Advances and Challenges in Drug-drug Interaction Prediction

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Abstract. Drug interaction (DDI) occurs when multiple drugs are used at the same time. Accurate prediction of the specific mechanisms behind DDI, known as DDI events or DDIE, is essential for clinical safe drug use. In the modern era, drug-drug drug interaction prediction is crucial to drug safety. Traditional DDI prediction has many shortcomings and deficiencies, such as DDI data is relatively limited, the generalization ability of traditional methods is weak and so on. Due to the excessive reliance of the model on the existing limited data, its prediction performance degrades dramatically when faced with brand-new drug molecules or unknown drug combinations. This makes it difficult for them to find novel ddis, which are urgently needed for drug development and clinical safety monitoring. In the latest research, people are developing towards the combination of multi-source data fusion and graph neural network. This paper aims to discuss and summarize the latest research progress in the field of DDI prediction. The research trend mentioned in this paper is changing from single data source to multi-source heterogeneous data fusion and graph neural network. By integrating the multi-modal data of drugs and using the adaptive fusion mechanism, the new model can understand the properties of drugs more comprehensively and accurately. At the same time, these innovative methods are committed to extending the prediction task from simple binary classification to refined event type prediction, thus laying the foundation for the development of more clinically practical DDI prediction models.

Keywords: Drug-drug interaction prediction, multi-source data fusion, Graph neural networks.

1. Introduction

Drug-drug interaction (DDI) is a phenomenon in which two or more drugs enter the body at the same time or in sequence, and their efficacy, toxicity or pharmacological effects are changed due to the interaction between drugs [1]. DDI is a safety issue that can not be ignored in clinical medication. It may lead to reduced efficacy, increased toxicity, and even serious health risks such as liver damage, arrhythmias, and kidney failure, even death. As the number of patients with population ageing and multiple chronic diseases increases, polypharmacy is becoming more common. According to statistics, up to 70% of drug prescriptions involve two or more drugs, which makes the incidence of DDI increased significantly. Therefore, it is crucial to accurately and efficiently predict and identify potential DDI in drug research and development, clinical practice and patient medication management, which can not only significantly improve the safety of medication, but also improve the safety of drug use, it also speeds up the development of new drugsOrganization of the Text.

Traditional DDI assays mainly rely on time-consuming and costly in vitro experiments, in vivo animal models or clinical trials. These approaches can usually only be performed on limited drug combinations and do not systematically screen out all potential ddis. More worryingly, many ddis are not discovered until after the drugs are on the market, which poses a potential risk and a huge socioeconomic burden to patients. In order to overcome these limitations, DDI prediction using computational methods has become a rapidly growing research field, providing a new way for comprehensive and large-scale evaluation of drug combination interactions.

So far, machine learning and deep learning methods have provided new opportunities to efficiently predict DDI, combining knowledge from multiple disciplines such as computer technology, medicinal chemistry, pharmacology, and bioinformatics, it provides important technical support for drug development and clinical drug management. Various deep learning-based computational methods have been developed for predicting DDI and have proven to be effective approaches to address this challenge. Therefore, DDI prediction research has attracted extensive attention in the

deep learning community [2]. In recent years, graph neural networks have been applied to various DDI tasks. Among them, the methods using GNN to extract features and predict DDI are drug molecular map-based and DDI network-based methods.

In recent years, DDI forecasting research has been deeply involved and developed in various fields, and many innovative methods have been produced. Recently, studies have begun to explore the integration of 2D and 3D molecular information, as well as multimodal feature fusion based on attention mechanism. For example, MOLORMER provides a new perspective for DDI prediction by combining two-dimensional molecular maps with spatial information. This method mainly enhances the molecular characterization by fusing two-dimensional structural features with some three-dimensional descriptors, thus improving the prediction performance. At the same time, MHCADDI (2023) uses a common attention mechanism to integrate various drug features, significantly improving the ability of models to capture complex relationships between drugs and providing a more effective solution for predicting novel drug interaction [3].

This article aims to discuss and summarize the latest research progress in the field of drug-drug interaction prediction (DDI) . In this paper, it is pointed out that the research in this field is shifting from relying on a single data source and traditional models to the combination of multi-source heterogeneous data fusion and advanced technologies such as graph neural networks. This transformation is reflected in many innovative methods, such as breaking the limitations of traditional models by integrating chemical structures, biological information and knowledge graph relationships of drugs. The concept of "Drug background data fusion" is also mentioned in this paper, that is, to capture the complex "Social relationships" of drugs in the body by constructing a complete "Drug background knowledge map".

