Data-driven model selection for model-informed precision dosing: a case study with vancomycin

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Background

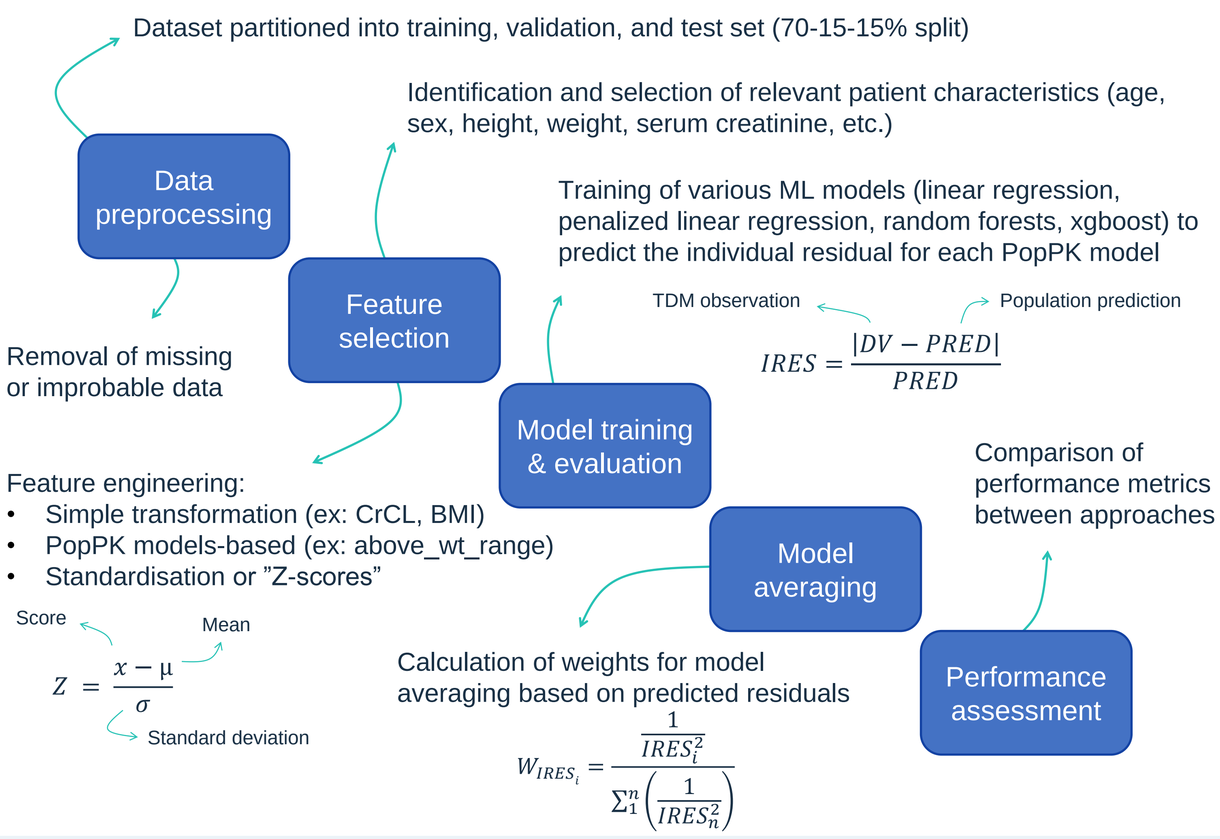
- Vancomycin is a widely-used antibiotic with a narrow therapeutic range.
- Achieving an optimal area under the concentration-time curve (AUC) between 400-600 mg·h/L is crucial for therapeutic success [1].
- Model-informed precision dosing (MIPD) combines therapeutic drug monitoring (TDM) with population pharmacokinetic (PopPK) models to guide dosing decisions.
- There are multiple PopPK models available for vancomycin, and Bayesian approaches to model selection and model averaging have demonstrated accuracy for vancomycin predictions with one or more TDM samples available [2].
- However, model selection before the first TDM sample becomes available remains challenging, and may be based on results from external validation studies, prior clinical experience and intuition.

Objective

Train a machine learning (ML) model to perform PopPK model selection/model averaging for vancomycin based on patients characteristics available before the first TDM sample, to optimize personalized vancomycin dosing.

Methods: Data source & workflow

De-identified data entered by users of the InsightRX Nova MIPD platform, between 01/01/2020 and 19/09/2023 were retrospectively analyzed. Adult patients with at least one recorded TDM sample and corresponding a priori predictions from six PopPK models were included [3–9].



