Ensemble Learning-based Prediction of Drug-pathway Interactions based on Features Integration

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Keywords: Drug-pathway Interaction, Ensemble Learning, AdaBoost, Bagging, Random SubSpace.

Abstract: Recently, developing computational methods to explore drug-pathway interaction relationships has attracted attention for their potentiality in discovering unknown targets and mechanisms of drug actions. However, mining suitable features of drugs and pathways is challenging for available prediction methods. This paper performed an ensemble learning-based method to predict potential drug-pathway interactions by integrating different drug-based and pathway-based features. The main characteristic of our method lies in using the Relief algorithm for feature selection and regarding three ensemble methods (AdaBoost, Bagging and Random Subspace) for classifiers. Cross validation results showed the AdaBoost algorithm that based on the Decision Tree classifier can obtain a higher prediction accuracy, which indicated the effectiveness of ensemble learning. Moreover, some new predicted interactions were validated by database searching, which demonstrated its potentiality for further biological experiment investigation.

1 INTRODUCTION

Traditional drug discovery primarily tries to seek the specific drug molecule to act on individual target (Hopkins, 2008). However, it is well recognized that many drugs are far beyond targeting individual proteins, but rather influencing the complex interactions among the relevant biological pathways. Therefore, the inferences of drug-pathway associations are critical for identifying unknown targeted pathways and drug action mechanisms (Ma and Zhao, 2012).

Increasing effort has been devoted to detecting these potential associations and several drug-pathway interactions prediction methods have been proposed from different aspects (Subramanian *et al*., 2005; Ma and Zhao, 2012). Generally, most of the methods attempted to analyze the drug-pathway interactions mainly based on gene expression data. For instance, 'iFad' mainly combined the gene expression and drug sensitivity datasets to analyze the drug-pathway interactions (Ma and Zhao, 2012), but it is always difficult to obtain adequate drug-pathway information merely on the gene expression data. To tackle the problem, some methods attempt to utilize different machine learning algorithms by integrating more chemical and biological information (Silberberg *et al*., 2012; Pratanwanich and Lio, 2014; Song *et al*., 2014). For instance, protein-protein interaction networks (PPI) (Silberberg *et al*., 2012), other target structure information have been utilized effectively recently. However, the extraction and fusion of the drug-pathway association information is still challenging for drug-pathway interactions prediction (Song *et al*., 2014).

Inspired by the challenges, we attempted to use the ensemble learning methods to predict potential drug-pathway associations. As similar drugs often act similar target proteins, we assume that similar drugs also act on similar pathways. Based on the fact that the drug mode of actions (MoA) is a central concept linking drug structures to a set of biological activities, we used drug structure and MoA similarity to represent drug feature information. Further, we used the 'RNA: AffyHG-U133 (A, B)' gene expression data of NCI-60 cell lines (Reinhold *et al*., 2012) to obtain related genes which covered by these pathways, then these genes ontology semantic similarity and sequence similarity are

Xin M., Fan J. and Jiang Z.
Ensemble Learning-based Prediction of Drug-pathway Interactions based on Features Integration.
DOI: 10.5220/0006096701170124
In *Proceedings of the 10th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2017)*, pages 117-124
ISBN: 978-989-758-214-1

calculated to represent pathway information. Further, the drug-pathway network topology information was merged into the drug and pathway feature profiles, respectively.

It is known that ensemble learning methods usually exhibits better generalization performance than a single classifier. In this study, we used three well-established methods: AdaBoost (Freund and Schapire, 1997), Bagging (Breiman, 1996) and Random SubSpace (Ho, 1998) to achieve a good ensemble result. Meanwhile, three widely used learning methods: Support Vector Machine (SVM) (Cortes and Vapnik, 1995), Navie Bayesian (NB) (Rish, 2001) and Decision Tree (DT) (Friedl and Brodley, 1997) are chosen as the base classifier. Compared of these method combinations, the AdaBoost algorithm that based on the DT classifier is selected as the final model to predict the drug-pathway interactions.