In addition, this paper also introduces an adaptive multi-view feature fusion framework that can dynamically assign weights to different data sources according to specific tasks, which significantly improves the accuracy and generalization ability of prediction. Collectively, these innovative approaches aim to provide a more comprehensive and precise understanding of drug properties and ultimately lay the foundation for the development of more clinically useful DDI prediction models. It is very important to evaluate the risk level of drug combination accurately for guiding clinical rational drug use and avoiding adverse reactions.

2. Research on multi-source data fusion

In the study by Xiaomin Shen et al. , reflecting that traditional DDI predictions utilize traditional models and apply a single data source, the article proposes that, by fusing the approach of multimodal data [4], the prediction of DDI can be improved, it breaks the limitation of traditional models relying on a single data source, and integrates the chemical structure, biological information and relational data in the knowledge graph of drugs into a unified framework. This multi-dimensional information fusion enables models to gain a more comprehensive understanding of the complex properties of drugs. At the same time, the concept of "Drug background data fusion" proposed in the study Changpeng Zhao et al. [5], a complete "Drug background knowledge map" can be constructed for DDI, which not only contains the drug, but also integrates its related entities such as diseases, targets, genes, and biological pathways, etc. , to capture the drug in the body of the complex "Social relations". By combining the background features extracted from the knowledge graph with the traditional drug structure features, the model is able to understand the drug from a more macro and comprehensive perspective, which is beneficial to the understanding of drug structure, significantly improved the accuracy of drug-drug interaction (DDI) predictions.

In the study of Fei Wang et al., the method of data fusion is also proposed. In this paper, an adaptive multi-view feature fusion framework is proposed [6]. The framework first constructs multiple diagrams for drugs from multiple perspectives, thereby capturing the complex properties of drugs at different levels. Subsequently, through an adaptive learning mechanism, it is able to assign different weights to each view dynamically according to specific prediction tasks, rather than simply

performing static fusion. This intelligent fusion method allows the model to use multi-source information more flexibly and accurately, and ultimately significantly improves the accuracy and generalization ability of drug-drug interaction (DDI) prediction. Its common workflow diagram is shown in Figure 1.

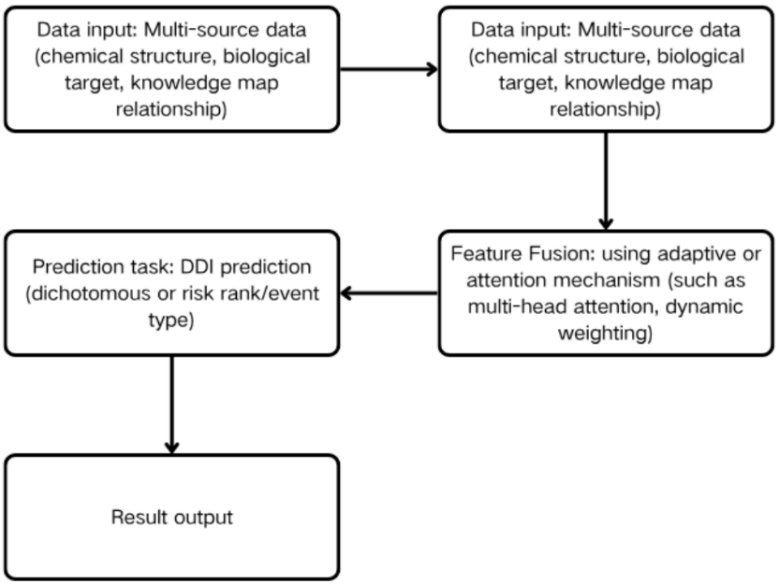

Figure 1. workflow of modern DDI forecasting model

Current modern computational methods also have partial flaws and shortcomings, often fail to fully analyze substructure components, and often ignore structural-level interactions, resulting in incomplete molecular characterizations, which can lead to the development of new computational methods for molecular characterization, this method can not capture the complex multi-level structure of drug molecules quickly and effectively. A co-attention mechanism-based hierarchical learning network (HLN-DDI) , which is specifically tailored for molecular structure characterization, was proposed in the study of Yue Luo et al. for predicting drug interaction (DDI) . This method improves the existing methods by explicitly coding the motif-level structure and capturing hierarchical molecular characterizations at the atomic, motif-level, and full-molecular scales. These hierarchical representations are integrated through a co-attention mechanism and combined with interaction type information to improve prediction performance. The comprehensive evaluation shows that HLN-DDI performs significantly better than the state-of-the-art methods on multiple benchmark datasets, with an accuracy of more than 98% in conduction scenarios and more than 99% in various evaluation metrics. In addition, HLN-DDI achieved a significant accuracy improvement of 2.75% in predicting DDI involving unknown drugs [7].

