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Letter to Editor

The prediction approach of drug-induced liver injury: response to the issues of reproducible science of artificial intelligence in real-world applications

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Abstract

In the previous study, we developed the generalized drug-induced liver injury (DILI) prediction model—ResNet18DNN to predict DILI based on multi-source combined DILI dataset and achieved better performance than that of previously published described DILI prediction models. Recently, we were honored to receive the invitation from the editor to response the Letter to Editor by Liu Zhichao, *et al*. We were glad that our research has attracted the attention of Liu's team and they has put forward their opinions on our research. In this response to Letter to the Editor, we will respond to these comments.

Keywords: ResNet18DNN, drug-induced liver injury, response to Letter to Editor, artificial intelligence

Background of our project

Three years ago, we began the project of the safety evaluation for the traditional Chinese medicine and Western medicine combination, which was to systematically predict the drug-induced multi-organs (liver, kidney, heart, lung, brain, etc.) injury. The research of ResNet18DNN [1] was only part of this project. Moreover, we have been developing an open-source and free prediction global system for drug-induced multi-organ (liver, kidney, heart, lung, brain, etc.) injury. So we cannot make data and codes available to the public now. The collection of the drug-induced liver injury (DILI) dataset in the ResNet18DNN research was completed 2 years ago. In order to obtain more comprehensive and accurate DILI dataset, we integrated DILI data sets from different sources. We hope to develop the DILI model with wider coverage and stronger generalization.

More than 1 year was spent on model selection and training, and finally a more excellent model (ResNet18DNN) was trained before DILIst [2] was published. The Letter to the Editor mainly raised three main issues: class labels of drug toxicity, details of model development, reproducibility of our model.

Class labels of drug toxicity

Hepatotoxic compounds were inconsistently in various DILI annotations. We combined the dataset from DILIrank [3], LiverTox [4], Hepatox [5] and published literatures [6–26]. We classified the potential DILI as 'DILI positive' with employing Likelihood scores in LiverTox [4]. Although the divergence of DILI annotations, the compounds with inconsistent and ambiguous annotations in various literatures and databases were excluded in previous research.

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Model development of ResNet18DNN

The ResNet18 architecture were adopted in this research to extract features of each molecular structure in the training set, test set.

Data imbalance was the common phenomenon in scientific research. We were relatively strict in the identification of negative DILI in the data screening process. Firstly, the drugs has not been reported to have DILI in the published literatures. Secondly, no drugs with potential DILI has been found in the public databases. Thirdly, no DILI event has been found during clinical use.

In the training process, we adopted the method of randomly dividing the samples many times, but found that different randomly splitting samples had less influence on the performance of ResNet18DNN model.

Different researches developed models based on their own data sets and compared the performance of the models in the current situation, which also reflected the overall understanding of DILI. Since we were unable to get all the codes for the models listed in ResNet18DNN.

Reproducibility for the previous study

We will collect the data in DILIst [2] that not included in our previous study as the DILI external validation set to validate the robustness and accuracy of ResNet18DNN.

Key Points

- Response to the 'Letter to Editor: 'Best practices and reproducible science are required to advance artificial intelligence in real-world application'.
- Due to the word limit of the letter, we hope that we can validate the robustness and accuracy of ResNet18DNN on the external validation data sets with the manuscript type of 'Problem solving protocol'.
- Best practices and reproducible science are required to implement in repeated validation and practice.

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Data availability statement

Any required links or identifiers for our data are present in the paper as described.