2 MATERIAL AND METHOD

2.1 Dataset

This study focus on 58 pathways that have been proved to be related to cancers (Ahmed *et al*., 2011) and 362 drugs obtained from KEGG database (Kanehisa *et al*., 2012), which contains most of pathways and molecular information in genomics, transcriptomics, proteomics and metabolomics. In addition, these drugs have complete drug information and most of them are proved to be related to these pathways.

2.1.1 Features Construction

(1) Drug features

Drug structure-based feature S_d : Drug structure similarity is calculated based on their molecular fingerprints which include 881 chemical substructures defined by the PubChem database (Chen *et al*., 2009). PaDel-Descriptor (Yap, 2011) was used to convert each drug *Mol* file into 881 dimensional binary vectors. Then the corresponding fingerprints are used to compute the similarity scores between two drugs by Tanimoto scores (Lipkus, 1999).

MoA based feature F_d : Since drugs which share a similar MoA are likely to target same pathways, thus the drug MoA similarity can be utilized to predict associations between drugs and pathways. Here we retrieved MoA information from DrugBank database (Wishart *et al*., 2006) and calculate the similarities based on 341 MoAs. We consider drugs as samples and each MoA as a label and take known drug-MoA association matrix *M* as local correlations. According to the local correlations between labels of samples in drug-MoA interaction network, we calculate the cosine similarity of each two drug vectors in *M*:

$$S'_d(i,j) = \cos(m_i, m_j) = \frac{m_i m_j{}^T}{\| m_i \| \| m_j \|}. \qquad (1)$$

(2)Pathway features

This study mainly concentrated on 1863 genes covered by the 58 pathways for the pathway features construction.

Gene ontology Semantic feature F_p : The Gene Ontology terms of 1863 genes were retrieved from Quick GO database (Binns *et al*., 2009), and semantic similarity scores between these pathway-related genes were calculated by the csbl.go R package (Ovaska *et al*., 2008). What's more, the similarity scores between the pathways from gene semantic similarity scores were computed in accordance with the reference (Song *et al*., 2014).

Gene sequence similarity S_p : Sequence similarity between the corresponding pathway-related genes was calculated based on a Smith-Waterman sequence alignment score (Smith *et al*., 1985), and the similarity between two pathways can be calculated as the sum of similarity between all the gene sequences related to the two pathways.

(3)Drug-pathway network topology feature

The drug-pathway network topology information was calculated based on the literature (Van *et al*., 2013). In the drug-pathway network, the average shortest path of each node and the number of shared drugs or pathways are denoted as $\overline{D_d}, \overline{D_p}, \overline{K_d}, \overline{K_p}$, respectively.

As showed in Table 1, the drug features Sim_d include drug structure information S_d , drug mode of actions M_d , network topology information $\overline{D_d}, \overline{K_d}$, and the pathway features Sim_p are combined by gene ontology semantic similarity G_p , gene sequence similarity S_p and $\overline{D_p}, \overline{K_p}$. Construction of the drug-pathway feature is followed the theory: for drug *i* and pathway *j*, their features can be constructed by combining row *i* in Sim_d and row *j* in Sim_p , namely.

$$Fea<drug(i),pathway(j)>= Sim_d\,(i)+ Sim_p\,(j). \qquad (2)$$

Table 1: The construction of drug-pathway features.

