Using Various Machine Learning Algorithms to Determine the Best Method for Predicting Population Physiologically Based Pharmacokinetic Model Plasma Profiles

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Abstract

The use of artificial intelligence (AI) for predicting drug pharmacokinetics (PK) is a relatively new effort. Several papers have been published covering various methods for using AI machine learning (ML) to predict PK. The objective of this study is to determine which ML method will best predict the plasma concentration of simulated subject taking various doses of labetalol. In the following experiment, we used various machine learning to determine which algorithm best predicted the data in males and females.

Objectives

To train and implement a machine learning algorithm that can accurately predict the pharmacokinetic profile of a drug based on the dose, indiscriminate of sex, and frequency given to a simulated patient.

Materials and Methods

The following methods were used to create the dataset for training the machine learning algorithms:

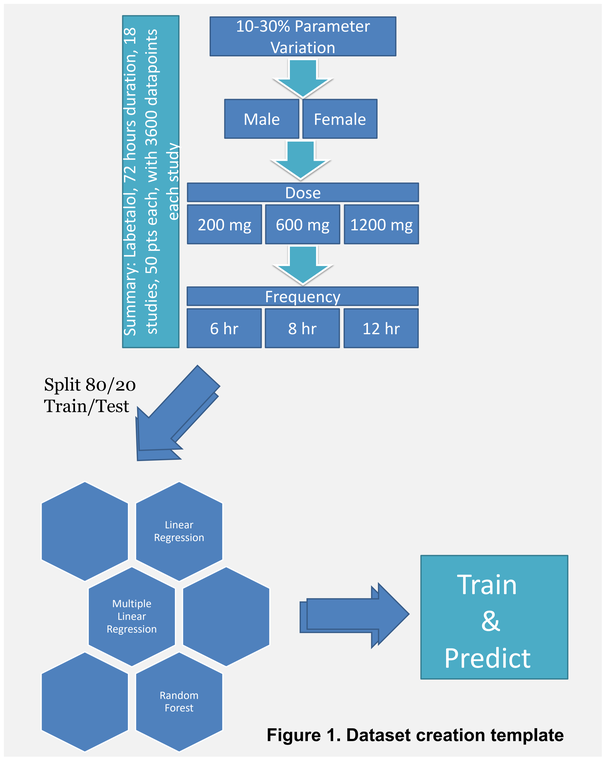


Figure 1. Dataset creation template

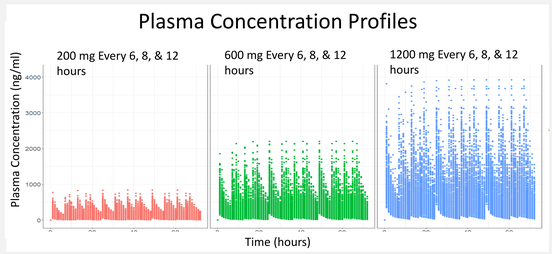
Materials and Methods (cont)

This methodology produced 18 distinct groups which were classified as individual studies consisting of 50 unique patient profiles collected for 72 data points. The studies were combined into one large dataset using R for training and testing. The dataset consisted of several headers similar to Lu et al 2021.

Data Wrangling & Cleaning

Berkeley Madonna 9.8.1 was used to build a validated PBPK model for labetalol for both men and women. The data generated from this model are shown in figure 2 and were combined in a loadable .csv file.

Figure 2. Data points for Machine Learning



Results and Discussion

Initial Model Exploration: Model Pre-Run

The initial run of a 5 patient test set from the same dosage (200mg) gave better results (table 1) compared to the full 600 patient data set.

Training MSE	Training R2	Test MSE	Test R2
Method: Linear Regression			
13882.445032	0.634974	15368.573685	0.605163
Method: Random Forest			
13916.635344	0.634075	14956.478024	0.61575
Method: Tweedie Regressor			
38031.416922	0.0	39176.351627	0.006487

The resulting graph of the linear regression model and the random forest model are shown in the figures to follow (figure 3 & 4).

When all points are considered the models do not properly predict the resulting PK with a R2 of less than 0.4. This indicated that of the models tested a higher order polynomial function may better predict the outcomes of the model.

