Networks and Algorithms in Heterogeneous Network-based Methods for Drug-target Interaction Prediction: A Survey and Comparison

Shanglin Gao[1][a], Zhixing Liu[2,*][b] and Ying Hong Li[1,*][c]
[1]*Chongqing Key Laboratory of Big Data for Bio Intelligence, Chongqing University of Posts and Telecommunications, Chongqing, China*
[2]*The Second People's Hospital of Jiulongpo District, Chongqing, China*

[*]*Corresponding author*

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Abstract: A key step in drug discovery is the identification of drug-target interactions (DTIs). However, only a small fraction of DTIs have been experimentally validated due to the time-consuming and expensive aspects of experimental validation. To improve the efficiency of drug discovery, many computer-aided drug-target prediction methods have been developed to guide experimental validation. There are numerous prediction methods for DTIs, among which heterogeneous network-based methods do not depend on the 3D structures of the targets or compound molecules and they avoid the shortcomings of machine learning methods for negative training dataset selection, exhibiting greater advantages than other methods. Currently, although many reviews of drug-target prediction methods exist, only a few of them have addressed network-based methods, and they have not been compared in terms of the heterogeneous networks and algorithms used. Therefore, this paper presents a review of the heterogeneous network-based methods for DTI prediction, compares the differences in the prediction performance of different heterogeneous networks and algorithms from the perspective of the networks and algorithms used by these methods, and provides suggestions for the selection of heterogeneous networks and algorithms.

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1 INTRODUCTION

Drug-target interactions (DTIs) can be experimentally validated by wet-laboratory methods (e.g., affinity chromatography, etc.) (Bi et al. 2015). However, these experiments are time-consuming and costly, and large-scale validation is not possible. Therefore, predicting DTIs by computer-assisted methods will significantly reduce the scope of experimental validation and improve the efficiency of drug discovery. With the rapid increase in the number of compounds (Kim et al. 2021), the proportion of compound molecules with known target characteristics and drug effects has decreased. In addition, researchers have accumulated a large amount of information on compounds, proteins, and interactions to construct larger datasets, making it possible to develop more accurate and efficient methods to predict DTIs.

DTI prediction has multiple applications, such as facilitating drug discovery (Chen Z. H. et al. 2020), drug repositioning (Chen Z. H. et al. 2020), and drug side-effect prediction (Pliakos & Vens 2020). The drug discovery process is long, has a low success rate, and consumes significant resources. It is estimated that it takes approximately 10–15 years to develop a new drug, consuming an average of $1.8 billion (Paul et al. 2010). Currently, the main reason why the vast majority of the compounds that have been discovered are not used as drugs is that the interaction of these compounds with proteins is unknown. Therefore, a computer-aided approach to predict compound-protein interactions would have the potential to significantly narrow the drug search space and improve the efficiency of drug discovery. Drug repositioning is a research strategy for new uses outside the scope of the original medical indication for a marketed drug or a clinical trial drug (Ashburn & Thor 2004). The safety of approved

[a] https://orcid.org/0000-0003-4735-7245
[b] https://orcid.org/0000-0002-1351-9149
[c] https://orcid.org/0000-0003-3629-519X

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drugs or clinical trial drugs has been widely confirmed due to the extensive clinical trials they have undergone. Since the outbreak of the COVID-19 pandemic, drug repositioning has become a method for the rapid development of potent anti-COVID-19 drugs. Drug repositioning studies can either directly predict drug molecules for treating a disease or to screen potential drug molecules by DTI prediction in the context of identifying therapeutic targets. DTI prediction has become an important research direction in drug repositioning. The combination of a drug with a therapeutic target may produce therapeutic effects, while the combination of a drug with other targets may produce side effects. Drug side effects have become a major cause of drug clinical trial failure (Pliakos & Vens 2020). Therefore, predicting possible drug side effects by DTI at the preclinical study stage will help in selecting more suitable drug molecules for clinical trials.

Therefore, DTI prediction will be very useful in drug development. Prediction methods for DTIs are generally divided into three categories (Sachdev & Gupta 2019): ligand-based methods, docking methods, and chemical genomics methods. Ligand-based methods were developed based on the idea that similar molecules usually bind to similar protein targets and display similar properties (Jacob & Vert 2008). Docking methods use simulations of the three-dimensional structures of proteins and drugs to predict whether they will interact with each other (Nagamine et al. 2009). Chemogenomic approaches use information from both drugs and proteins for interaction predictions (Zhao et al. 2019).