Drug-Pathway Features		
Drug Features Sim_d	Drug structure similarity	S_d
	Drug mode of actions similarity	M_d
	Drug-pathway interaction topology information	$\overline{D_d}, \overline{K_d}$
Pathway Features Sim_p	Pathway-related gene ontology semantic feature	G_p
	Pathway-related gene sequence similarity	S_p
	Drug-pathway interaction topology information	D_p, K_p

2.1.2 Features Selection

Existing facts demonstrate that irrelevant and redundant features can lead the model to overfit. Here we perform the Relief method (Sun *et al.*, 2011) to avoid redundancy of feature variables. At each iteration, the algorithm picks randomly a sample K, then picks at random the feature sample of the instance closest to K from each class, the same class instance is called 'near-hit' and the different class instance is called 'near-miss'. Then the weight vector is updated as:

$$W_i = W_i - (x_i - nearHit_i)^2 + (x_i - nearMiss_i)^2 \qquad (3)$$

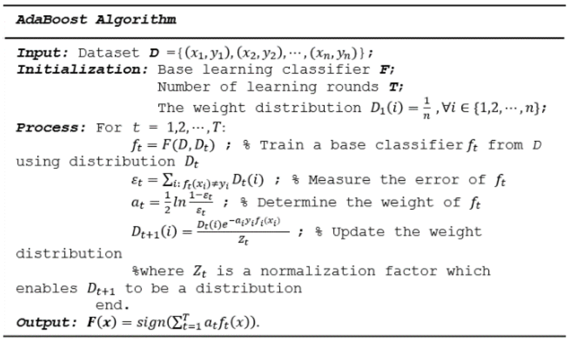
Thus, the weight of any given feature increases if the distance between K and near-hit is shorter than the distance between K and near-miss for the feature, and decreases otherwise. After *n* iterations, the relevance vector is updated by dividing each element of the weight vector by *n*, then feature are selected if their relevance is greater than a threshold *k*. In this study, we set the threshold as zero and finally selected 551 features with positive weight from 764 features.

2.2 Ensemble Learning Method

Ensemble learning is a machine learning paradigm which constructs a set of classifiers and then combines them for classifying data by taking a vote of their predictions (Schwenker, 2013). Here we take three well-established methods in practice to achieve a good ensemble. AdaBoost and Bagging are two instance partitioning methods and Random Subspace is a feature partitioning method (Van *et al.*, 2013).

2.2.1 AdaBoost

AdaBoost is an iterative algorithm where the conjuncture of many weak classifiers is employed to construct a 'strong' classifier (Ho, 1998). It works by choosing a base algorithm and iteratively improving it by accounting for the incorrectly classified examples in the training set. The final predictions are retrieved from a weighted vote. The AdaBoost algorithm's pseudo code is shown as followed:

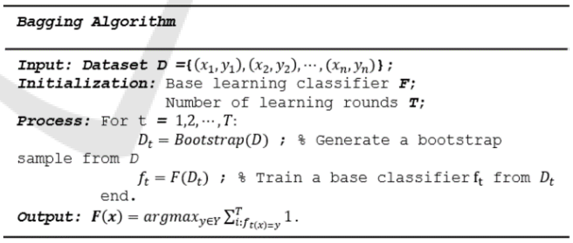


```
AdaBoost Algorithm

Input: Dataset D ={$(x_1,y_1),(x_2,y_2),\cdots,(x_n,y_n)$};
Initialization: Base learning classifier F;
                Number of learning rounds T;
                The weight distribution $D_1(i)=\frac{1}{n}, \forall i \in \{1,2,\cdots,n\}$;
Process: For t = $1,2,\cdots,T$:
           $f_t = F(D, D_t)$ ; % Train a base classifier $f_t$ from D
using distribution $D_t$
           $\varepsilon_t = \sum_{i:\, f_t(x_i)\neq y_i} D_t(i)$ ; % Measure the error of $f_t$
           $a_t = \frac{1}{2} ln \frac{1-\varepsilon_t}{\varepsilon_t}$ ; % Determine the weight of $f_t$
           $D_{t+1}(i) = \frac{D_t(i)e^{-a_i y_i f_i(x_i)}}{Z_t}$ ; % Update the weight
distribution
           %where $Z_t$ is a normalization factor which
enables $D_{t+1}$ to be a distribution
         end.
Output: $F(x) = sign(\sum_{t=1}^{T} a_t f_t(x))$.
```

