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Application of artificial intelligence in drug repositioning

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Abstract

The use of artificial intelligence technologies in biology, pharmacy, and medicine has brought about a dramatic change in these industries. Drug repositioning is a method of drug development in the process of applying existing therapeutic agents to new diseases. This paper first outlines the use of artificial intelligence technology in the field of drug repositioning, then reviews a variety of application methods of artificial intelligence in the realm of drug repositioning, and finally summarizes the advantages and disadvantages of these methods, and proposes the difficulties faced by artificial intelligence in drug repositioning in the future and the corresponding suggestions to achieve the goal of helping researchers to develop more effective methods of drug repositioning.

Keywords: Drug repositioning; Drug targets; Deep learning; Artificial intelligence; Drug target interaction

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1. Introduction

More and more artificial intelligence technologies have been applied in the medical field in recent years. Artificial intelligence technology was first applied in pharmaceutical research and development in the field of health care, and has been widely used and developed in many areas such as drug mining, drug dispensing, health management, assisted diagnosis and treatment, and even the rational use of clinical drugs. With the exponential growth of modern technology, artificial intelligence technology has also quietly entered the ranks of drug repositioning.

Drug repositioning (also known as drug reconfiguration or drug repurposing) is the process of taking an existing drug and treating it for a new disease[1]. Drug repositioning can save R&D time and development costs compared to conventional drug development methods. A major benefit of drug repositioning is that it is safe for humans in clinical models and has a low failure rate because only the effectiveness of the drug is tested against a specific disease[2]. In addition, repositioned drugs save the early cost and time required to bring medicines to market, thereby accelerating the transition from basic research efforts to clinical treatments. Nosengo *et al.* concluded that it currently takes 13 – 15 years to bring new drugs to market, costs between $2 and $3 billion, and is increasing in cost[3]. However, the average cost of repositioning a drug is only $300 million and takes about 6.5 years to enter the market.

The recent drug development case of COVID-19[4] is a typical case of faster and further exploration of drug repositioning. Traditional new drug development requires a lot of investment, takes a long time, and is risky. With the help of artificial intelligence technology, virtual high-throughput screening of candidate compounds can be performed, thus enhancing the efficiency of drug development. The techniques related to artificial intelligence are applied in different aspects of drug repositioning to solve many key problems[5]. For example, active compound screening, molecule generation, drug target discovery, and protein structure and protein-ligand interaction prediction are widely used.

In this paper, we introduce the research progress of drug repositioning in recent years, focusing on three categories: Network-based methods, feature-based methods, and matrix-based methods, as shown in Figure 1.

2. Net-based approach

For modeling biological and biomedical entities, and their relationships and interactions, networks are the best way to go. Networks can provide models of how drugs and indications, as well as drug targets, work to determine therapeutic drug potential. When representing biological data by networks, usually genes, molecules, proteins, and other biological entities can be represented by nodes; and their relationships such as mode of action, similarity, association, and interaction are represented by edges[6]. For specific attribution information, it is generally represented by the weighted values of edges and node; examples include gene-gene interaction networks, networks of drug-target interactions, and networks of interactions between various other biological entities. For learning graphical data with nonlinear relationships, the graphical neural network in neural networks can be used; the network can also be used to represent biological entity data. Moreover, a network-based chemical similarity correlation analysis method can be used to discover side effects of new drugs as well as to reposition the already marketed drugs.

Many network-based drug repositioning methods have been proposed by researchers in recent years, as shown in Table 1.

A network-based inference method was invented by Cheng *et al.*[7]. To derive new targets for already marketed drugs, this method only needs to use the drug-target dichotomous network topological similarity. Guney *et al.*'s team used the metric of disease-drug similarity to calculate the magnitude of the interaction between a disease and a drug target[8]. The method is highly systematic and comprehensive by introducing chemical similarity for correlation and by considering the necessary biological information. Wang *et al.* team invented a heterogeneous network modeling framework that computes by capturing various interrelationships between targets, drugs, and diseases with each other to predict the effectiveness of new drug use[9].