Heterogeneous network-based methods are the best type of chemical genomics methods for prediction (Ezzat et al. 2019), which do not depend on the 3D structure of targets and compound molecules or avoid the defects of negative data selection of machine learning methods, showing greater advantages than other methods. The methods based on heterogeneous networks can be generally classified into network inference (Saint-Antoine & Singh 2020; Cheng et al. 2012), network propagation (Engin et al. 2014), and matrix decomposition (Hodos et al. 2016; Abbou et al. 2021) (Fig. 1). Several review articles have been published about the prediction methods for DTIs, which also contain a summary of the network-based prediction methods (Wu et al. 2018). However, these reviews do not provide a systematic comparison of the heterogeneous networks and algorithms used by these prediction algorithms. Therefore, this thesis reviews recent heterogeneous network-based forecasting methods for DTIs and proposes recommendations for heterogeneous network construction and algorithm selection after a systematic comparison of the heterogeneous networks and algorithms used.

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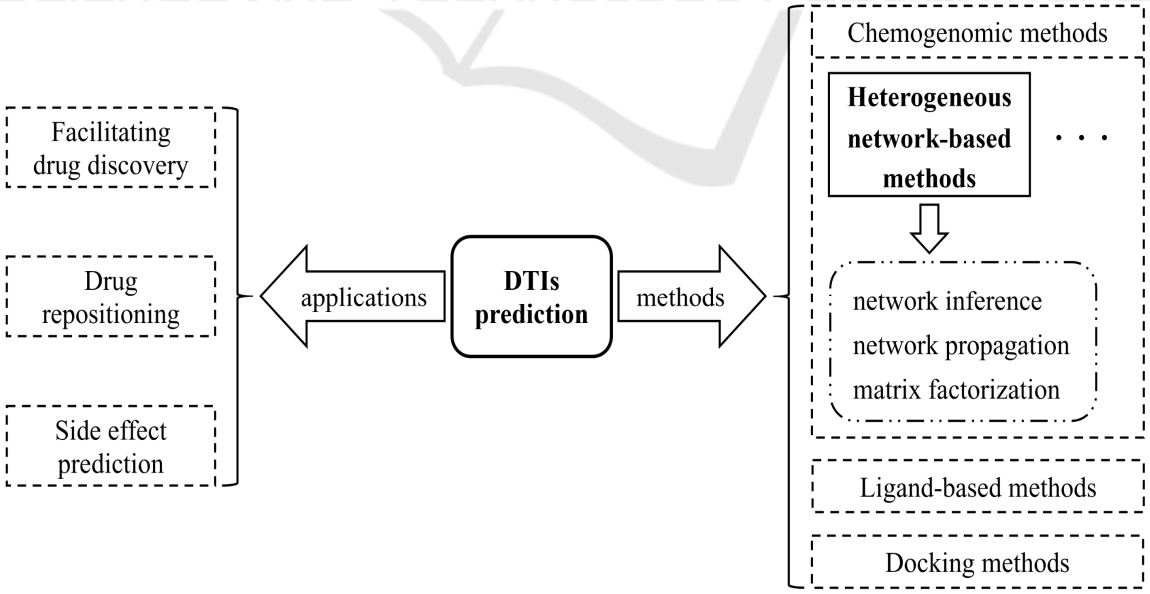

Figure 1: The application and classification of DTIs.

2 DTIs PREDICTIONS METHODS

This review summarizes the newly published prediction methods for DTIs in recent years and classifies them into the following categories: network propagation, network inference, and matrix factorization (Table 1).