2.2.2 Bagging

Bagging is an ensemble meta-estimator where each base classifier is trained on random subsets of the original dataset and then aggregated their individual predictions to form a final prediction (Breiman, 1996). It improves the stability and reduces variance, and avoids overfitting of learning algorithms. The base classifiers' combination strategy for Bagging is majority vote. The Bagging algorithm pseudo code is shown as followed:



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Bagging Algorithm

Input: Dataset D ={$(x_1,y_1),(x_2,y_2),\cdots,(x_n,y_n)$};
Initialization: Base learning classifier F;
                Number of learning rounds T;
Process: For t = $1,2,\cdots,T$:
           $D_t = Bootstrap(D)$ ; % Generate a bootstrap
sample from D
           $f_t = F(D_t)$ ; % Train a base classifier $f_t$ from $D_t$
         end.
Output: $F(x) = argmax_{y\in Y} \sum_{i:f_{t(x)=y}}^{T} 1$.
```

2.2.3 Random Subspace

Random Subspace is a combination model that consists of several classifiers and each are trained on randomly chosen subspaces of the original feature space (Ho, 1998). The outputs of the models are usually combined by majority vote. The Random Subspace algorithm's pseudo codes are shown as followed:

```
Random SubSpace Algorithm
Input: Dataset D ={$(x_1,y_1),(x_2,y_2),\cdots,(x_n,y_n)$};
Initialization: Base learning classifier F;
                Number of random subspace rate k;
                Number of learning rounds T;
Process: For t = $1,2,\cdots,T$:
             $D_t = RS(D,k)$ ; % Random generate a subspace
sample from D
             $f_t = F(D_t)$ ; % Train a base classifier $f_t$ from
the subspace sample
         end.
Output: $F(x) = argmax_{y\in Y}\sum_{i:f_{t(x)=y}}^{T} 1$.
```

2.3 Procedure

In this model, we choose four widely used base classifier for implementing the three ensemble methods: SVM, NB and DT. SVM algorithm has been used for a variety of application and it performs structural risk minimization on a nested set structure of separating hyperplanes (Cortes and Vapnik, 1995). Navie Bayesian algorithm is a simple classification based on the Bayes theory for conditional probability. Decision Tree algorithm is an easily understandable and transparent sequential model but it has relatively low prediction accuracy compared to other methods. In this study, we chose the widely used method C4.5. Here we use the toolkit WEKA, which includes a collection of machine learning algorithms for solving data mining problems (Hall *et al*., 2009). The AdaBoost, Bagging and Random SubSpace are selected to implement the ensemble algorithms. The drug-pathway associations we used include 643 positive samples and 17390 negative samples, and the positive sample density of the dataset is 0.036.