On the basis of similarity-based heterogeneous networks, deep learning techniques can be used to represent proteins

Table 1. Net-based approach

Methods	Features	References
NBI	Using only drug-target dichotomous network topological similarities to infer new targets for known drugs	[7]
Drug-disease proximity	A drug-disease similarity metric was introduced	[8]
TL_HGBI	Using Disease Information to Predict New Drug Targets	[9]
NRWRH	Enables large-scale prediction of potential drug-target interactions	[10]
DTI-CNN	Drug-target interactions based on feature representation learning and deep neural networks	[12]

NBI: Network-based inference, TL_HGBI: Triple-layer heterogeneous graph-based inference, NRWRH: Network-based random walk with restart on the heterogeneous network, DTI-CNN: Drug target interaction prediction.

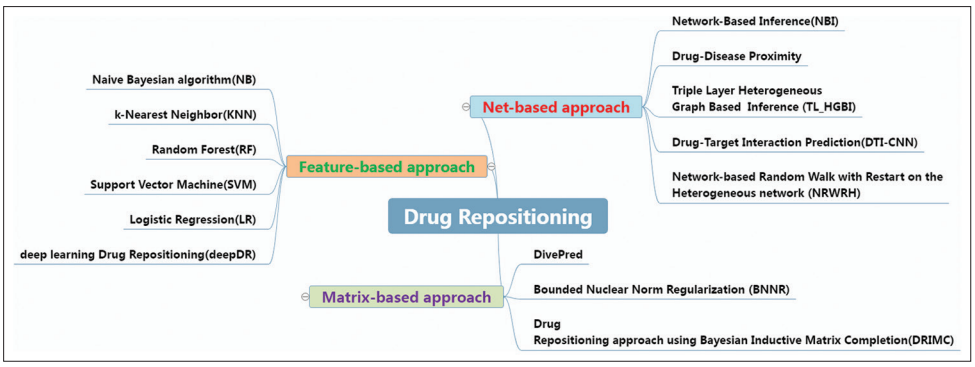

Figure 1. Artificial intelligence technology applied in various aspects of drug repositioning.

and drugs in heterogeneous networks more easily and efficiently. Chen *et al.* invented a heterogeneous network supporting different relationships, which include drugs and proteins linked by known drug-target interaction, chemical similarity between drugs, and sequence similarity between proteins to mine potential drug-disease associations[10]. In 2018, Olayan RS used a nonlinear fusion approach to fuse drug-protein features from different similarity networks and pathway-based features in these networks together[11]. Peng *et al.* completed random wandering with restarts using a similarity-based heterogeneous network model, and based on that, a denoising autoencoder was used to implement a convolutional neural network predictive classifier and learn the basic features[12]. Ji *et al.* used a heterogeneous network combining a large amount of functional information and a large amount of information about the structure of the network nodes to perfectly solve the problem of excessive feature generation by the nodes in the heterogeneous network to calculate the final feature vector[13]. Lu *et al.* investigated a drug-target interaction prediction method based on multisource data fusion and network structure perturbation[14]. He *et al.* invented and disclosed a computational drug relocation method based on memory networks and attention[15]. Wang *et al.* investigated a hybrid graph network and ion channel-based drug repositioning technique for COVID-19[16]. They designed a hybrid graph network model for predicting the affinity of COVID-19 ion channel targets to drugs. Based on the simplified specification of drug molecular input line input (SMILES) code, the atomic features were first extracted to construct the point set, and the atomic bonds were used to construct the edge set; then, RDKit was used to generate undirected graphs with atomic features, and drug feature information was extracted using the graph attention layer. A convolutional neural network was used to extract protein features from five ion channel target proteins screened from the SARS-CoV-2 whole-genome sequence of the NCBI database. The extracted drug features were then connected with the target feature information using graph convolutional network (GCN) and attention mechanism. The drug-target affinity is outputted after two layers of fully connected operation, and finally the drug-target affinity model is obtained. One of the hybrid graphs network-based drug-target affinity prediction model framework is shown in Figure 2.

