Artificial Intelligence-Based Prediction of Drug-Target Interactions in Mental Illnesses

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Abstract. Mental illnesses are a serious problem worldwide, and many aspects of their disease mechanisms and drug development remain unclear. Traditional drug development processes face several major challenges, including slow speed, high costs, and difficulty in achieving successful cures. However, drug-target interaction based on artificial intelligence is gradually becoming a research hotspot due to its advantages such as accessibility and low cost. This article reviews drug-target interaction research in the development of drugs for mental illnesses. It systematically summarizes and analyzes relevant research progress from three aspects: traditional biomedical methods, machine learning methods, and commonly used datasets, comparing the basic principles, application characteristics, advantages, and limitations of different methods. Based on this, it summarizes current research problems such as insufficient data quality, limited model generalization ability, insufficient interpretability, and insufficient depth in research targeting specific disease stages. Finally, it looks forward to the future development direction of artificial intelligence technology in intelligent drug discovery for mental illnesses, aiming to provide theoretical reference and practical guidance for subsequent related research.

1 Introduction

Mental illness is now a global issue, not just an emotional problem but also a challenge to global public health. According to the World Health Organization (WHO) 2026 report, more than 300 million people worldwide suffer from depression, and this number has increased by more than 18% between 2005 and 2015 [1]. Depression is a potentially chronic mental disorder with a lifetime prevalence of 15-18%, which is one of the leading causes of the global disease burden, causing huge healthcare and social costs, and patients with depression have a higher risk of premature death compared to the general population [2].

In this context, computational models provide an effective and economical approach to the difficulties of treating depression, rendering drug-target interaction (DTI) prediction via computational models a focal point of research. The development cycle of new drugs can be shortened by using huge amounts of biomedical data to find patterns and new ways to use computers to speed up drug screening. As knowledge graph and neural network technologies have matured, it is now possible to build predictive frameworks that take into account disease specificity. This can not only speed up and improve the accuracy of drug development, but it can also show how drugs work and how they cure diseases, which is very important and valuable from a scientific point of view.

2 Biomedical-based methods

Traditional biomedical approaches mainly concentrate on comprehending and analyzing disease mechanisms, pinpointing drugs through the interactions among various targets within biological networks. They generally think that drugs work by interacting with these things.

Kobayashi et al. put forth a framework for analyzing gene regulatory networks that is based on the transcriptome. This study indicated that elucidating the alterations in drug resistance in epilepsy treatment is challenging when relying on overexpressed genes and heightened transcription. The authors analyzed the gene modules that changed in the brain tissue of patients through receptor proteins, gene expression and clinical experiments to find the key nodes of drug failure. Their research path of mining disease-related molecular networks and potential drug targets through multidimensional biological information has reference significance for the network modeling and mechanism identification of drug target interaction prediction in other mental diseases [3].

Zhang et al. pointed out in their study that the treatment of depression often relies on the synergistic effect of multiple components and multiple targets rather than the blockade of a single molecule. Through network pharmacology, the construction of a multi-layered network of "compound-target-pathway-disease" allows for visualization and quantification of this

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synergistic effect. Network topology analysis can reveal the molecular basis for the synergistic effect of multiple targets in the treatment of depression and improve the screening efficiency for key targets. This approach, in addition to studying individual proteins, looks at the comprehensive functioning of networks and provides a systems biology approach to unraveling the complex mechanisms of depression and other related disorders [4].

3 Machine learning-based methods

As artificial intelligence technologies advance further, machine learning is becoming an innovative approach for researching disease mechanisms and for aiding in drug development. In contrast to traditional methodologies, machine learning can analyze and manage high-dimensional, nonlinear, and sparse biomedical data and predict, based on available data, the interactions between drug molecules and protein targets.

Glory et al. proposed a deep learning model called DrugSchizoNet to address the problems of data imbalance, noise interference, and poor generalization ability in the prediction of drug-target interactions in schizophrenia. The model first obtains drug-related data from DrugBank and repoDB databases, and performs data cleaning, normalization and feature extraction in sequence to improve data quality. In terms of model architecture, a fully connected layer is used to extract features, an LSTM layer is used to capture the sequence characteristics of drug interactions, and Dropout regularization is introduced to prevent overfitting. Hyperparameters are tuned using the OB-MOA algorithm to improve prediction accuracy. Experimental results show that the model outperforms existing models such as CNN-RNN, DANN, CKA-MKL, DGAN and CNN in accuracy (98.70%) as well as multiple evaluation indicators such as recall, specificity, precision, F1 score, AUPR and AUROC, providing an efficient DTI prediction tool for the development of drugs for schizophrenia [5].

Romão et al. conducted a systematic evaluation of machine learning in drug development and related fields. The study pointed out that machine learning algorithms such as support vector machine (SVM), random forest (RF) and naive Bayes have been widely used in drug-target interaction (DTI), especially with good performance in small sample data. Graph neural network (GNN) and Transformer architecture can directly extract relevant features of drugs and sequence information of proteins, and no longer rely on manual input. This analysis shows that machine learning not only helps to improve the diagnostic accuracy of mental illnesses but also provides a new research path for drug-target interaction prediction and the development of new treatment strategies [6].

In conclusion, machine learning has already shown a very positive role in the development of antidepressant drugs, especially with the breakthroughs in deep learning in recent years, which have made it possible to use machine learning to predict drugs in the future.

4 Dataset

In machine learning, high-quality, large-scale datasets are fundamental to drug-target interaction (DTI) prediction models. Currently, there are three relevant datasets: DrugBank, Comparative Toxicogenomics Database (CTD), and STRING Database (Table 1).