In order to evaluate the performances of different models, 10-fold cross validation tests are executed on the models. For the datasets, all of the drug-pathway samples are randomly spilt into ten subsets with equal size, and nine subsets are combined as the training set and the remaining one subset is taken as the testing set each time. The overview procedure of the model is shown in the Fig.1.

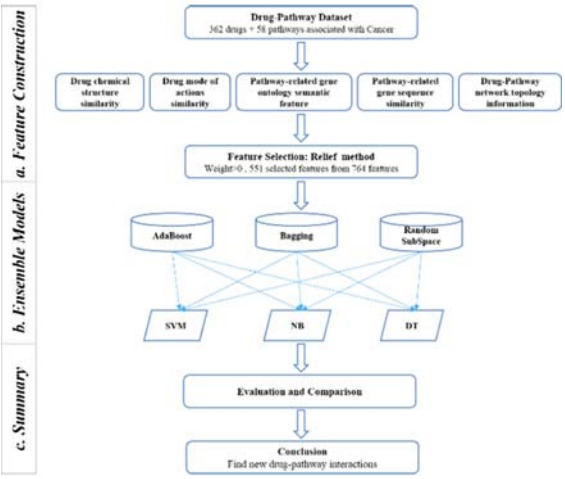
a. Feature Construction
b. Ensemble Models
c. Summary
Drug-Pathway Dataset
362 drugs + 58 pathways associated with Cancer
Drug chemical structure similarity
Drug mode of actions similarity
Pathway-related gene ontology semantic feature
Pathway-related gene sequence similarity
Drug-Pathway network topology information
Feature Selection: Relief method
Weight>0 , 551 selected features from 764 features
AdaBoost
Bagging
Random SubSpace
SVM
NB
DT
Evaluation and Comparison
Conclusion
Find new drug-pathway interactions

Figure 1: Figure summarizes the overview of this model. The model is mainly composed of three sections: (a) the process of feature construction. (b) ensemble methods operation. (c) the comparison of these methods.

3 RESULTS

3.1 Performance Evaluation

Here several metrics, i.e., precision, recall, accuracy (ACC), area under ROC curve (AUC) and the area under the precision-recall curve (AUPR), F-measure (F), are used to evaluate the performances of the models. Among the metrics, accuracy represents the overall accuracy of the classification, precision represents the measure of the reliability of positive instances prediction and recall represents the probability of correct prediction. F-measure is a score from 0 to 1 as a measure of test accuracy. The metrics were calculated in a 10-fold cross-validation procedure by using the equations as followed:

$$\begin{aligned} precision &= \frac{TP}{TP+FP} \\ recall &= \frac{TP}{TP+FN} \\ ACC &= \frac{TP+TN}{TP+TN+FP+FN} \\ F &= 2\times\frac{(precision\times recall)}{precision+recall} \end{aligned} \tag{4}$$

where TP, FP, TN and FN represent the number of true positive, false positive, true negative and false negative samples, respectively.

3.2 Performance of Features Integration

To quantitatively assess the efficiency of all the features and each single feature in predicting the drug-pathway interactions, we performed a 10-fold cross validation with the AdaBoost algorithm based on DT classifier, respectively. As a result, the model that integrated features exhibits a better performance than those with single feature (See in Fig. 2).

Further, the Relief method is performed to avoid the redundancy of feature variables. In our study, we get 551 features with positive weight from 764 features after feature selection. By comparison, the selected features have better classification performances than the original features (See in Fig.3).

3.3 Performance of Ensemble Methods

