Oral Presentation 8

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口頭発表 8
『ADME・毒性/その他』
ADMET/Others

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Takashi Mizuma (Teikyo Heisei University)
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O2-08

The prediction of food effect on drug oral absorption by machine learning

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Keywords: Pharmacokinetics, oral absorption, food effects, machine learning, random forest

The prediction of food effect on drug absorption has been previously reported by several methods including BCS, GUT framework and PBPK model, which were investigated based on observed availability changes of approximately 100 drugs. The purpose of present study was to develop a reliable model for prediction of food effect on drug absorption from the chemical structure based on observations of 470 drugs by using machine learning. Changes in oral availability by food were collected from previous reports[1-4] and the product labels. The food effects were classified into negative, no, and positive for drugs whose availability ratios (fed/fasted), mainly AUC ratios, are less than 0.8(14% of the drugs), 0.8 to 1.25 (57% of the drugs), and greater than 1.25 (29% of the drugs), respectively. Approximately 360 features including solubilities in various conditions were calculated from chemical structures with ADMET Predictor (Simulations Plus, Inc.). Features of monotonous or highly correlated were excluded, and then Boruta method was used to select informative features. The data was divided into a training set and a test set, and a training set was further divided into a real training set and a validation set for hyperparameter optimization (nested cross validation). The decision tree algorithm of random forest was used for training of food effect from the selected features. F1-score was used for evaluation of the model performance. F1-scores of the final model in the test set (average of five trainings of different division ways) for negative, no, and positive food effects were 0.304, 0.651 and 0.669, respectively. The F1-score of negative food effect was the smallest due to the lowest frequency of this class (14%). Using information collected in this study, the prediction performance was evaluated also with the BCS method in which drugs were classified by dose, predicted permeability and solubility. F1-scores of negative (class 3), no (class 1), and positive (class 2 and 4) effects were 0.350, 0.379, and 0.580, respectively. The ratio of erroneous negative prediction for positive drugs and that of erroneous positive prediction for negative drugs were 0.058 and 0.166, respectively, in the machine learning model, whereas those in the BCS method were 0.146 and 0.328, respectively. Therefore, the machine learning model predicted changes in availability of drugs more accurately for no or positive food effects and with noticeably less risk of opposite predictions, compared with the BCS method.

[1] Singh, B.N., A quantitative approach to probe the dependence and correlation of food-effect with aqueous solubility, dose/solubility ratio, and partition coefficient (Log P) for orally active drugs administered as immediate-release formulations, Drug Dev Res, 65: 55-75, 2005.

[2] Gu, C.H. *et al.*, Predicting effect of food on extent of drug absorption based on physicochemical properties, *Pharm Res*, 24: 1118-1130, 2007.

[3] O'Shea, J.P. *et al.*, Food for thought: formulating away the food effect - a PEARRL review, *J Pharm Pharmacol*, 71:510-535, 2019.

[4] Deng, J. *et al.*, A Review of Food-Drug Interactions on Oral Drug Absorption, Drugs, 77:1833-1855, 2017.

O2-09

Prediction of the inhibitory activity of rat drug-metabolizing enzyme by *in silico* method

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Keywords: Applicability domain, Drug-metabolizing enzymes, Machine learning method, Synthetic Minority Over-sampling TEchnique

Some chemical substances exhibit their toxicity, especially hepatotoxicity, through their reactive metabolites formed by drug-metabolizing enzymes. In this study, we sought to develop in silico models for predicting the inhibitory activity of chemical substances against rat drug-metabolizing enzymes based on chemical structure information to gain an insight into the chemical-induced toxicity.

We selected 218 commercially available substances from the rat repeated-dose toxicity test database of Hazard Evaluation Support System Integrated Platform (HESS) [1] and used them as test substances for inhibition assays against rat drug-metabolizing enzymes. We used the data of 6 rat cytochrome P450s (CYP1A1, CYP1A2, CYP2B1, CYP2C6, CYP2D1, CYP3A2) and rat UDP-glucuronosyltransferases (UGT) as targets. Substance that showed inhibition by 15% or more were considered as “reactive” and the others as “non-reactive”. The performance of generated prediction models was evaluated in terms of sensitivity and area under the curve (ROC-AUC).

