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

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***Abstract*— This study developed a two-compartment deep learning model (PKRNN-2CM) for therapeutic drug monitoring (TDM) of vancomycin (VAN), a commonly used antibiotic. The model, which uses irregularly sampled electronic health record (EHR) data, outperformed a one-compartment model (PKRNN) in predicting VAN concentration. Simulation results also demonstrated the superiority of the PKRNN-2CM model, suggesting that it could improve the accuracy and effectiveness of personalized VAN TDM, leading to better clinical outcomes.**

Keywords—Vancomycin, Pharmacokinetics, Compartmental model, Deep learning, Recurrent neural network.

I. Introduction

VAN is a widely used antibiotic that requires TDM for optimized individual dosage. The pharmacokinetic (PK) parameters for VAN TDM can be estimated using deep learning (DL) techniques that have the advantage of handling irregularly sampled time series EHR data [1]. The choice of how many compartments to include in population PK models is important, with the two-compartment model being the most commonly used for VAN in adults [2]. However, previous DL attempt PKRNN [1], a recurrent neural network (RNN) model to predict VAN concentration, was only focused on a one-compartment (1CM) model. Here, we aimed to develop a two-compartment (2CM) VAN TDM model (PKRNN-2CM) and compare its performance with PKRNN.

II. Methods

Similar to the PKRNN model [1], the PKRNN-2CM model is an autoregressive RNN model that uses an EHR code embedding layer, an RNN layer, and a 2CM PK layer to predict VAN concentration per time step. This study utilized the same dataset as the PKRNN paper [1], which included 5,483 patients with 9,504 encounters who received VAN from Memorial Hermann Hospital System (MHHS). Due to the dataset's sparseness and irregular sampling, simulation was used for model evaluation under different sampling strategies. Simulated datasets follow as much actual patient information as possible to resemble real-world MHHS data, the only simulated data was the measurements. The simulation input used VAN concentrations predicted by PKRNN-2CM (defined as the "underlying model") fit from MMHS data as measurements, with sampling points aligned to the infusion cycle. The inference models PKRNN and PKRNN-2CM were evaluated with measurements at either peaks or troughs based on hours (2-3 hours for the peak dataset, 10 hours for the trough), and RMSE was calculated at both peak and trough time points to evaluate how our inference models can capture the entire VAN concentration curve. The dataset was split 70:15:15 for training, validation, and test sets.

III. Results and discussion

For real data, PKRNN-2CM exhibited a better RMSE of 5.62 compared to PKRNN with an RMSE of 5.84 (p-value= 0.01, unpaired two sample t-test). The simulation results (Table 1) indicate that the PKRNN-2CM model outperforms the PKRNN model, even at time points where the curve was not sampled. The results that the lowest RMSE was obtained by sampling peak inputs suggest that in a noise-free scenario, accurate peak measurements may enhance model performance. Overall, the results highlight the potential of the PKRNN-2CM model to improve personalized VAN TDM.

TABLE I. Results: PKRNN-2CM outperforms PKRNN.

Model		**Avg. test RMSE (Standard Deviation)**	
PKRNN		5.84 (0.10)	
PKRNN-2CM		5.62 (0.02)	
Sampling time points		**Avg. RMSE (Standard Deviation) from the inference model**	
Input	***Output***	***PKRNN***	***PKRNN-2CM***
Peak	Peak	6.09 (0.11)	1.71 (0.09)
	Trough	3.29 (0.2)	**1.25 (0.16)**
Trough	Peak	10.48 (0.52)	4.34 (0.30)
	Trough	7.90 (0.53)	3.49 (0.24)

References

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