3. Feature-based approach

The feature extraction method uses a new feature space of lower dimensionality to map the original feature projection, while the new features are usually a combination of the original features, with the aim of finding more meaningful information. The common feature extraction techniques are principal component analysis and singular value decomposition[17]. The purpose of the selection method is to select small portions of features from the complete set of input features based on some design criteria to be used as input to the model. In the process of predicting drug sensitivity, a priori biological knowledge is usually incorporated into the feature fraction.

At present, drug repositioning approaches are not only limited to relying on biomedical data of drug similarity alone but also innovative machine learning methods have also been applied. The combination of machine learning algorithms with drug-target interaction network information provides new ideas for drug development. The main methods include the use of plain Bayes, k-nearest neighbors (KNN)[18], random forest[19], and support vector machines (SVMs)[20], and more recently for binary classification, superclass classification, and value prediction, as shown in Table 2.

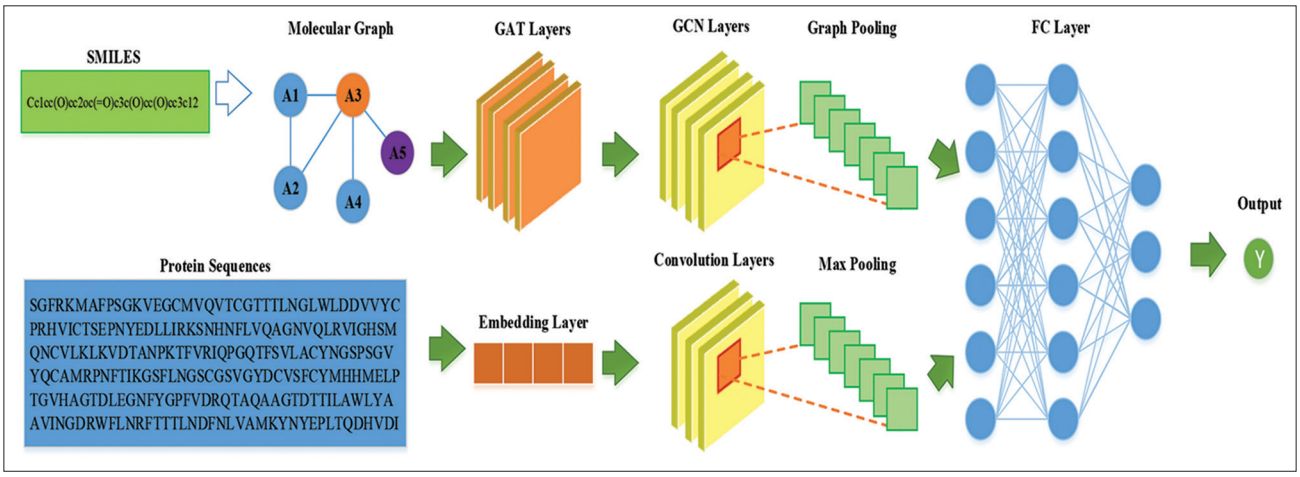

Figure 2. Framework of hybrid graph network-based drug-target affinity prediction model.

Table 2. Feature-based approach

Methods	Features	References
KNN	No need to estimate parameters and train drug target data	[18]
SVM	Requires a relatively small number of drug target samples	[20]
DT	Can handle both continuous and discrete drug target data	[22]
LR	The weights of the target features can see how different features affect the final results	[24]

KNN: K-nearest neighbor, SVM: Support vector machine, DT: Decision tree, LR: Logistic regression.