References

1. Chen Z, Jiang Y, Zhang X, *et al.* ResNet18DNN: prediction approach of drug-induced liver injury by deep neural network with ResNet18. *Brief Bioinform* 2022;**23**:bbab503.
2. Thakkar S, Li T, Liu Z, *et al.* Drug-induced liver injury severity and toxicity (DILIst): binary classification of 1279 drugs by human hepatotoxicity. *Drug Discov Today* 2020;**25**:201–8.
3. Chen M, Suzuki A, Thakkar S, *et al.* DILIrank: the largest reference drug list ranked by the risk for developing drug-induced liver injury in humans. *Drug Discov Today* 2016;**21**:648–53.
4. Hoofnagle JH, Serrano J, Knoben JE, *et al.* LiverTox: a website on drug-induced liver injury. *Hepatology* 2013;**57**:873–4.
5. Quinton A, Latry P, Biour M. Hepatox: database on hepatotoxic drugs. *Gastroenterol Clin Biol* 1993;**17**:H116–20.
6. Chen M, Zhang J, Wang Y, *et al.* The liver toxicity knowledge base: a systems approach to a complex end point. *Clin Pharmacol Ther* 2013;**93**:409–12.
7. Chen M, Hong H, Fang H, *et al.* Quantitative structure-activity relationship models for predicting drug-induced liver injury based on FDA-approved drug labeling annotation and using a large collection of drugs. *Toxicol Sci* 2013;**136**:242–9.
8. Greene N, Fisk L, Naven RT, *et al.* Developing structure-activity relationships for the prediction of hepatotoxicity. *Chem Res Toxicol* 2010;**23**:1215–22.
9. Huang SH, Tung CW, Fulop F, *et al.* Developing a QSAR model for hepatotoxicity screening of the active compounds in traditional Chinese medicines. *Food Chem Toxicol* 2015;**78**:71–7.
10. Liew CY, Lim YC, Yap CW. Mixed learning algorithms and features ensemble in hepatotoxicity prediction. *J Comput Aided Mol Des* 2011;**25**:855–71.
11. Liu Z, Shi Q, Ding D, *et al.* Translating clinical findings into knowledge in drug safety evaluation–drug induced liver injury prediction system (DILIps). *PLoS Comput Biol* 2011;**7**:e1002310.
12. Low Y, Uehara T, Minowa Y, *et al.* Predicting drug-induced hepatotoxicity using QSAR and toxicogenomics approaches. *Chem Res Toxicol* 2011;**24**:1251–62.
13. O'Brien PJ, Irwin W, Diaz D, *et al.* High concordance of drug-induced human hepatotoxicity with in vitro cytotoxicity measured in a novel cell-based model using high content screening. *Arch Toxicol* 2006;**80**:580–604.
14. Rodgers AD, Zhu H, Fourches D, *et al.* Modeling liver-related adverse effects of drugs using k nearest neighbor quantitative structure– activity relationship method. *Chem Res Toxicol* 2010;**23**:724–32.
15. Xu JJ, Henstock PV, Dunn MC, *et al.* Cellular imaging predictions of clinical drug-induced liver injury. *Toxicol Sci* 2008;**105**:97–105.
16. Zhu X, Kruhlak NL. Construction and analysis of a human hepatotoxicity database suitable for QSAR modeling using post-market safety data. *Toxicology* 2014;**321**:62–72.
17. Li T, Tong W, Roberts R, *et al.* DeepDILI: deep learning-powered drug-induced liver injury prediction using model-level representation. *Chem Res Toxicol* 2020;**34**:550–65.
18. Xu Y, Dai Z, Chen F, *et al.* Deep learning for drug-induced liver injury. *J Chem Inf Model* 2015;**55**:2085–93.

19. Nguyen-Vo T-H, Nguyen L, Do N, *et al.* Predicting drug-induced liver injury using convolutional neural network and molecular fingerprint-embedded features. *ACS omega* 2020;**5**:25432–9.
20. Minerali E, Foil DH, Zorn KM, *et al.* Comparing machine learning algorithms for predicting drug-induced liver injury (DILI). *Mol Pharm* 2020;**17**:2628–37.
21. Banerjee P, Eckert AO, Schrey AK, *et al.* ProTox-II: a webserver for the prediction of toxicity of chemicals. *Nucleic Acids Res* 2018;**46**:W257–63.
22. Ma H, An W, Wang Y, *et al.* Deep graph learning with property augmentation for predicting drug-induced liver injury. *Chem Res Toxicol* 2020;**34**:495–506.
23. Ai H, Chen W, Zhang L, *et al.* Predicting drug-induced liver injury using ensemble learning methods and molecular fingerprints. *Toxicol Sci* 2018;**165**:100–7.
24. Zhang C, Cheng F, Li W, *et al.* In silico prediction of drug induced liver toxicity using substructure pattern recognition method. *Mol Inform* 2016;**35**:136–44.
25. Mulliner D, Schmidt F, Stolte M, *et al.* Computational models for human and animal hepatotoxicity with a global application scope. *Chem Res Toxicol* 2016;**29**:757–67.
26. Kotsampasakou E, Montanari F, Ecker GF. Predicting drug-induced liver injury: the importance of data curation. *Toxicology* 2017;**389**:139–45.