Advances in the Application of Machine Learning and Deep Learning in Drug–Drug Interaction Prediction

Junru Lu

{2400302129@stu.gdpu.edu.cn}

School of Pharmacy, Guangdong Pharmaceutical University, Guangzhou, Guangdong, China

Abstract. While drug combination therapy can enhance efficacy, it may also trigger drug interactions. Traditional detection methods are time-consuming and costly, making artificial intelligence an important auxiliary technology. This article reviews traditional machine learning methods and deep learning methods perspectives. Traditional machine learning methods can use the Drug–Drug Interaction (DDI) information database of pharmacokinetics (PK) for prediction, but this method has a relatively high bias risk for all models. Deep learning methods often establish models based on neural networks, and the results are relatively more accurate. Artificial intelligence has played an important role in DDI prediction, but there are still limitations such as insufficient consideration of clinical factors and inconsistent use of data sets, which are expected to be resolved. This article summarizes the current application status of artificial intelligence in DDI prediction, which can promote existing pharmacological theories and provide practical references for clinical medication.

Keywords: Drug–Drug Interaction Prediction, Artificial intelligence, Machine learning, Deep learning.

1 Introduction

In clinical practice, combination therapy with drugs is a common treatment approach used throughout the treatment of various diseases and at different stages of the disease, playing a crucial role and being an effective method for treating a wide range of diseases including cancer, hypertension, asthma, etc. [1]. Based on theoretical research and clinical experiments, combination therapy of drugs has improved the therapeutic effect of drugs and reduced the risk of drug resistance, and to some extent, alleviated the toxic side effects of drugs [2].

However, combined medication can also cause adverse reactions during the treatment process, which are often accompanied by the risks brought by drug-drug interactions (DDI) [1,2,3]. DDI refers to the phenomenon where the effect or toxicity of one drug is affected by another drug when two or more drugs are used together. Adverse drug reactions caused by DDI are one of the main reasons for drug withdrawal from the market [4]. The purpose of DDI research is to confirm whether DDI occurs in the human body and to assess its severity [3].

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Due to the traditional experimental-based methods for predicting DDI mainly relying on clinical trials, in vitro experiments, and adverse drug reaction monitoring after drug approval, DDI research has problems of long detection cycles and high costs [3,5].

In recent years, DDI research has increasingly widely utilized computers and artificial intelligence as detection methods [1,2]. By establishing existing drug interaction data through traditional machine learning or deep learning methods, and then establishing models to achieve DDI prediction, this can significantly improve the efficiency of DDI prediction [1]. Machine learning methods mainly learn the mapping relationship between features and labels from labeled data to predict the classification of unknown drugs [5,6]. While deep learning methods automatically learn the hierarchical features of data from multi-layer neural networks for prediction. Currently, deep learning is a more mainstream prediction method, and many studies have applied deep learning models such as graph neural networks, long short-term memory networks, and attention mechanisms to DDI prediction [1,2,7].

In the current era of rapid development of AI, analyzing the current application status of artificial intelligence methods in DDI prediction not only advances the existing pharmacological theories but also provides practical references for clinical medication. The main purpose of this article is to review the research progress of DDI based on machine learning and deep learning methods, introduce the two major research methods of machine learning and deep learning respectively, and analyze the existing limitations and future prospects. This article can be used as a reference for drug researchers and clinical workers, helping them understand the application prospects of AI in the field of pharmacology.

2 Basic Information

Drug combination therapy may affect multiple properties such as drug pharmacokinetics and drug pharmacodynamic properties, thereby influencing the processes of drug absorption, distribution, metabolism, and excretion [3]. DDI usually manifests in three types: synergistic effect, additive effect, and antagonistic effect, or synergistic effect, adverse effect, and irrelevant effect [2, 8]. Yao et al. clarified that DDI research requires identifying factors that may affect drug disposition to elucidate potential DDI mechanisms and their degree of influence, and to obtain kinetic parameters for further research. The main contents include determining the main elimination pathway of the drug, evaluating the contribution of related metabolic enzymes and transporters to drug disposition, and examining the impact of the drug on metabolic enzymes and transporters [3].

3 Prediction of Drug Interactions Based on Artificial Intelligence Methods

3.1 Drug interaction prediction based on machine learning methods

Liang et al. utilized the DDI information database of PK and proposed a machine learning model that can predict the change in AUC [5]. This method extracted DDI and AUC data from FDA-certified drug labels. Then, it retrieved relevant peptide and PD information through DrugBank, normalized the matrix, and constructed a multi-dimensional feature vector. Finally,

the impact of drug features on drug efficacy was used as the dependent variable to train and optimize the Bagged model. This study verified the effects of 16 drugs on tacrolimus, and the results showed that the accuracy rate of DDI prediction with or without DDI was 81.25%, and the deviation between strong and weak predictions was small. It has clinical value in preclinical DDI assessment.