In 2006, Guengerich used machine learning algorithms to reveal the role of P450 enzymes arising in drug metabolism and toxicity[21]. In 2011, Dr. Feixiong Cheng proposed a method to predict P450 enzymes using traditional classifiers such as KNN, DT, and SVM[22]. A large number of new algorithms to predict human cytochrome P450 enzymes were published immediately afterward. Napolitano *et al.* applied non-linear SVMs to the classification of drug efficacy[23]. Gottlieb *et al.* used logistic regression algorithm for drug repositioning[24]. Gönen used Bayesian algorithm in machine learning for drug-target protein prediction to find new drug-target protein association relationships. First, drug and side effect information, drug chemical structure information, and disease and gene-related information were integrated, and then, the training data were obtained by feature selection and feature extraction. Then, suitable machine learning algorithms were selected to train them, and finally, the trained algorithm models are used to obtain drug repositioning results[25].

Nowadays, the technology of drug repositioning is influenced by deep learning, of which feature learning is the main embodiment of deep learning technology. Deep learning builds computational models by simulating the human brain, which can not only extract features automatically but also obtain effective feature information at different levels. Based on these advantages, deep learning has also been applied in drug repositioning. Deep learning technique is a concept closely related to artificial neural network.

To predict the pharmacological characteristics of a drug, Aliper *et al.* fully used connected deep neural networks to make predictions. The drug characteristics were also used to calculate the therapeutic potential as well as new drug indications. They constructed a deep neural network model using gene expression signature data and pathway data. This model has a high accuracy in prediction for drug indication classification and has better performance than support vector machine model. Therefore, this deep neural network model was used for drug repurposing. In addition, they proposed that a deep neural network confusion matrix can be used for drug repositioning[26]. Segler *et al.*'s[27] method based on deep learning combined with Monte Carlo algorithm is simple and efficient and has been affirmed by professionals. Hughes *et al.* developed the first model capable of fast screening of compounds using deep learning models[28]. Turk *et al.* extracted matched molecules from the ChEMBL database as a dataset for deep learning models[29]. Zhang *et al.* proposed an extraction strategy based on multisource features to construct a protein-ligand interaction prediction model using an integrated learning approach, which outperformed the single classifier prediction model in terms of sensitivity and Youden index and could effectively solve the data imbalance problem[30]. Chen *et al.* proposed a multisimilarity fusion-based drug relocation recommendation algorithm to address the shortcomings of traditional drug relocation recommendation algorithms. First, disease similarity was calculated based on drug-disease data sources. Then, three similarities were calculated based on drug-chemical structure, drug-target protein, and drug side effect data sources and were fused into drug similarity. Finally, the predicted values of drug-disease correspondence were calculated using two similarities and fused into the final predicted values by the prediction fusion method[31]. Zhang *et al.* obtained knowledge associations from PubMed, DrugBank, CTD, and other databases, constructed semantic knowledge graphs by knowledge fusion, attribute definition, and used drug repositioning as empirical evidence to reason about new uses of drugs in tumor therapy by two methods: Path search and link prediction[32]. Zeng *et al.* investigated a deep learning drug repositioning (deepDR) based on a network deep learning approach using multimodal deep self-encoder and variational self-encoder models to discover drug-disease associations, which is shown in the steps in Figure 3. They combined many drug association data phases into one dataset (drug-disease association, drug-target association, drug-drug association, and drug side effects) and then used this dataset to train a multimodal deep autoencoder and then define advanced drug features[33]. Next, to identify new indications based on features that can be identified, they used a variational autoencoder to encode and decode combinations of advanced drug features and disease-drug associations in clinical reports. These studies have been tested on datasets with common disease-drug associations and have shown better results than previous machine learning models.

