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The use of Full Random Effects Models (FREM) in Model-Informed Precision Dosing (MIPD)

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Objective

To benchmark FREM performance against a reference fixed effect model (REF) under ideal conditions (no missing covariates), as well as under different missing covariate scenarios for a priori and a posteriori dose predictions.

Background

MIPD uses mathematical models for a priori and a posteriori dosing predictions [1]. A key challenge is missing covariate data, typically handled via mean imputation in fixed effect models (FEM). Conversely, FREM treat covariates as observed data rather than error-free predictors and have been shown to predict typical individual values closer to the non-missing situation [2,3]. FREM can be used to derive FEM for any available subset of patient covariate data without the need for parameter re-estimation.

Data and methods

Individual covariate data were derived from NHANES [4] with complete records for age, sex, weight, height, serum creatinine, eGFR, and BSA. REF (covariates: age, BSA, eGFR on CL; BSA on V) and FREM (all covariates & dummy random variable) were estimated using simulated observation data from an established population PK model for linezolid [5].

Dose predictions from FREM-derived FEM and REF were calculated as Dose=AUC_{target}*CL. An AUC_{target}=100 mg·h/L was used, based on the minimum of the AUC_{24h}/MIC efficacy threshold for linezolid [6] (assuming MIC = 1 mg/L). To reflect clinical application, doses were also classified to 300 mg increments (max: 1200 mg).

Scenarios tested included ideal conditions and various missing covariate configurations for a priori dosing as well as a posteriori dosing using a single sample at 2, 5, or 12 hours post-dose.

Model simulation and estimation was performed using NONMEM 7.5.1 and PsN 5.6.1. Visualization and post-processing of outputs was performed using R 4.2.2.

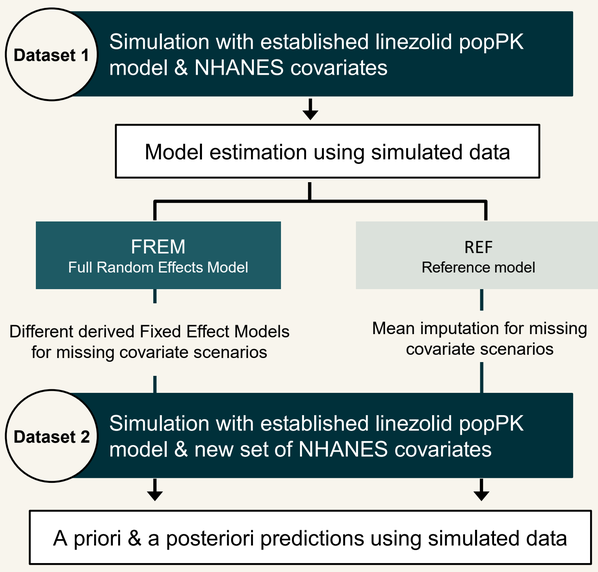

Figure 1. Schematic overview of workflow.

Predictive performance was assessed via Root Mean Squared Relative Error (RMSE), Mean Absolute Prediction Error (MAPE) and the percentage of classified dose predictions not matching the true dose.

Conclusions

- For a priori predictions FREM-derived FEM outperformed REF in missing covariate data scenarios and has the advantage of utilizing covariates beyond those included in REF to generate more accurate predictions.
- A posteriori performance was comparable for FREM-derived FEM and REF, as covariates explained only a small fraction of the total variability (Figure 4), allowing clinical samples to outweigh any differences between the missing covariate handling strategies.
- As a next step, an example where covariates explain a larger proportion of variability should be explored to further evaluate performance differences.

Results

FREM-derived FEM were superior to REF across all missing covariate scenarios for a priori dose predictions. FEM including BSA and eGFR was the best performing model (RMSE=4.59%). Amongst the univariable models for the covariates included in REF, FEM with eGFR was the best with RMSE of 11.77% (REF: RMSE=15.72%).