In this model, we compared the performance of 12 methods, including SVM, NB and DT, and their corresponding ensemble methods of AdaBoost, Bagging and Random Subspace. The performance of base classifiers and ensemble methods based on three base classifiers is shown in Table 2. As demonstrated in Table 2, we find all the three base classifiers have a poorer performance than the ensemble methods, and AdaBoost method has the best performance in every base classifier. The possible reason for this situation is that AdaBoost more fully account the weight of each classifier relative to other algorithms.

Next, we compared the three base classifiers in the case of AdaBoost ensemble models. The ROC and PR curves of the three approaches are shown in the Fig. 4, we can see that the AdaBoost ensemble algorithm based on the DT classifier can achieve the best performance.

3.4 New Predictions

Here we used the Comparative Toxicogenomics Database (CTD) (Davis *et al.*, 2015) as reference to validate the predicted interactions. The CTD database integrates chemical, gene, disease and their interactions from curated literatures. There are 502 new predicted interactions and 241 associations have been proved existence by searching the CTD database. For instance, the interaction between the drug ‘Theophylline’ and the pathway ‘Neuroactive ligand-receptor interaction’ can be found in both KEGG database and CTD database. Some predicted samples that have been confirmed in CTD database are listed in Table 3.

In addition, we focused on the pathway: Kegg05223 and associated predicted drugs. We found there are 15 predicted drugs related with the pathway ‘Non-small cell lung cancer’. Meanwhile, we confirmed that eleven drugs have associations with the pathway in CTD database. Among the other four drugs, we cannot find the interactions between the drug and the pathway ‘Non-small cell lung cancer’, but from the aspect of disease we find that the three drug ‘Aminoglutethimide’, ‘Sunitinib malate’ and ‘sunitinib’ have been tested in clinical trials for lung cancer in the literatures (Xiao *et al*., 2010; Chen *et al*., 2011; Shin *et al*., 2013; Xue *et al*., 2014), which have been laterally validated that the drugs have associations with this pathway.

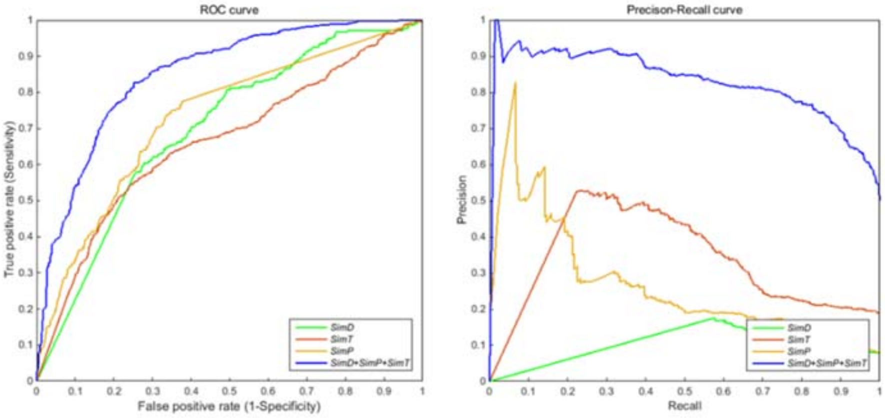

Figure 2: The comparison between the integrated features and each single feature.

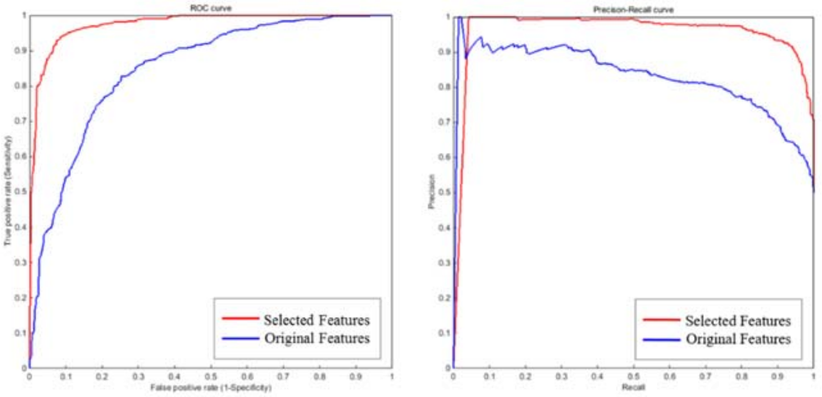

Figure 3: The comparison between selected features and original features.

Table 2: Performance comparisons of different learning methods.

Method	AUC	AUPR	Recall	Precision	ACC	F
SVM	0.827	0.770	0.827	0.827	0.653	0.827
AdaBoost SVM	0.922	0.925	0.834	0.835	0.669	0.834
Bagging SVM	0.856	0.811	0.826	0.826	0.652	0.826
RS SVM	0.859	0.821	0.804	0.804	0.608	0.804
NB	0.772	0.732	0.715	0.715	0.429	0.715
AdaBoost NB	0.851	0.845	0.779	0.779	0.558	0.778
Bagging NB	0.813	0.792	0.725	0.726	0.451	0.725
RS NB	0.804	0.790	0.708	0.709	0.418	0.708