DrugBank is a web-based database containing comprehensive molecular information on drugs, including drug mechanisms of action, interactions and targets. The database is comprehensive and free to access, containing detailed drug information on drugs approved by the U.S. Food and Drug Administration (FDA) and experimental drugs under FDA review, including drug targets, drug effects and drug interactions. Relying on its rich, high-quality and reliable original data, it has become one of the most widely used drug reference resources in the world, and is widely used by the public, educators, pharmacists, pharmacologists, medicinal chemists, drug researchers and the pharmaceutical industry. Its advantages are high-accuracy data and rich metadata, but its limitations are that the range of targets covered is relatively limited and the update speed lags behind the latest basic research findings [7].

The Comparative Toxicogenomics Database (CTD) coordinates cross-species heterogeneous chemical exposure and its biological effects data by manually organizing and associating information on chemicals, genes, phenotypes, anatomy, diseases, taxa and exposures from published literature. This organized information is integrated to generate inferences, provide potential molecular mediators, thereby constructing testable hypotheses and filling knowledge gaps in the field of environmental health. At the same time, it has launched a new tool: CTD Tetramers. By computationally generating four-unit information blocks that connect chemicals, genes, phenotypes and diseases, potential molecular mechanism pathways are constructed. It integrates multiple data types, transforming a carefully organized knowledge base into a discovery base. This method identifies potential intermediate links that can connect different data types through computation [8].

The STRING database collects and integrates data regarding protein-protein interactions, pertaining both to physical interactions and functional associations. These data originate from diverse methodologies, including data mined from the scientific literature, interactions predicted by computational methods based on co-expression, and data from conserved genomic contexts, experimental interaction databases, and known complexes or pathways from selected resources [9].

Table 1. Datasets

Dataset	Data Type	Main Content	Strengths	Limitations
DrugBank	Drug–target interaction, pharmacological data	Provides comprehensive information on drugs, including mechanisms of action, targets, interactions, and FDA-approved as well as experimental drugs	High data accuracy; rich annotations; widely validated and authoritative	Limited coverage of novel or less-studied targets; relatively slow updates compared to latest research
CTD (Comparative Toxicogenomics Database)	Chemical–gene–disease relationships	Manually curated database linking chemicals, genes, phenotypes, diseases, and exposures; supports cross-species analysis and hypothesis generation	Highly structured and curated; integrates heterogeneous biological relationships; supports mechanistic inference (e.g., CTD Tetramers)	Complex data structure; indirect associations may introduce noise for DTI tasks
STRING	Protein–protein interaction (PPI) networks	Integrates known and predicted protein–protein interactions from experiments, literature mining, co-expression, and computational predictions	Large-scale interaction network; integrates multiple evidence sources; useful for capturing functional associations	Contains predicted interactions with varying confidence; may include false positives

5 Existing limitations and prospects

Despite significant progress in this field over the past few years, many areas still face serious challenges.

First, there is a lack of data and insufficient coverage. There are still undiscovered DTIs in the existing knowledge graphs, and the current knowledge graphs are more biased towards including popular diseases and their related drugs, while lacking data on some rare diseases and some disease subtypes [10]. This will result in high efficiency and excellent performance when facing drugs related to known targets, but its ability may be limited and its performance may be frustrated when facing some rare diseases. At the same time, the different inclusion standards between different databases will also lead to deviations in the databases required for their research in some aspects [11].

Secondly, there is the interpretability of the model and its rationality in biology. High-performance learning models are often regarded as black boxes, and the results they predict are difficult for some biologists to adopt or believe [12], or researchers do not know the mechanism of the drug and cannot conduct continuous research or evaluation on it, resulting in the inability to conduct further clinical research or experiments [13].

Finally, the breadth of coverage is different. Most of the current large model training focuses on specific fields or diseases, which makes it impossible to apply the learned knowledge to related fields and limits the universal value of the research [14].

6 Conclusion

This article reviews research on drug-target interaction prediction for mental illnesses based on computational models, and analyzes and summarizes it from three dimensions: traditional biomedical methods, machine learning methods, and commonly used datasets.

In terms of traditional biomedical methods, network pharmacology and gene regulatory network analysis, by constructing multi-layered networks of "compound-target-pathway-disease," have revealed the molecular mechanisms of synergistic effects of multiple drug targets, providing a systems biology perspective for understanding the treatment mechanisms of mental illnesses. Regarding machine learning methods, deep learning models, represented by DrugSchizoNet, have demonstrated excellent performance in predicting disease-related intellectual property (DTI) in conditions such as schizophrenia.

Some of the algorithms that have demonstrated exclusivity in analyzing small sample data and automatically feature extracting include Support Vector Machines, Random Forests, Graph Neural Networks, and Transformers. The high-quality biomedical data to be trained are available in public databases such as DrugBank, CTD, and STRING. Nevertheless, these databases vary in their target coverage, speed of updates and data integration standards.

Although much progress has been made in this field, it still has three large issues: First, there is not enough data coverage since the known knowledge graphs are skewed towards common diseases and not rare diseases or disease subtypes. In addition, various databases might share inconsistent standards and this might result in prejudiced research findings. Second, models are not readily interpretable: high-performance learning models have been viewed as black-boxes, and thus biologists have struggled to apply their predictions or apply them to conduct additional mechanistic studies. Third, most of the models encompass only some areas of disease, and the cross-domain transfer of knowledge should be improved.

In conclusion, a new, fast and low cost method of making drugs to treat mental illnesses is through computer model prediction of drug-target interactions. This practice, however, is still in its infancy and is under development. The future directions of research need to focus on designing a larger and more balanced biomedical knowledge graph, developing more interpretable artificial intelligence algorithms to enhance the biological validity of models, and exploring

multimodal data fusion and cross-domain transfer learning solutions to enable the practical application of computational models in the accurate diagnosis and treatment of mental diseases.

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