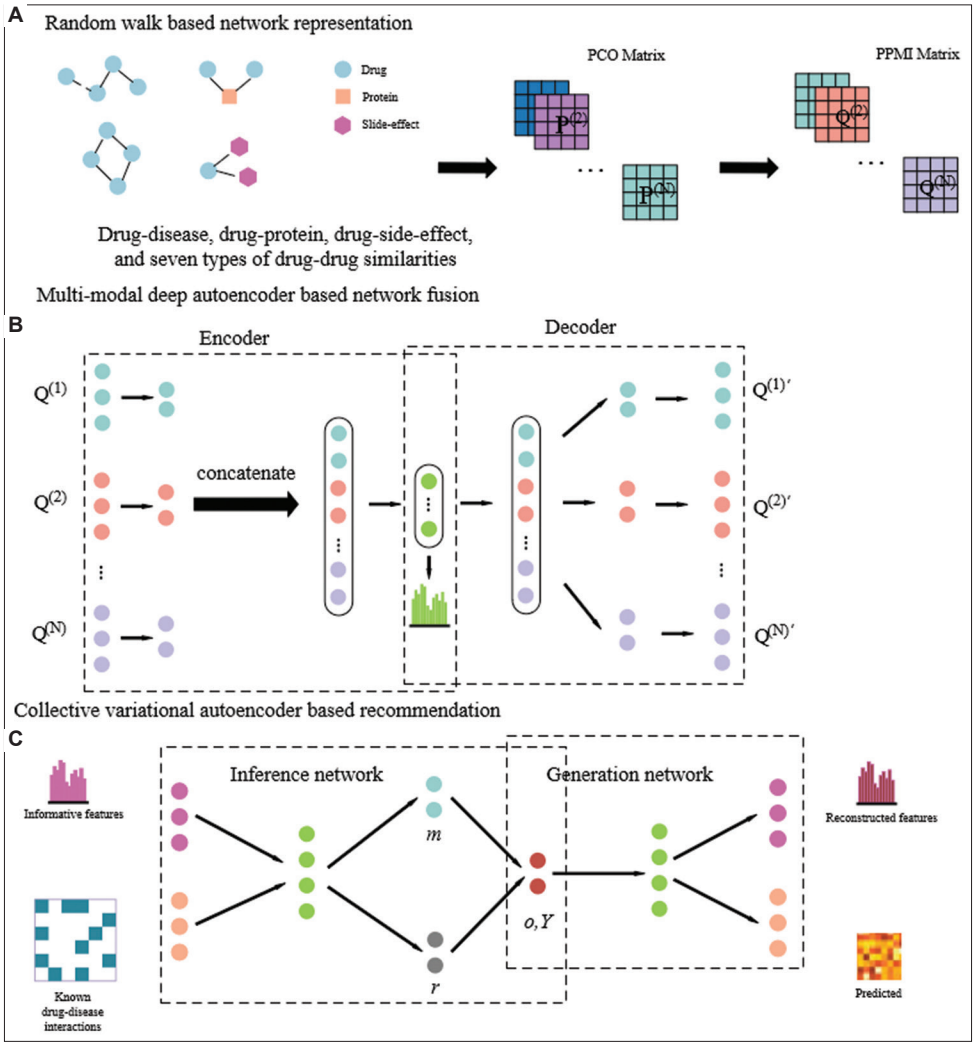

Figure 3. deepDR method steps. (A) deepDR generates random walk-based network representations from multiple drug-related complex heterogeneous networks. (B) deepDR uses multimodal deep autoencoder (MDA) to take the entire punctual mutual information (PPMI) matrix in each network into compact low-dimensional features shared by all networks and then obtains the low-dimensional features in the intermediate layer of MDA. (C) deepDR uses a collective variant autoencoder (cVAE) for prediction of disease-drug relationships.

4. Matrix-based approach

Both network-based drug relocation methods and feature-based drug relocation methods perform well, but both methods require feature extraction as well as the selection of appropriate negative samples. To remedy this deficiency, more efficient methods, matrix decomposition, and matrix complementation methods have emerged. In recent years, researchers have proposed various methods to predict drug-target interaction, among which, Bayesian-based matrix decomposition methods are widely used for drug-target interaction matrices. Matrix decomposition can map higher dimensional data to the product of two lower dimensional matrices, which can solve the problem of data sparsity, and the specific implementation and solution of matrix decomposition are concise and easy to

