A deep-learning-based two-compartment predictive model (PKRNN-2CM) for vancomycin therapeutic drug monitoring

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Introduction

Vancomycin is a widely used antibiotic that requires therapeutic drug monitoring (TDM) for optimized individual dosage. The use of deep learning techniques to estimate vancomycin pharmacokinetic (PK) parameters has the advantage of handling irregularly sampled time series electronic health record (EHR) data. One-, two-, and three-compartment models have been applied to describe vancomycin PK, with a two-compartment model most commonly considered to describe vancomycin PK in adults. The mathematical simplicity of the one-compartment PK model makes it the preferred method for clinicians to predict vancomycin concentrations.

This study aims to develop a two-compartment vancomycin TDM model (PKRNN-2CM) with recurrent neural network (RNN) to predict vancomycin concentration. In the PKRNN-2CM model, RNN is used to predict PK parameters based on time steps in the time series EHR data, and a two-compartment PK model is used to calculate vancomycin concentrations.

Methods

Figure 1: PK-RNN-2CM model architecture

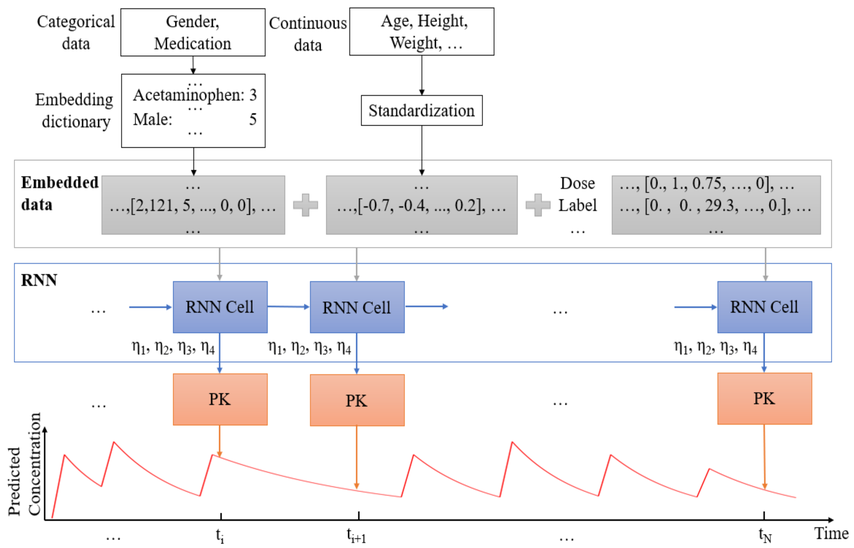
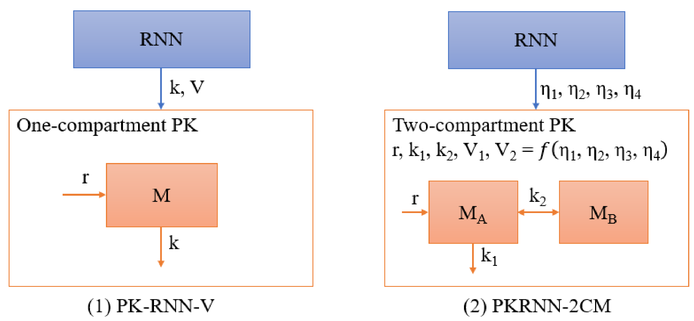


Figure 2: The main difference between PK-RNN-V and PKRNN-2CM



(1) The RNN and PK layers of the PK-RNN-V model.

k: elimination rate; V: volume distribution, r: infusion rate; M: mass of the compartment.

(2) The RNN and PK layers of the PKRNN-2CM model.

η1, η2, η3, and η4: PK parameters that satisfy a multivariate Gaussian distribution; k1: elimination rate of the two-compartment system; k2: exchange elimination rate between the two compartments; MA: mass of the central compartment; MB: mass of the peripheral compartment.

A schematic that shows the model structure of PKRNN-2CM by every time step (time step is defined by vancomycin administration time, vancomycin level obtained, or the end of the day). In this figure, there are N time steps. Each time step is fed with the time-series EHR data after preprocessing, which contains categorical data, continuous data, doses, measurements, and other information. After the embedding layer, the RNN layer predicts 4 parameters η1, η2, η3, and η4. The PK layer then computes the predicted vancomycin concentration based on the two-compartment PK model as the model output.

Results

Figure 3: Concentration-time curves for specific patients from PK-RNN-V and PKRNN-2CM

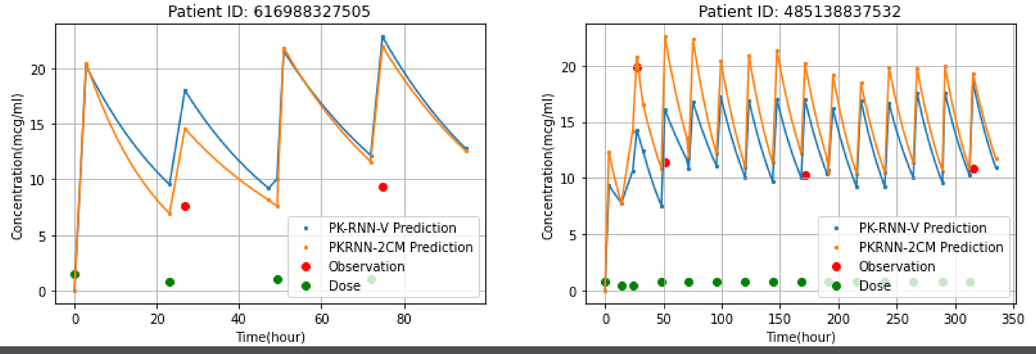


Table 1: Results and comparison for different models

Model	Average (RMSE)	Variance (RMSE)	
PK-RNN-V	5.840926	0.0104	P-value: 0.0168
PK-RNN-2CM	5.615921	0.0003	
PK-RNN-2CM-SI	5.846087	0.0161	N/A

SI = specific initialized. By setting the initial k2 to an extremely small value, the PKRNN-2CM-SI model converts the PKRNN-2CM model into a one-compartment PK model.

Discussion

Contribution

PKRNN-2CM is the first model that demonstrates the two-compartment PK model is significantly better than the one-compartment PK model by using sparse, irregularly sampled data obtained from real-world data.

Limitations

- PKRNN-2CM didn't predict the area under the curve (AUC), which is a widely used evaluation metric for vancomycin TDM;
- The PKRNN-2CM model can only be converted to a one-compartment PK model by setting different initializations.

Conclusion

- The two-compartment PK model provides more accurate vancomycin concentration prediction than the one-compartment PK model when using deep learning techniques as part of the predictive model;
- May provide potential direction for future clinical settings involving vancomycin TDM.

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