Bioanalytical Drug Tolerance Limit Prediction and Optimization Model Developed Through Machine Learning With TensorFlow

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Introduction

Assay drug tolerance limit is a crucial aspect in bioanalytical immunogenicity assay development (Haas, Manro, Shannon, et al., 2012; FDA Guidance Document. 2019). Drug tolerance limit refers to the highest limit of the drug residual in the study sample that yields successful detection of anti-drug antibodies. Most current studies focus on how to improve drug tolerance, such as using acid dissociation and solid phase extraction (Bütikofer, Lemaillet & Faust, 2012; Smith, Butterfield, & Sun, 2007; Butterfield, Chain, Ackermann & Konrad, 2010). However, no existing study was found to develop models to predict the drug tolerance limit in the early phase of a study, which hinders the speed of assay development. Therefore, a tool to predict drug tolerance can facilitate assay optimization. Despite the fact that more disciplines are using machine learning to advance their exploration, including drug discovery and development, in the field of bioanalytical immunogenicity assay development, machine learning is still underdeveloped (Murphy, 2011; Whale, 2010; Vanhaelen, 2019). This project uses a machine learning tool, TensorFlow, as an “experience collector”, to gather historical data from actual validated methods with known drug tolerance and to generate estimated drug tolerance limit from new experiment data. The learned model makes it possible to predict drug tolerance by tuning assay criteria with machine learning such as sample dilution, negative control signal, estimated screening cut point factor, estimated sensitivity, capture and detection drug concentration without performing experiments repeatedly. This project contributes to the field of bioanalytical assay development by developing a drug tolerance limit determination tool with machine learning algorithm, which helps minimize drug development cost, shortens drug development cycle, and ultimately helps improve the efficiency of drug development process.

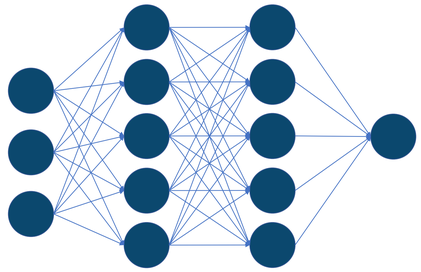
Method

Previous bioanalytical assay results were fed into the TensorFlow model using keras and trained with deep learning neural networks. The input training data consists of multiple assay criteria from early test run. For example, the dilution fold of the sample, the sensitivity of the positive control, the capture and detection concentration in master mix, etc. Another input training data is the actual drug tolerance verified from previous validated studies. All of the training data was obtained from validated methods with good performance under FDA guidance. All the codes were written in Python on Google Colab platform.

Result

Data fed into the TensorFlow model included values of sample dilution, negative control signal, estimated screening cut point factor, estimated sensitivity, capture and detection drug concentration of samples from 16 validated ADA projects. Actual drug tolerance values of the projects were also fed into TensorFlow to train the model. The assay range prediction model successfully predicted drug tolerance limit with the limited given assay parameters during early assay development, with the testing set mean absolute error set around 5 ug/mL for drug tolerance limit, which stands for small variation in predicting drug tolerance during method development.

Neural Network Used in Training Model



Trained Sequential Model Parameters

Model: "sequential_2"

Layer (type)	Output Shape	Param #
dense_8 (Dense)	(None, 64)	512
dense_9 (Dense)	(None, 64)	4160
dense_10 (Dense)	(None, 64)	4160
dense_11 (Dense)	(None, 1)	65

Assays (Bridging format)	Predict result using testing set (µg/mL)	Actual result using testing set (µg/mL)	Acceptable
Assay 1	49.98	50.00	Yes
Assay 2	249.86	250.00	Yes
Assay 3	49.91	50.00	Yes
Assay 4	178.78	150.00	Yes
Assay 5	191.40	100.00	Yes
Assay 6	168.51	50.00	No

Two-fold difference is considered acceptable since the drug concentration is diluted in two-fold in actual run testing.

Conclusion

This study examines the understudied field of drug tolerance limit prediction with TensorFlow as a machine learning tool. It combines the usage of Python and TensorFlow using keras to create models to predict drug tolerance limit in bioanalytical immunogenicity assay development. It can maximize the assay drug tolerance limit with validated historical data, and it can also serve as an assay troubleshooting tool. Successfully predicted drug tolerance limit with mean absolute error set at a small variation, this method provides a brand new perspective and path for scientists to obtain drug tolerance limit without the need of performing experiments repeatedly. It is the turn of a new page in the field of bioanalytical assay development because it makes it possible to shorten the drug development cycle and improve the efficiency of the drug development process.

Reference

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