DT	0.891	0.857	0.882	0.883	0.765	0.882
AdaBoost DT	0.975	0.976	0.925	0.925	0.850	0.925
Bagging DT	0.965	0.966	0.901	0.902	0.803	0.900
RS DT	0.974	0.972	0.916	0.916	0.833	0.916

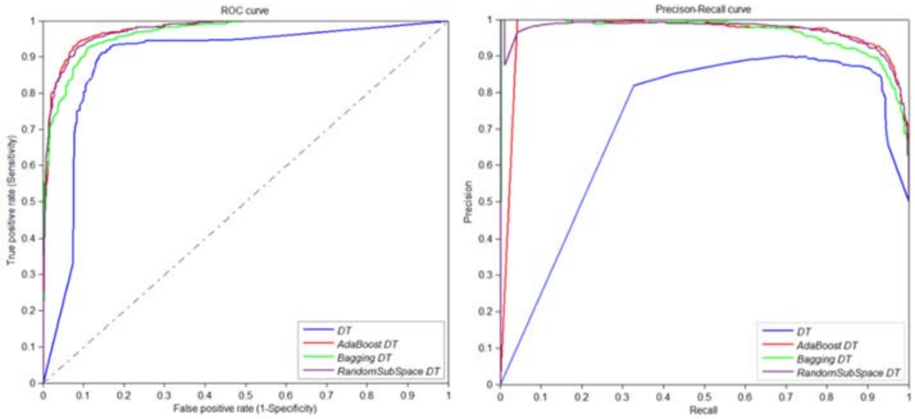

Figure 4: The evaluation of the four methods: DT, AdaBoost DT, Bagging DT and Random SubSpace DT.

Table 3: The top 20 confirmed drug-pathway interactions.

DrugID (Kegg)	Drug Name	Pathway Name	Validated Database
D00371	Theophylline	Neuroactive ligand-receptor interaction	Kegg; CTD
D04197	Floxuridine	Natural killer cell mediated cytotoxicity	CTD
D04023	Erlotinib hydrochloride	Chronic myeloid leukemia	CTD
D03881	Dobutamine tartrate	Vascular smooth muscle contraction	CTD
D03879	Dobutamine	Vascular smooth muscle contraction	CTD
D00371	Theophylline	Vascular smooth muscle contraction	Kegg; CTD
D00632	Dobutamine hydrochloride	Vascular smooth muscle contraction	CTD
D08111	Lercanidipine	Vascular smooth muscle contraction	Kegg; CTD
D01849	Lercanidipine hydrochloride	Vascular smooth muscle contraction	Kegg; CTD
D00126	Ibuprofen	Insulin signaling pathway	CTD
D01366	Bezafibrate	Insulin signaling pathway	CTD
D00341	Hydroxycarbamide	Natural killer cell mediated cytotoxicity	CTD
D00330	Flurbiprofen	Insulin signaling pathway	CTD
D00565	Fenofibrate	Insulin signaling pathway	CTD
D00586	Flutamide	Non-small cell lung cancer	CTD
D04023	Erlotinib hydrochloride	Pancreatic cancer	CTD
D00562	Propylthiouracil	Natural killer cell mediated cytotoxicity	CTD
D02368	Gemcitabine	Cytokine-cytokine receptor interaction	CTD
D01441	Imatinib mesilate	Non-small cell lung cancer	CTD
D01155	Gemcitabine hydrochloride	Jak-STAT signaling pathway	CTD

4 CONCLUSIONS

In this article, we evaluated the ensemble algorithms: AdaBoost, Bagging and Random SubSpace, for predicting drug-pathway interactions based on three base classifiers: SVM, NB and DT. Our results show that ensemble methods have the advantage over the individual classifier on drug-pathway interactions prediction. The merit of this study lied in selecting the effective features obtained from drug chemical structure information, drug mode of actions and pathway-related gene information. Some validated results to some extent demonstrated the reliability of the models.

Although our method has utilized different types of drug-based and pathway-based information, more useful drug-pathway information can be further mined. Therefore, our future study will focus on fusing more biological prior information to improve the prediction reliability.

ACKNOWLEDGEMENTS

This work was partly supported by National Natural Science Foundation of China (Grants No. 81330049), National Major Scientific and Technological Special Project for "Significant New Drugs Development" (2013ZX09507001) and the Science and Technology Commission of Shanghai Municipality (14DZ2270100).

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