Network propagation is a common approach used to analyze heterogeneous networks, and a variety of DTI prediction tools have been developed based on this approach. NRWRH (Chen et al. 2012) is a large-scale method for predicting DTIs constructed by Chen et al. using a restarting random walk algorithm under the assumption that similar drugs usually have similar targets. This method integrates three different networks (a protein similarity network, a drug similarity network, and a drug-target interaction network) into a "drug-target" heterogeneous network. NRWRH was compared with traditional supervised or semisupervised methods such as NRWR (Chen et al. 2012), RWRH (Li & Patra 2010), and RWR (Camoglu et al. 2005; Kohler et al. 2008), which makes full use of network-based information to achieve random walking on the "drug-target" heterogeneous network and improve the accuracy of predicting DTIs, but the method still has certain shortcomings, such as the problem of randomness, which is mainly caused by the choice of the initial probability (Ganegoda et al. 2015). LPMIHN (Yan et al. 2016) is a label propagation method optimized by Yan et al. based on the NRWRH method. Its "drug-target" heterogeneous network consists of a drug similarity network, a target similarity network, and a drug-target interaction network. Compared with NRWRH, LPMIHN used a label propagation algorithm on the constructed "drug-target" heterogeneous network to infer potential DTIs, which reduces the network sparsity problem caused by rare drug-target interactions and further improves the prediction accuracy. DTINet (Luo et al. 2017) is a computational prediction pipeline developed by Luo et al. that integrates multiple drug-related information. Particularly, this method integrated six different networks (including a drug-protein interaction network, a protein similarity network, a protein-disease association network, a drug-disease association network, a drug similarity network, and a drug-side effect association network) into the "drug-disease-target-side effect" heterogeneous networks and utilized the restart random walk algorithm to accurately explain the topological characteristics of each node in this heterogeneous network. In addition, in experiments, Luo et al. verified the novel interaction relationship between the three drugs and the cyclooxygenase protein predicted by DTINet and proved the new potential application of these cyclooxygenase inhibitors in the prevention of inflammatory diseases. Compared with HNM (Wang et al. 2014), BLMNII (Mei et al. 2013), NetLapRLS (Xia Z. et al. 2010), CMF (Xia L. Y. et al. 2019), DTINet had a better predictive effect, which was 6.9% and 5.9% higher. Shahreza et al. developed a semisupervised machine learning approach, Heter-LP, using a label propagation algorithm on the "drug-target-disease" heterogeneous network (Lotfi Shahreza et al. 2019). The network of this approach consists of a drug-disease association network, a drug-target interaction network, and a disease-target association network. In particular, Shahreza et al. applied Heter-LP to analyze innovative putative drug-disease, drug-target, and disease-target relationships, including cosyntropin (drug) and DHCR7, IGF1R, MC1R, MAP3K3, and TOP2A (protein targets), for a rare disease adrenocortical carcinoma (ACC). Heter-LP provided a new way for the treatment of ACC (Lotfi Shahreza et al. 2017). DHLP-1 (Maleki et al. 2020) and DHLP-2 (Maleki et al. 2020), with two distributed label propagation methods based on the "drug-target-disease" heterogeneous network developed by Maleki et al. Its heterogeneous network consists of a drug-disease association network, a drug-target interaction network, and a disease-target association network. Compared with the two nondistributed methods, MINProp (Lotfi Shahreza et al. 2017) and Heter-LP, the two methods had superior results in terms of running time and accuracy.

Network-based inference (NBI) is another common approach to analyze heterogeneous networks and it is frequently used in the prediction methods for DTIs. HGBI (Wang et al. 2013) is a new heterogeneous network-based inference method proposed by Wang et al. This method constructs a "drug-target" heterogeneous network by the known drug-target interaction network, a drug similarity network, and a target similarity network, and it predicts DTIs based on this heterogeneous network. Its prediction accuracy was improved compared with NBI (Cheng et al. 2012) and BLM (Bleakley & Yamanishi 2009). Wang et al. developed TL_HGBI (Wang et al. 2014), which adopts the guilt-by-association principle to integrate five networks (including a disease similarity network, a drug-disease association network, a drug similarity network, a drug-target interaction network, and a target similarity network) into the "drug-target-disease" heterogeneous network. It optimized the

HGBI method, particularly compared with other methods. When the heterogeneous network model was changed or the iterative algorithm was updated, TL_HGBI could not only automatically construct a new drug-target relationship network but also automatically add drug-target information for drug-disease relationship prediction. DT hybrid (domain tuned-hybrid) (Alaimo et al. 2013) is an NBI recommendation method based on heterogeneous networks developed by Alaimo et al., integrating NBI and Hybrid (Alaimo et al. 2013) tools. The "drug-target" heterogeneous network of this method includes a drug similarity network, a target similarity network, and a drug-target interaction network. Different from the traditional NBI recommendation method, the DT hybrid takes into account the important characteristics of the drug target domain (Alaimo et al. 2015). SDTNBI (Wu et al. 2017) is an NBI method based on a "drug-substructure-target" heterogeneous network developed by Wu et al. The heterogeneous network consists of a new chemical entity-substructure network, a substructure-drug network, and a drug-target interaction network. This method prioritizes potential targets of old drugs, failed drugs, and new chemical entities and combines network and chemical information to establish relationships between new chemical entities and known DTI networks. The advantage of SDTNBI is that it can predict potential targets of new chemical entities, whereas traditional network-based methods cannot.