Gao et al. (2010) , who proposed a comprehensive feature fusion technique based on multi-source drug data, and a novel multi-modal drug interaction (MMDDI) model, the model aims to improve the accuracy and depth of DDI predictions [8].

This study is based on a real-world DrugBank database, which covers a wealth of drug-related information and aims to predict the multiple interaction events that may occur between drugs, and to identify the potential interactions between drugs, and to explore the underlying mechanism of action. The MMDDI model completes high-precision prediction through four core steps, including drug feature extraction, drug pairing method, feature fusion network, and multi-source information integration. This method uses advanced data fusion strategies and machine learning techniques to perform multi-dimensional analysis of drug attributes and their interaction events. The MMDDI model is systematically verified on three typical prediction tasks. The experimental results show that the model outperforms the existing mainstream methods in terms of accuracy, generalization and interpretability. On the specific test set, MMDDI achieved a prediction accuracy of 93% , and the AUC-ROC value reached 0.9505, showing excellent discrimination ability. In addition, the interpretability analysis of the model also revealed the complex association between drug attributes

and the intrinsic mechanism of interaction, providing a new scientific basis for clinical rational drug use [8].

At present, most of the existing methods are still mainly limited to binary classification tasks, and it is difficult to quantify the difference in the degree of risk between different drug interaction, it also performs poorly in dealing with problems such as unbalanced data distribution and insufficient semantic alignment of heterogeneous features. In order to deal with the above challenges, this paper systematically summarizes the existing problems and proposes corresponding solutions, and then proposes a drug combination risk level prediction model MSFCL based on multi-source feature fusion and contrastive learning. The model integrates molecular structure features extracted by TrimNet and combines high-order topological relationships captured by graph convolutional networks. In order to improve the robustness of the feature, we combine the similarity matrix based on Morgan fingerprint with the prior constraint of the identity matrix. Aiming at the problem of data imbalance, an adaptive gradient noise hybrid perturbation strategy is designed, which achieves contrast learning without relying on data enhancement by Dynamic equilibrium gradient direction guidance and Gauss Noise Injection. In addition, the model introduces multi-head attention mechanism and residual connection to optimize the multi-source feature alignment process, and combines label smoothing and focus loss function to further optimize the training objectives. Extensive experiments on three public benchmark datasets show that MSFCL outperforms state-of-the-art methods in all evaluation metrics. Specifically, on the DDINTER dataset, MSFCL improves the precision by an average of 9.84% , the macro F1 score by an average of 14.97% , the macro recall by an average of 11.91% , and the macro precision by an average of 12.94% . Moreover, MSFCL also showed excellent generalization ability in multi-category classification tasks on DrugBank and MDF-SA-DDI datasets [9].

3. Challenges and prospects

Although advanced techniques such as multi-source data fusion and graph neural networks have brought new breakthroughs in drug-drug drug interaction prediction (DDI) , there are still many key challenges in this field. These challenges not only restrict the performance and practicability of the model, but also point out the direction for future research

At the data level, DDI forecasting has always been plagued by data scarcity and high imbalance. The number of validated ddis is limited, and the drug pair combination space is extremely large, resulting in far fewer positive samples with interaction records than negative samples, and the model is prone to predict“No interaction”. In addition, multi-source data-such as chemical structures, biological pathways, and clinical reports-come from a variety of sources and formats, with significant heterogeneity and quality differences, it brings great difficulties to data cleaning, alignment and fusion. In the future, researchers can generate credible synthetic samples through generative artificial intelligence (such as Gan and Diffusion models) to alleviate data imbalance, and promote the construction of a unified and standardized large-scale DDI knowledge graph across databases, self-supervised learning is widely introduced to pre-train the generic representation of drugs from a large number of unlabeled data to reduce the dependence on expensive labeled data.