Zhang et al. evaluated the DDI prediction model constructed based on machine learning [6]. This study retrieved databases such as PubMed and CNKI, and included 54 DDI prediction models involving 21 machine learning algorithms. Among them, the models using drug structure features as predictors had an AUC range of 0.83-0.99. The experimental results showed that all models had a high risk of bias, mainly due to information bias and the black box effect. This indicates that DDI research should use more interpretable models.

3.2 Drug interaction prediction based on machine learning methods

Shen proposed a drug interaction prediction model based on Graph Neural Network (GNN) [7]. This model represents drug molecules using a graph structure, with atoms as nodes and chemical bonds as edges for convolutional calculation to extract molecular features, and finally uses a multi-layer perceptron to complete DDI prediction. Experimental results on the DrugBank dataset showed that the prediction accuracy of this model reached 93%, and it was more accurate than existing methods in terms of AURROC and AURPRC indicators, indicating that this model has potential application in the drug development stage.

Liu aimed to solve the problem that the distributed representation of text only stays at superficial features such as words and has not effectively utilized the dependency syntactic information. He proposed a drug relationship extraction model based on dual-channel convolutional neural network (CNN) [9]. This model adopts a dual-channel structure, using word vectors plus drug description information and word vectors plus dependency information, and explores the improvement effect on extraction performance through setting control experiments. After experimental verification, the model based on the fusion of the two pieces of information achieved a comprehensive evaluation rate of 80.59%, and dependency information and drug description information can effectively improve the extraction performance.

Yan et al. mentioned the technical progress and application cases of deep learning and large language models (LLMs) in DDI prediction [10]. This research was conducted by clinical pharmacists through a single-blind design, comprehensively evaluating the performance of five mainstream LLMs, namely CahtGPT-4, DouBao, ERNIE Bot, Kimi Chat, and DeepSeek-R1, in the verifiable drug combination DDI analysis task, and the disputes were arbitrated by a third-party senior pharmacist. Based on the test results, several LLMs performed well in DDI prediction, but there were deviations in understanding different data information, and the results remained uncertain.

4 Current Limitations and Future Prospects

Although the research on DDI prediction based on artificial intelligence has achieved significant technological breakthroughs, there are still several limitations that prevent its clinical application. Firstly, most existing models rely on the structural features and biological

properties of drugs, and do not adequately consider the complex factors in clinical drug use. One is the dosage factor: the same drug may show different interaction results under different dosages, while the drugs in existing models are static. Secondly, the temporal factor: the sequence of drug administration may affect the absorption, distribution, metabolism, and excretion of the drug, but most models do not consider this factor. Thirdly, individual differences: different patients' genotypes, age, liver and kidney functions, etc. directly affect the drug's metabolic ability, and most models have not considered this factor.

Secondly, different studies use different datasets and evaluation indicators, making it difficult to make horizontal comparisons. One is the single data source: most research data come from public databases such as DrugBank, which indeed show the verification of clinical data. Therefore, the accuracy of the model in the laboratory environment may not necessarily translate to reality. Secondly, the evaluation criteria are not unified: different studies use their own indicators to evaluate the accuracy rate, and the data sets are also diverse. It is difficult to make horizontal comparisons among studies.

These limitations can be resolved. If more real clinical data can be integrated into future research to make it closer to the real drug use scenario, and at the same time promote the standardization of the prediction model to make different models comparable, artificial intelligence will move from papers to tools, and is expected to become an important tool for DDI prediction research.

5 Conclusion

From the perspective of technological advancement, the DDI prediction field has evolved from traditional machine learning methods based on feature engineering to end-to-end feature learning through deep learning, and has gradually utilized large language models. In the field of machine learning, existing models have shown good performance in DDI prediction, but often have high bias risks and insufficient interpretability. In the field of deep learning, models such as graph neural networks and convolutional neural networks can accurately predict DDI. Modeling that integrates multiple sources of information significantly enhances the feature extraction ability, and large language models have also become a new path for DDI prediction. Existing studies have shown that in the DDI predic tion field, deep learning methods generally have higher accuracy rates than traditional machine learning. However, these models still face challenges such as insufficient consideration of clinical factors and inconsistent data sets and evaluation standards. Future research should focus on integrating clinical data and other data sets into the models, and establishing unified evaluation standards. Only by effectively connecting technology and clinical practice can artificial intelligence better serve clinical medication safety.

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