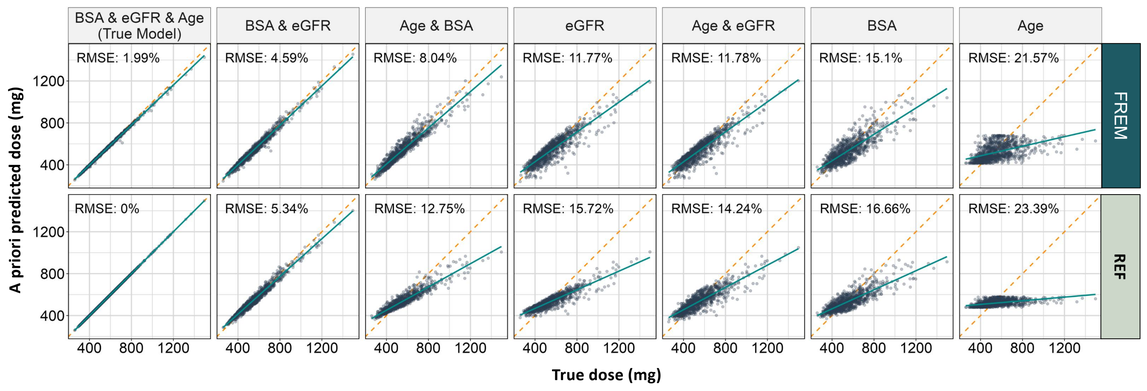

Figure 2. Continuous Predicted vs. True Dose from FREM-derived FEM (top) and REF (bottom) for different scenarios of covariate availability of covariates included originally in REF, ranked by ascending FEM RMSE, where true doses = doses from REF with all covariate information available (ie, typical individual clearance values)

For the univariable FEM of covariates that were not included in REF, FEM with weight performed best with RMSE of 16.24%, which can be compared to an RMSE of 26.12% for the REF with no covariate information.

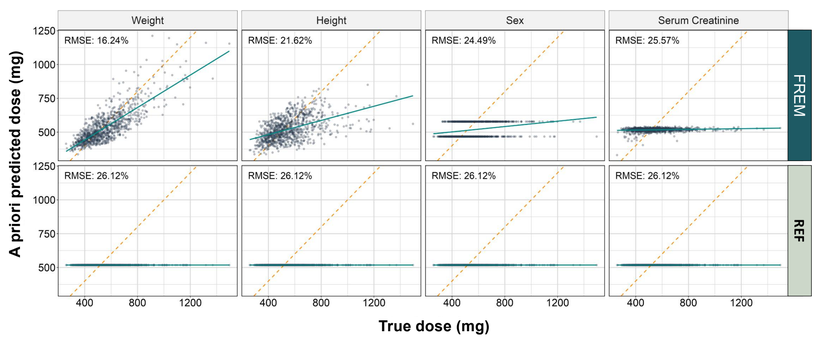

Figure 3. Continuous Predicted vs. True Dose from FREM-derived FEM (top) and REF (bottom) for different scenarios of covariates not included originally in REF, ranked by ascending FEM RMSE, where true doses = doses from REF with all covariate information available (ie, typical individual clearance values)

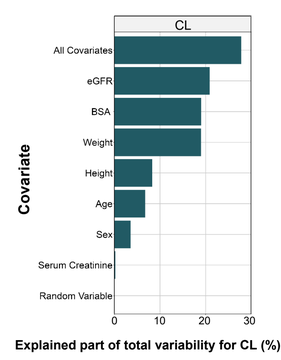

Figure 4. Plot of explained part of total variability for clearance from FREM.

A posteriori performance was comparable across both model types (Figures 5 & 6), as high interindividual variability of CL minimizes the population prior's influence, allowing clinical observations to dominate the Bayesian estimation.