Table 3. Matrix-based approach

Methods	Features	References
DivePred	Projection of high-dimensional drug features into a low-dimensional feature space to generate a dense feature representation of the drug	[34]
BNNR	Balancing the approximation error and the rank property by introducing a regularization term	[35]
DRIMC	Integrates drug and disease multisource data and models the probability of correlation through inductive matrix completion (IMC)	[36]
MLMC	Introduction of matrix completion as a preprocessing of sparse correlation matrix	[38]

BNNR: Bounded nuclear norm regularization, DRIMC: Repositioning approach using Bayesian inductive completion, MLMC: Multiview learning with matrix completion.

understand. Matrix completion is the decomposition of an incomplete matrix to obtain two or more submatrices, which are multiplied together to obtain a new matrix that approximates the original missing matrix, and then, the values in the new matrix are used to fill the missing values in the missing matrix. Many matrix-based drug repositioning methods have been proposed by researchers in recent years, as shown in Table 3.

Xuan *et al.* proposed a prediction method for disease-drug associations, and this method uses a non-negative matrix decomposition (DivePred) technique. To indicate the characteristics of drugs from various perspectives, DivePred incorporates the similarities of various drugs[34]. A low-rank matrix complementation method was proposed by Yang *et al.* This method can use the regularization term to reduce the similarity noise, while the resultant values