The matrix factorization method can solve the data sparsity problem well with better prediction accuracy and has been widely used in the prediction of DTIs. Liu et al. built a "drug-target" heterogeneous network by integrating a drug similarity network, a target similarity network, and a drug-target interaction network while using the matrix factorization method to develop NRLMF (Liu et al. 2016). This method used the neighborhood regularization logistic matrix factorization algorithm to establish the interaction probability model between the drug and the target, in which the attributes of the drug and the target were represented by the drug-specific and target-specific potential vectors, respectively. The average AUC and AUPR values of NRLMF in the gold standard dataset are better than those of NetLapRLS (Xia Z. et al. 2010), BLM-NII (Mei et al. 2013), WNN-GIP (van Laarhoven & Marchiori 2013), KBMF2K (Gonen 2012), CMF (Xia L. Y. et al. 2019). KMDR (Kuang Q. F. et al. 2017) is a heterogeneous network method based on the kernel matrix reduction dimension algorithm developed by Kuang et al. The "drug-target" heterogeneous

Table 1: Drug-target interaction predictions methods.

Name	Networks	Algorithm classification	Algorithms	Datasets for network construction	Ref
NRWRH	drug-target (protein-protein + drug-drug + drug-target)	Network propagation	Random walk with restarts (RWR)	DrugBank, KEGG, SuperTarget, Yamanishi et al. (Yamanishi et al. 2008)	(Chen et al. 2012)
HGBI	drug-target (drug-drug + target-target + drug-target)	Network inference	Network inference	Sophic Integrated Druggable Genome Database (Sophic 2012), OMIM, DrugBank, InterPro (Hunter et al. 2009)	(Wang et al. 2013)
TL_HGBI	drug-target-disease (disease-disease + disease-drug + drug-drug + drug-target + target-target)	Network inference	Triple layer heterogeneous graph based inference	DrugBank, Sophic Integrated Druggable Genome Database (Sophic 2012), OMIM, Gottlieb et al. (Gottlieb et al. 2011)	(Wang et al. 2014)
DT-Hybrid	drug-target (drug-drug + target-target + drug-target)	Network inference	Bipartite network projection	DrugBank, Yamanishi et al. (Yamanishi et al. 2008)	(Alaimo et al. 2013)
DASPfind	drug-target (drug-drug + target-target + drug-target)	Network path analysis	Simple paths finding	DrugBank, KEGG, SuperTarget, BRENDA, Yamanishi et al. (Yamanishi et al. 2008)	(Ba-Alawi et al. 2016)
NRLMF	drug-target (drug-drug + target-target + drug-target)	Matrix factorization	Neighborhood regularized logistic matrix factorization	Matador, ChEMBL, DrugBank, KEGG, SuperTarget, BRENDA	(Liu et al. 2016)
LPMIHN	drug-target (drug-drug + target-target + drug-target)	Network propagation	Label propagation	ChEMBL, DrugBank, KEGG, SuperTarget,	(Yan et al. 2016)