Model generalization and interpretability is another bottleneck at present. In the face of new drugs (“Cold start” problem), models often perform poorly, which limits their application in early drug research and development. At the same time, despite the high precision of complex models such as graph neural networks, their decision-making process often lacks transparency and is difficult to provide reasonable explanations at the pharmacological or biochemical level, resulting in low clinical acceptance. To address these challenges, future research should explore zero-sample/few-sample learning mechanisms that enable models to infer potential interactions of new drugs by drawing on the knowledge of known drugs; interpretable artificial intelligence (Xai-RRB- techniques should also be introduced, and future research should focus on the potential interactions of new drugs, for example, visualizing key molecular structures through attention mechanisms, or generating counterfactual explanations to enhance decision-making credibility. In addition, the model needs to

be rigorously evaluated under an external dataset and a time validation framework to ensure its generalization ability.

Computational efficiency and clinical translation are key barriers to moving DDI predictions from the laboratory to practical applications. The current multi-modal fusion model is difficult to be integrated into the real-time decision support system of medical institutions due to its large scale of parameters and high computational overhead. More importantly, most models can only predict whether interactions occur and can not output the severity grading, risk quantification, or medication adjustment recommendations that are urgently needed in the clinic. In order to promote the real landing, it is necessary to focus on the lightweight of the model in the future, such as reducing the computational requirements through knowledge distillation and model pruning. At the same time, a hierarchical and hierarchical prediction framework should be developed, combining the DDI type with clinical guidelines to provide operational advice directly, and conducting prospective clinical trials to verify its effectiveness in reducing medication errors in real medical settings.

Multi-modal fusion itself still has room for optimization. Current fusion methods (such as early splicing or simple weighting) often do not fully consider the contribution differences of different data sources in different contexts, and some modes may have noise or conflict, which affects the fusion effect. In the future, it is necessary to develop more adaptive and fine-grained fusion mechanisms, such as feature coordination models based on cross-modal attention, meta-learning or memory networks, so that the system can dynamically evaluate the reliability of each modal information. Furthermore, causal inference model can be introduced, which not only focuses on statistical correlation, but also tries to infer the biological causal path of drug-drug interaction, so as to improve the interpretability and reliability of the model.

In the future, DDI and artificial intelligence should also have more connections and development. Artificial intelligence can integrate heterogeneous biomedical data and simulate complex pharmacokinetics and pharmacodynamic relationships, and identify new interaction patterns that are beyond the reach of traditional methods. By leveraging machine learning, deep learning, graph-based models, and natural language processing, we can improve the performance of our algorithms, ai-driven systems can analytical chemistry structures, biological pathways, clinical records, and real-world pharmacovigilance data with remarkable scalability and accuracy. These models hold promise for early DDI detection, personalized risk assessment, and continuous postmarketing surveillance, leading to improved patient safety and optimized treatment strategies [10]. In the future development of this direction, researchers need to conduct in-depth research into multimodality and the special protection of patients' private information, with the help of AI, make predictive models more transparent, universal, and reliable, thereby promoting health care around the world.

In short, DDI prediction research is gradually moving from a purely computational-oriented to a multidisciplinary integration phase centered on clinical needs. The challenges of data, models, computation, and clinical applicability need to be systematically addressed through cross-disciplinary collaboration, only in this way can we build a truly reliable, interpretable, and clinically acceptable next-generation DDI prediction system, and ultimately provide a solid support for global drug safety and precision medicine.

4. Conclusion

This article highlights recent advances in the field of DDI . The research shows that the research in this field is changing from relying on a single data source and traditional models to the combination of multi-source heterogeneous data fusion and advanced graph neural network technology. By integrating multi-modal information such as chemical structure, biological characteristics and knowledge graph relationship of drugs, and adopting adaptive fusion mechanisms (such as multi-view feature dynamic weighting, drug background knowledge graph-RRB, the multi-modal information of drugs is integrated, the new model can characterize the complex properties of drugs more comprehensively and accurately, which significantly improves the prediction accuracy and

enhances the generalization ability of the model. Future research needs to further expand the prediction task from simple binary classification to more refined DDI event type prediction, and promote the development of the model in the direction of more clinical practicability, finally, it provides reliable computing support for drug safety early warning and precision medicine.

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