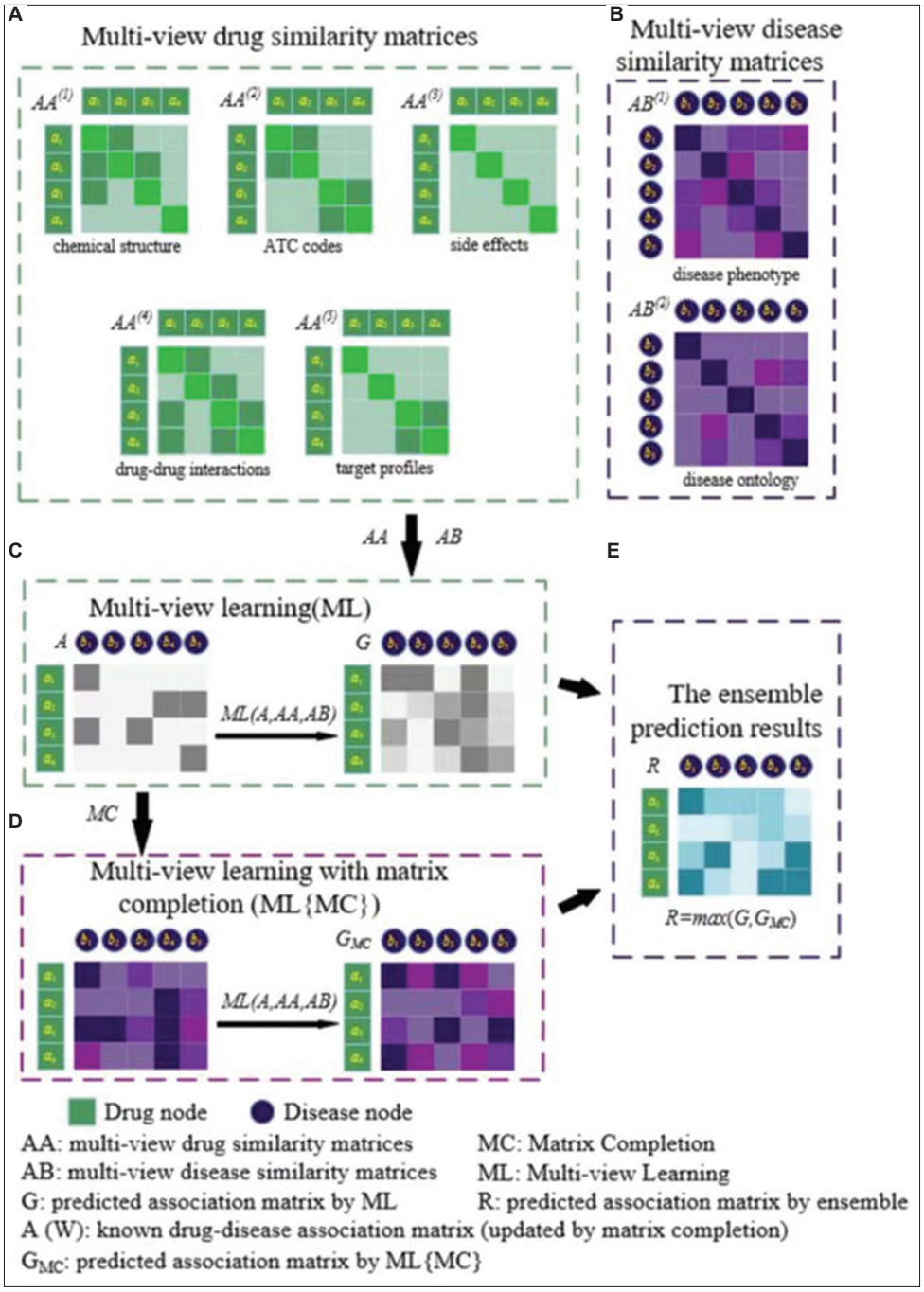

Figure 4. (A-E) Overall workflow of multiview learning with matrix completion.

can be obtained within their own specified range[35]. A new method called DRIMC was proposed by Zhang *et al.* The DRIMC method integrates data from multiple sources such as drugs and diseases, while using inductive matrices to complete the modeling of relevant probabilities[36]. Peng *et al.* proposed a drug-target relationship prediction method based on deep forest and positive and unlabeled (PU) learning, which constructs a similarity matrix between drugs and a similarity matrix between targets based on drug structure information and target sequence information, respectively[37]. Yi *et al.* developed a multiple attempt learning based on matrix completion for drug repositioning method multiview learning with matrix completion (MLMC)[38]. They used multiple view learning so as to predict new indications, while using matrix completion for the associated sparse matrices for preprocessing so that features between multiple similarity matrices can be computed. First, to calculate the best similarity matrix, they used multiview learning to predict multiple disease similarity matrices and multiple drug similarity matrices. Second, to make the multiview learning predictions more accurate, the values of the related matrices were populated using matrix complementation methods. Finally, the above two steps were merged into one strategy in MLMC. The execution flow of MLMC is shown in Figure 4.

4. Conclusion

This paper presents the research progress of artificial intelligence-based drug repositioning, focusing on network-based approach, feature-based approach, and matrix-based approach.

Each method of AI-based drug repositioning has its advantages and disadvantages. Network-based approaches are simple and reliable and are able to explore disease-drug target network relationships, but they cannot predict the targets of new drugs and are very limited. However, network-based approaches have great potential for deciphering the underlying mechanisms of complex diseases, the mode of action of drugs, and for repositioning disease-specific drugs. With feature-based approaches, drug development takes relatively long because the data requirements are relatively high and require specialized expertise to design the label. In particular, the development of robust model for feature-based computational drug repositioning is a very complex process. One of the biggest difficulties is to put theoretical computational approach into practice, because mapping between the theoretical approach and the behavior of biological organisms is more complex. As for matrix-based methods, because they do not rely on feature extraction and negative sample selection, they do not require setting labels and have a relatively short development time. However, inaccuracy, extreme data, and missing data can occur among samples, there is a deviation between the calculated and actual results of the matrix approach.

Hence, it is recommended that researchers combine different strategies and methods to achieve higher rates of success. The effective combination of different methodological strategies and available data will also lead to great advances in the field of drug repositioning. As artificial intelligence technology develops, more and more effective ways will emerge to help understand disease mechanisms and develop appropriate treatments. More algorithms being used in the drug development process in the future, combined with the foundation of traditional biological experiments, will be the basis for newly developed drugs with greater relevance and adaptability to the human body.

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Conflict of interest

The authors declare that they have no competing interests.

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Writing – review & editing: Qingkai Hu and Xianfang Wang

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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