				BRENDA	
KMDR	drug-target (drug-drug + target-target + drug-target)	Matrix factorization	Kernel matrix dimension reduction	DrugBank, KEGG, UniProt	(Kuang Q. F. et al. 2017)
DTINet	drug-disease-target-side effect (drug-protein + protein-protein + protein-disease + disease-drug + drug-drug + drug-side effect)	Network propagation	RWR and diffusion component analysis	DrugBank, HPRD, CTD, SIDER	(Luo et al. 2017)
DNILMF	drug-target (drug-drug + target-target + drug-target)	Matrix factorization	A dual-network integrated logistic matrix factorization	DrugBank, KEGG, BRENDA, SuperTarget, COMPOUND	(Hao et al. 2017)
GRMF	drug-target (drug-drug + target-target + drug-target)	Matrix factorization	Graph regularized matrix factorization	Yamanishi et al. (Yamanishi et al. 2008)	(Ezzat et al. 2017)
SDTNBI	substructure-drug-target (drug-substructure + drug-target + new chemical entity-substructure)	Network inference	Network inference	ChEMBL, DrugBank, BindingDB	(Wu et al. 2017)
Heter-LP	drug-target-disease (drug-disease + drug-target + disease-target)	Network propagation	Label propagation	DrugBank, SuperTarget	(Lotfi Shahreza et al. 2019)
DHLP-1 DHLP-2	drug-target-disease (drug-disease + drug-target + disease-target)	Network propagation	Label propagation	Yamanishi et al. (Yamanishi et al. 2008)	(Maleki et al. 2020)
iDrug	drug-target-disease (drug-target + drug-disease + drug-drug + target-target + disease-disease)	Matrix factorization	Matrix factorization	CTD, Gottlieb et al. (Gottlieb et al. 2011)	(Chen H. et al. 2020)

network of KMDR consists of a drug similarity network, a target similarity network, and a drug-target interaction network. KMDR can reduce the prediction bias, and it has a better DTI performance than the regularized least squares classifier (RLS) (Kuang Q. et al. 2014) and a semisupervised link prediction classifier (SLP) (Kuang Q. et al. 2014). DNILMF (Hao et al. 2017) is a dual-network integrated logistic matrix factorization algorithm developed by Hao et al., and its "drug-target" heterogeneous network consists of a drug similarity network, a target similarity network, and a drug-target interaction network. This method used a domain regularization logistic matrix factorization algorithm, which was optimized based on NRLMF, to improve the drug-target prediction accuracy, and its prediction results had higher AUC and AUPR values than NRLMF. Ezzat et al. developed a network-based regularized matrix decomposition tool, GRMF (Ezzat et al. 2017), whose "drug-target" heterogeneity network consists of a drug similarity network, a target similarity network, and a drug-target interaction network.In addition, this method took into account the situation in which many non-occurring edges in the network were unknown or missing cases and it added edges with intermediate interaction probability scores in the preprocessing step to improve the prediction results of the new drugs and new targets. As a result, GRMF performed very well in predicting the left-out interactions. Chen et al. integrated a drug-target interaction network, a drug-disease association network, a drug similarity network, a disease similarity network, and a target similarity network to form the "drug-disease-target" heterogeneous network and thus developed the iDrug (Chen H. et al. 2020) method. This method utilized a matrix factorization method to connect a drug-disease association network and a drug-target interaction network through drugs. MBiRW has better drug-target prediction and drug-disease prediction performance than TH_HGBI, and it can also identify new drug-miRNA interactions.

In addition to the above three types of DTI prediction methods, there are other methods, such as network path analysis. DASPfind (Ba-Alawi et al. 2016) is a network path analysis method based on a heterogeneous network developed by Ba-Alawi et al. Its "drug-target" heterogeneous network consists of a drug similarity network, a target similarity network, and a drug-target interaction network. Compared with the other methods, the advantage of this method is that it can better predict DTIs with unknown targets or drugs with fewer targets and it has a better prediction performance than HGBI, DT-Hybrid, and NRWRH.

3 RESULTS AND DISCUSSION

3.1 Comparison of DTIs Prediction Methods

Common algorithm evaluation methods include independent dataset testing, ab initio prediction, leave-one-out verification, and external dataset verification, and the most commonly used cross-validation is the tenfold cross-validation method, which is widely used in the evaluation of algorithm accuracy. The AUC value is the area under the ROC curve, which can usually indicate the overall performance of the algorithm, and it can be used to compare the relative performance of different algorithms, with larger values indicating better algorithm performance (Sing et al. 2005). The PR curve (precision recall curve) shows the relationship between precision and recall. In most of the literature, the indicators used to evaluate the prediction performance of the algorithm are the area under the curve (AUC) and the area under the precision recall curve (AUPR) (Nascimento et al. 2016).

We collected the AUC and AUPR values of more than a dozen methods, including NRWRH, DT-Hybrid, DHLP, etc. on the gold standard dataset (Lotfi Shahreza et al. 2018) (http://web.kuicr.kyoto-u.ac.jp/supp/yoshi/drugtarget/), which was divided into four parts (Yamanishi et al. 2008): enzyme, ion channel, GPCR, and nuclear receptor (Table 2).