Methods: Performance assessment

- Relative root mean square error:

$$rRMSE(\%) = \sqrt{\frac{1}{n} \times \sum_1^i \left(\frac{(pred_i - true_i)^2}{true_i^2}\right)} \times 100$$

- Percentage error: $PE(\%) = \left(\frac{pred_i - true_i}{true_i}\right) \times 100$

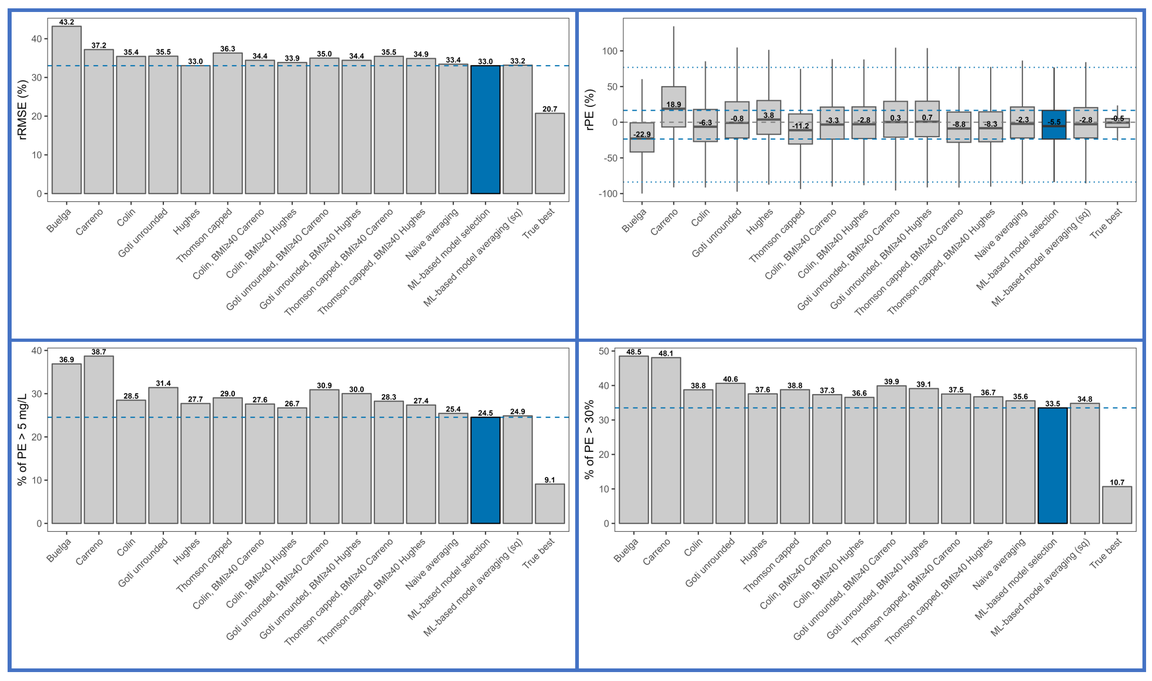
→ MdPE = median(PE_1, PE_2, …, PE_n)
→ Q_1PE = percentile$_{25}$(PE_1, PE_2, …, PE_n)
→ Q_3PE = percentile$_{75}$(PE_1, PE_2, …, PE_n)

- Percentage of large prediction errors (PE >5 mg/L or PE >30 %)

Results

- Final analysis dataset: 334,683 TDM observations and corresponding *a priori* predictions for each included PopPK models.
- Best models obtained using xgboost with Huber loss function (delta 0.5)

Variable	n (%)	Mean (SD)	Median	Range
Male	191,421 (57.2)			
Age (year)		62.6 (16.8)	64.4	18.0-109
Serum creatinine (mg/dL)		1.20 (1.03)	0.95	0.05-20.0
Weight (kg)		88.2 (29.4)	83.0	30.0-388
Height (cm)		171 (11.1)	170	120-218
TDM observation (mg/L)		14.6 (7.04)	13.4	0.10-50.0



- Feature importance – top 8 ranking across all 6 PopPK models:
  1. Age
  2. BMI
  3. CrCL (Cockcroft-Gault)
  4. Serum creatinine
  5. Sex
  6. BSA
  7. Weight
  8. Height

Conclusion

- ML-based model selection and averaging:
  - Outperformed individual PopPK models and naive averaging in predicting vancomycin concentrations.
  - Show promise in MIPD settings before TDM samples are available.
- Performance gap observed:
  - Between prospectively predicted and retrospectively identified best models.
  - Indicates current patient characteristics explain only part of vancomycin exposure variability.
- Emphasizes the importance of TDM and the value of Bayesian approaches to model selection and averaging.

References & acknowledgement

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