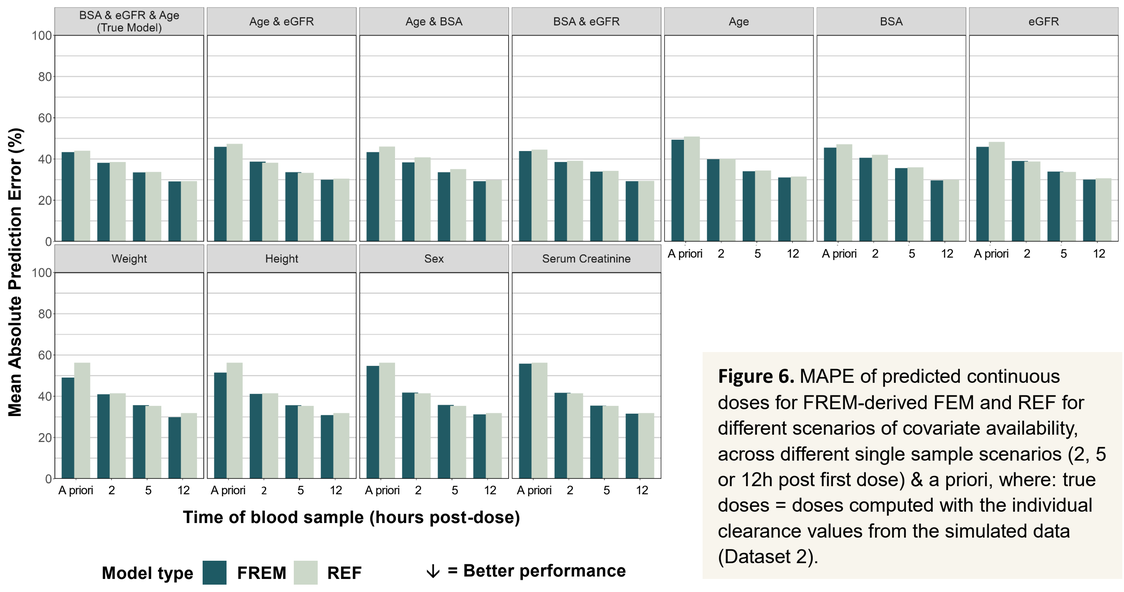

Figure 6. MAPE of predicted continuous doses for FREM-derived FEM and REF for different scenarios of covariate availability, across different single sample scenarios (2, 5 or 12h post first dose) & a priori, where: true doses = doses computed with the individual clearance values from the simulated data (Dataset 2).

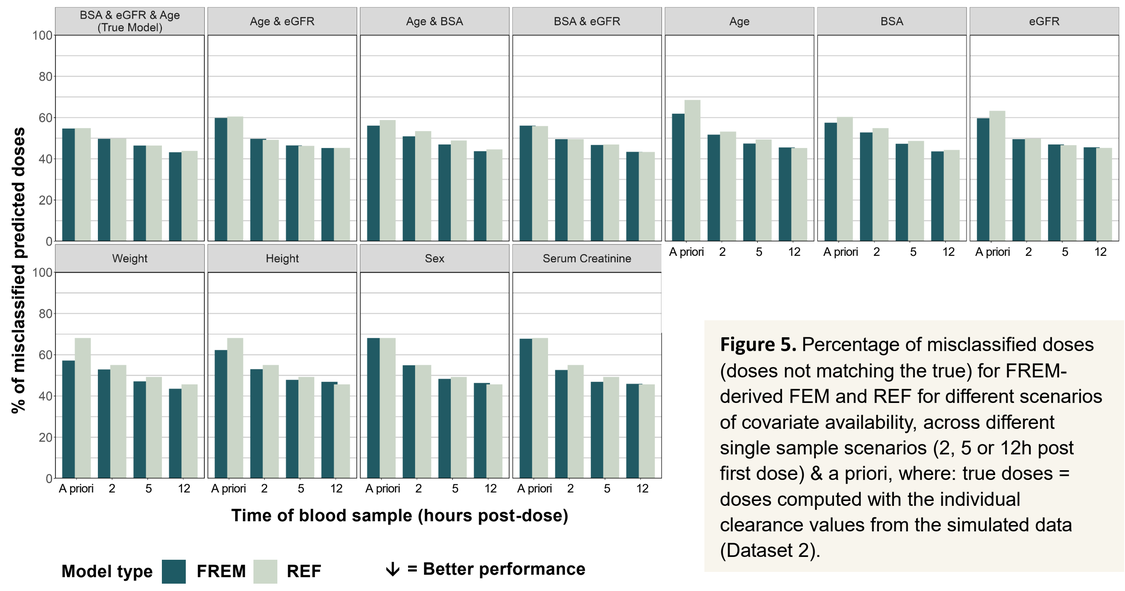

Figure 5. Percentage of misclassified doses (doses not matching the true) for FREM-derived FEM and REF for different scenarios of covariate availability, across different single sample scenarios (2, 5 or 12h post first dose) & a priori, where: true doses = doses computed with the individual clearance values from the simulated data (Dataset 2).

References

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