Using the results of the in vitro inhibition assays, we constructed classification models for each target discriminating “reactive” and “non-reactive” using a random forest (RF) algorism with molecular descriptors calculated by Mordred [2]. We randomly divided the 218 substances into the training set and test set at a 3 to 1 ratio, maintaining the reactive/non-reactive ratio. To improve the prediction of imbalanced data, we applied the Synthetic Minority Over-sampling TEchnique (SMOTE). We also set the applicability domains (ADs), which are the chemical spaces that can provide highly reliable prediction results in the test set. The established models showed the following prediction performance: Sensitivity; 0.79 or more, and ROC-AUC; 0.83 or more.

In this study, we have demonstrated that the incorporation of the SMOTE and ADs is useful to develop high-performance and reliable classification models that predict the inhibitory activity of chemical substances against drug-metabolizing enzymes.

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[1] http://www.nite.go.jp/en/chem/qsar/hess-e.html
[2] http://mordred-descriptor.github.io/documentation/master/index.html

O2-10

Introduction to the Issues of Dataset Construction in Pharmacokinetic Models

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Keywords: Pharmacokinetics, Dataset

Developing a new drug normally takes over ten years and costs hundreds of billions of yen. In addition, Significant loss of time and money occurs when development is discontinued due to pharmacokinetic problems. The prediction of pharmacokinetic parameters using machine learning is expected to allow the development of new drugs at a lower cost over a shorter period of time. However, the available data are limited, and it is rare that the framework of machine learning can be applied immediately. In this presentation, we will discuss the problems faced when combining the Well-Stirred Model and machine learning, using the estimation of hepatic clearance (CL_h), one of a pharmacokinetic index, as an example. Machine learning is used for the regression prediction of pharmacokinetic parameters (intrinsic clearance (CL_{int}), fraction unbound in plasma ($f_{u,p,}$), blood/plasma ratio (R_b)). In particular, we point out two problems that were revealed through the construction of evaluation data for CL_h and the model construction of R_b. The first is "lack of data." The number of compounds with a set of ((CL_{int}, $f_{u,p,}$ R_b), CL_h) necessary for the evaluation of CL_h prediction was only 5 out of 5,201 (0.096%). The second is "quality of data." With regard to the distribution of R_b, approximately 20% of all data are unevenly distributed at R_b=1. It can be inferred that 20% of the values for Rb have been set to 1 for some reason. The identification flag is necessary to eliminate the mixture of data, but no metadata for quality assurance was included to flag which values are set and which are actual measurements. Finally, we would like to summarize the insights gained from this activity and propose the data curation policy for machine-learning on pharmacokinetic parameters and its predictions.

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[3] Levy V. A new future for R&D? Measuring the return from pharmaceutical innovation 2017, Deloitte Centre for Health Solutions 2017(https://www2.deloitte.com/ch/en/pages/ life-sciences-and-healthcare/articles/new-future-for-r-and- d.html)

O2-11

Analysis of monkey pose estimation using deep learning.

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Keywords: Nonclinical study, behavior, deep learning

Recent technological innovations have had a great impact on the development of new drugs, one of which is deep learning. This technology allows us to utilize a much larger amount of data for drug development than humans alone could. This study was conducted with the expectation of discovering a new method of utilizing deep learning in video monitoring of animals, which would allow monitoring for a longer period than previously performed by humans alone. The ultimate goal of this study is to develop a deep learning model that can classify toxic features such as changes in activity level, abnormal posture, ataxia, and vomiting/nausea from videos recorded for a long period of time in normal cages with a shield. As a preliminary step, we herein report on detection of monkey skeleton.

A skeleton detection model was used. In order to avoid bias in the learning data, still images cut out from RGB + depth videos were clustered by image pattern, and still images were selected evenly from each cluster. The coordinates of the head, neck and extremities were input to the selected still images and used as learning data. The skeletal detection was learned by CNN from the still images, and inferences were made based on videos of the same individuals over different time zones.

In the same individuals, the accuracy of the detected parts in the selected still images was 94%.

As a result, identification of the positions of the monkey's head, neck and extremities using a skeleton detection model was considered effective. We will further investigate whether toxic features can be detected from these positions in monkeys showing toxic features.