As shown in Table 2, DT-Hybrid, LPMIHN, DNILMF, MINProp, NRLMF, and SDTNBI have high AUC values on the same benchmark datasets, and their AUC values on the four parts of benchmark datasets are above 90%. In particular, DT-Hybrid has a high prediction accuracy of DTIs with AUC values of approximately 99% on the four types of benchmark datasets. In addition, LPMIHN has the highest AUPR value and has better application prospects.

3.2 Comparison of Heterogeneous Networks and Algorithms

In addition to the above comparison of the performance of the DTI prediction methods through the AUC and AUPR values, this paper also provided statistics and comparisons of the effects of different heterogeneous networks and different algorithms on the prediction results (Table 3).

The comparisons shown in Table 3 indicate that most of the methods with higher accuracy in predicting DTIs used “drug-target” heterogeneous networks constructed by a drug similarity network, a target similarity network, and a drug-target interaction network. The “drug-disease-target” heterogeneous network constructed by adding disease information did not contribute significantly to an improvement of the prediction accuracy. Using the same “drug-target” heterogeneous network, the prediction accuracy of DNILMF and NRLMF using the logistic matrix-based decomposition method was higher than that of GRMF using only the matrix decomposition method, and the AUPR value increased from 76.3% to more than 98%. Therefore, logistic matrix factorization was chosen as superior for the prediction method of DTIs based on heterogeneous networks. In addition, among the methods using “drug-target” heterogeneous networks, network propagation methods and network inference methods were used for better prediction.

Table 2: Reported AUC and AUPR on gold standard datasets in literature.

Method	Enzyme		Ion channel		GPCR		Nuclear receptor		Ref
	AUC	AUPR	AUC	AUPR	AUC	AUPR	AUC	AUPR	
NRWRH	0.953	-	0.971	-	0.945	-	0.867	-	(Chen et al. 2012)
DT-Hybrid	**0.999**	-	0.997	-	**0.999**	-	**1.000**	-	(Eslami Manoochehri & Nourani 2020)
SDTNBI	0.958	-	0.971	-	0.966	-	0.932	-	(Wu et al. 2017)
DASPfind	0.929	-	0.907	-	0.881	-	0.853	-	(Eslami Manoochehri & Nourani 2020)
HGBI	0.916	-	0.889	-	0.913	-	0.876	-	(Eslami Manoochehri & Nourani 2020)

NRLMF	0.987	0.892	0.989	0.906	0.969	0.749	0.950	0.728	(Liu et al. 2016)
LPMIHN	**0.999**	**0.929**	**0.998**	**0.961**	0.998 6	**0.973**	0.996	**0.970**	(Yan et al. 2016)
GRMF	-	0.763	-	0.745	-	0.567	-	0.423	(Ezzat et al. 2017)
DHLP-1	-	-	-	-	0.976	0.766	-	-	(Maleki et al. 2020)
DLHP-2	-	-	-	-	0.955	0.956	-	-	(Maleki et al. 2020)
HeterLP	-	-	-	-	0.967	0.796	-	-	(Maleki et al. 2020)
DNILMF	0.989	0.922	0.990	0.938	0.975	0.821	0.955	0.751	(Hao et al. 2017)

4 CONCLUSIONS

In this paper, we systematically reviewed the heterogeneous network-based prediction methods for DTIs, and the statistical analysis of the heterogeneous networks showed that most of the DTI prediction methods used the "drug-target" heterogeneous network, which was comprised of a drug similarity network, a target similarity network, and a drug-target interaction network. In terms of the algorithm selection methods, network inference, network propagation and matrix factorization were used for the prediction of DTIs. By comparing the performance of these DTI methods against the gold standard dataset, DT-Hybrid and LPMIHN were found to have the best prediction performance. By comparing the heterogeneous networks and algorithms against the gold standard dataset, it was found that the method using "drug-target" heterogeneous networks had better prediction performance and that the triple-layer heterogeneous networks constructed by adding disease information were of limited use in improving the prediction accuracy. Among the "drug-target" heterogeneous networks, network propagation and network inference methods were found to have better prediction performance.

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