Comparison of the one- and two-compartment deep-learning-based vancomycin therapeutic drug monitoring models using simulated data

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BMI 7304: Advanced Research Design

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Introduction

There are two deep-learning-based vancomycin therapeutic drug monitoring (TDM) models (PK-RNN) where the two-compartment pharmacokinetic (PK) model theoretically outperforms the one-compartment model on prediction tasks. The results from a real-world dataset show that the two-compartment PK-RNN model does not consistently outperform the one-compartment PK-RNN model.

The hypothesis this research design wants to use simulation to test is whether the two-compartment PK-RNN model will definitely give more accurate predictions than the one-compartment PK-RNN model after adding enough measurements.

Method

The original dataset: EHR data were retrospectively retrieved from Memorial Hermann Hospital (MHH) System to generate the PK-RNN model. All patients who received vancomycin and had any vancomycin levels were eligible. 5,483 patients with 9,504 encounters were included in the dataset.

Simulation: There will be 10 measurements simulated per dose for every patient.

The dataset for the recommended design: the same inclusion and exclusion criteria will be used on the MIMIC IV dataset to select suitable patients for the recommended design followed by the same simulation.

Description of the PK-RNN model

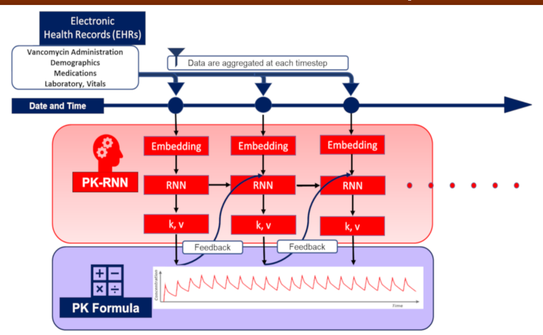


Figure 1: PK-RNN model architecture

All data were aggregated at the timestep, and the data were fed into the models. RNN updates k (vancomycin elimination rate) and v (volume distribution of vancomycin). Those two parameters and infusion data (dose and timing) were used to generate vancomycin pharmacokinetic (PK) curves with the PK formula.

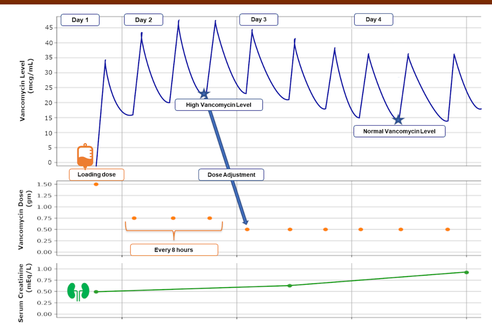
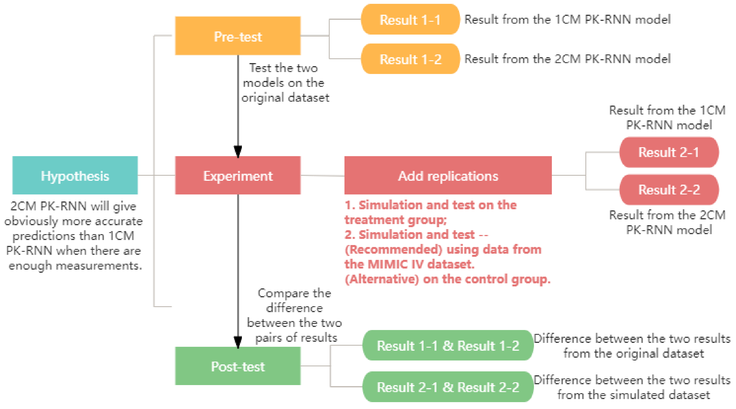


Figure 2: The simple schematic time sequence of an example patient

The vancomycin serum concentration is demonstrated in the upper figure. Blue line demonstrates the predicted vancomycin serum concentration in the patient. Blue stars indicate the actual vancomycin levels. In the middle graph, orange dots are vancomycin doses, and the green line in the lower figure is creatinine level.

Research designs



Statistical analysis for the simulated dataset and model quality test will be provided by training the models 10 times on both datasets after the simulation and then calculating the mean and standard deviation of all the results.

Three model evaluation metrics will be used, which are Root Mean Square Error (RMSE), Mean Absolute Error (MAE), and Mean Absolute Percentage Error (MAPE).

Figure 3: Workflow of the two research designs

Table 1: Discussion

Types of validity	Recommended research design	Alternative research design
Statistical Conclusion	**(+)** Adding multiple replications will **increase** statistical conclusion validity because it will improve the confidence and significance of the results.	**(+)** Adding switching replications will **increase** statistical conclusion validity because it will improve the confidence and significance of the results.
Internal	**(+)** The randomness in the simulation will **increase** the internal validity.	**(+)** Switching replications make the data after simulation used for every individual in the MHH dataset, thus will **increase** the internal validity.
Construct	**(-)** The original dataset has more patients with stable PK parameters, which may **decrease** construct validity.	**(-)** The lack of tests on other datasets will **decrease** the construct validity of this research design.
External	**(+)** The external validity will be **increased** since this design contains tests on different datasets.	**(-)** The external validity will be **decreased** since this design contains tests only on one dataset.

Conclusion

The two research designs will improve the pre-test experiment which is training and evaluating the two models on the MHH dataset. The main difference is that the recommended research design will add multiple replications while the alternative design will add switching replications. The recommended design will test the PK-RNN models on a different dataset which is important for deep learning models when considering the generalizability.

In conclusion, the recommended research design will be more suitable for both interrupted time-series data and the two types of PK-RNN models.

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