Results and Discussion

Figure 3. Linear Regression Plot

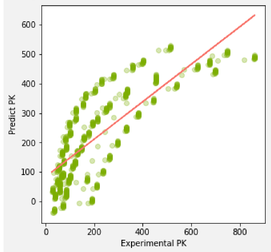


Figure 4. Random Forest Plot

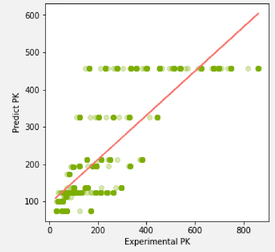
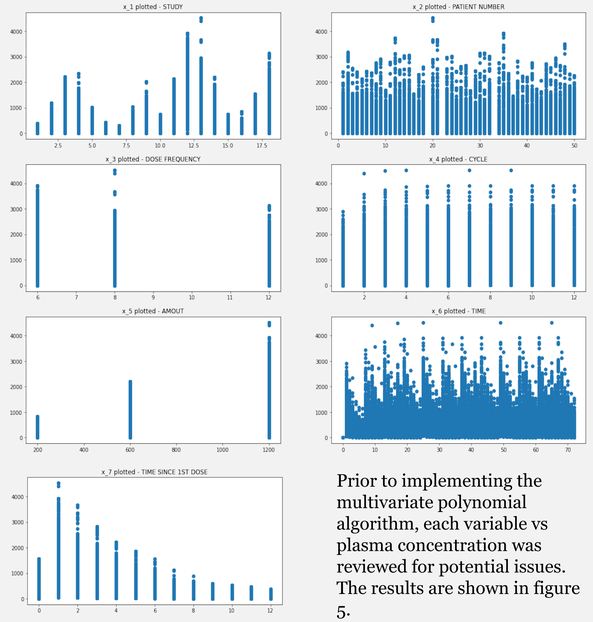


Figure 5. Variables versus Plasma Concentration for the full data set



Prior to implementing the multivariate polynomial algorithm, each variable vs plasma concentration was reviewed for potential issues. The results are shown in figure 5.

The multivariate polynomial function was tested on the 5 patient and the "full dataset". (figure 6 & 7). The lowest degrees are 3 and 6 with a MSE of 102.7 and 233.3, respectively.

The multivariate model was ran with 7 degrees chosen. The resulting graphs for the 5 patient data set and full dataset predicted versus experimental PK is shown in figure 8 & 9. The root mean squared error (RMSE) and coefficient of correlation (R2) for the test and training data is shown in table 2.

Figure 6. Five Patient Test Sample

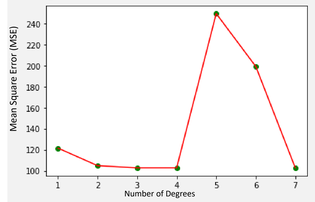
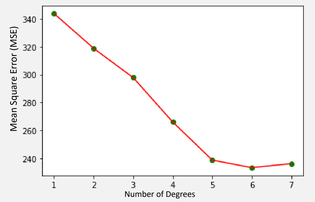


Figure 7. Full Dataset



Method	Training RMSE	Training R^2	Test RMSE	Test R^2
Multivariate Polynomial Regression – 5 patient	9.541	0.998	16.198	0.993
Multivariate Polynomial Regression –Full Set	232.453	0.736	234.142	0.710

Figure 8. Multivariate Polynomial Regression Five Patient

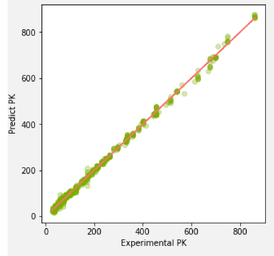
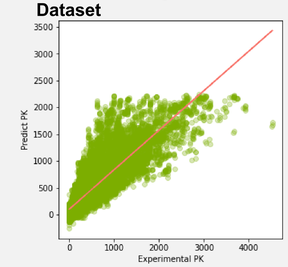


Figure 9. Multivariate Polynomial Regression Full Dataset



Conclusion

The initial algorithms used did not predict the plasma concentration well. Instead they provided guidance as to a more appropriate algorithm for this PK prediction. The multivariate model showed better correlation to the data and provide a base for further exploration of algorithms to best predict PK from the available data. Next steps are to further validate the model by comparing clinical observations to the predicted values.

Acknowledgments

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References will be provided upon request.