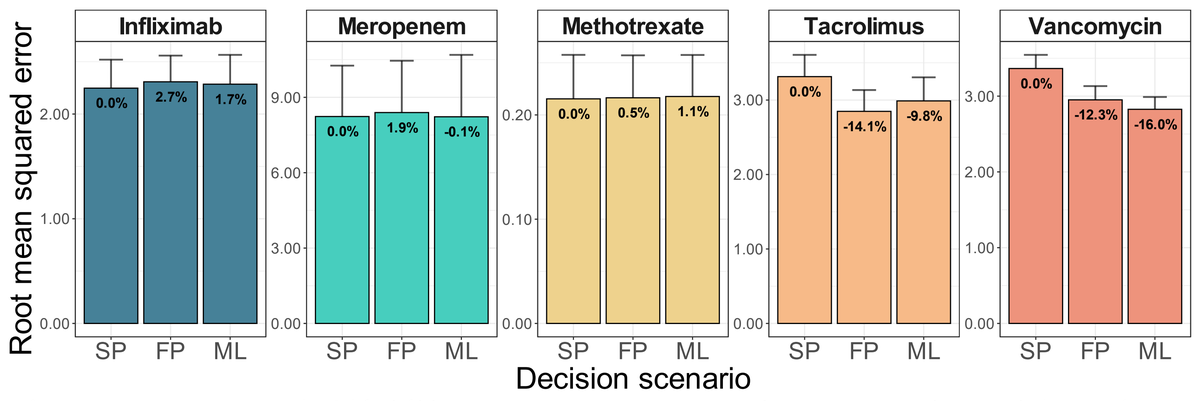


Figure 2 Root mean square error (RMSE) for infliximab, meropenem, methotrexate, tacrolimus, and vancomycin, respectively, under four decision scenarios for future datapoints. Percentages indicate RMSE change relative to SP. Error bars represent the 95% confidence interval obtained through bootstrapping. Abbreviations: See below.

Discussion

- ✔ Successful setup of a **simulation framework** [4-16].
- ✔ Predicted relative improvements in MPE and RMSE for vancomycin are **in agreement** with **reported values** [3].
- ✔ For other compounds [4-11]: **no substantial improvement** in predictive performance (MPE *and* RMSE)
- ✘ **Explanation** for this finding is still **lacking** (ongoing analysis).
- ✘ Model **selection bias** is expected (ongoing analysis).

Conclusion

Machine learning-driven flattening of model priors is not universally beneficial for all compounds and models.

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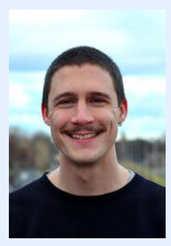
Abbreviations

BS	Best scenario
FP	Flattened prior (λ = 0.125)
IIV	Interindividual variance
L	Label
MAP	Maximum a posteriori
MIPD	Model-informed precision dosing
ML	Machine learning
RUV	Residual unexplained variability
SP	Standard prior (λ = 1.00)



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