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Prediction of Synergistic Drug Combinations by Learning from Deep Representations of Multiple Networks

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Abstract

Drug combination therapy can improve drug efficacy, reduce drug dosage, and overcome drug resistance. Many studies have focused on predicting synergistic drug combinations. However, existing methods fail to consider the heterogeneous characteristics of drugs fully, and it is difficult to identify effective drug combinations. Therefore, we propose a new integrated prediction model based on deep representations by integrating information from multiple domains to accurately and effectively predict drug combinations.

Keywords:

Heuristics; Deep Learning; Drug Therapy, Combination

Introduction

It is common for providers to prescribe a single drug that is precisely targeted to a diagnosis. However, in some cases, single drug use limits the efficacy of the drug and the condition's resistance to that drug [1]. One application of drug combination that covers a large number of people is the treatment of chronic diseases. In general patients with chronic diseases are older, with multiple diseases, and need two or more doses of drugs in daily treatment [2]. This type of synergistic drug combinations aims to cover all therapeutic targets and reduce the off-target effect.

Similarly, cancer treatment is also a difficult task that needs to be solved with polypharmacy. The identification of effective combinations of drugs is crucial to finding effective treatment for drug-resistant cancer. Recently, regulators have treated drug combinations as new, special drugs for the treatment of various cancers [3-4]. Although the combination of drugs is effective, it is not feasible for doctors to screen all possible drug combinations when prescribing. In addition, it is extremely time consuming to find effective compound drugs through biological experiments.

Many studies have shown that multiple biomedical variables are associated with patients' responses to drugs [5]. With the emergence of various related databases and the development of EMR systems, integrating various biomedical information to predict effective drug combinations will be an ideal clinical tool for medication treatment. Currently, machine learning methods based on drug features are the main methods used to predict synergistic drug combinations. One study has proposed a new prediction method for synergistic drug combinations, combining molecular and pharmacological information [6]. Further, more sophisticated algorithms have integrated a series of related properties such as drug-drug interactions, protein-protein interactions, and pathways together, and then use random forests with feature selection methods to predict synergistic drug combinations [7]. Ding et al. [8] introduced more related features of drugs, converted feature expressions into similarity networks, and integrated multiple networks to achieve the purpose of prediction with ensemble learning. Unfortunately, these methods directly concatenate the features, failed to keep the network structure information, and performed network embedding after concatenating.

To address these challanges, we propose a deep representation model to fuse multiple similarity networks for synergistic drug combination prediction called DSDC. The experimental results presented here indicate that our method outperformed the state-of-the-art approaches on the real-world dataset.

Methods

Figure 1 displays the the procedure of the proposed DSDC. We first constructed the similarity networks for various properties that could be calculated according to object features. Then we applied the network integration method to fuse the multiple similarity network to one network. Deep Auto-Encoder was used to conduct network embedding, and the classifier used the network representation to train the prediction model.

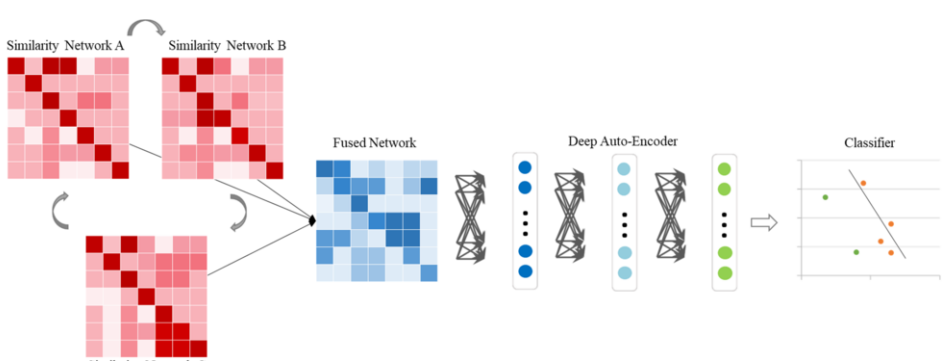

Figure 1– Flow Diagram of DSDC

Materials

Synergistic Drug Combination

The drug combination information used in this study was obtained from a widely used database, DCDB (http://www.cls.zju.edu.cn/dcdb). The validated drug combinations recorded (1363 records) by database records were collected from the FDA, clinicalite.gov, and PubMed literature. To obtain various types of measurements, we used the methods of Bai et al. [9] to collect transporters, targets, pathways, enzymes, and side effects of drugs from multiple data sources for the drug similarity network learning.

Similarity Network Learning

Suppose we have n samples and m measurements; this means there are m networks for one kind of drug properties. Let $G = \{V, E\}$ represent one kind of network, where $V = \{u_1, u_2, \dots, u_n\}$ is a set of n nodes representing all the drugs in the network, and the $E = \{e_{ij}\}$ is the edge set containing the edges between pairwise drugs, and their values represent how similar these nodes are. The edge weights are constructed by an $n \times n$ similarity matrix N.

Network Integration

Since the influence of each attribute on the target is different, a weighted combination strategy was used to integrate the similarity in order to adjust the deviation of each similarity and balance multiple networks. In order to achieve an integrated network from multiple networks, DSDC used m weight parameters to control the weight for each network. The integrated similarity network IS can be defined as follows: $IS = \frac{\sum_{v=1}^{m} W_v N_v}{\sum_{v=1}^{m} W_v}$, $v = 1,2,3, \dots, m$.

Deep Representation and Prediction

Then, we imported Stacked Auto-Encoder as an unsupervised learning model to get new deep representations from the integrated network. One effective classifier was used to predict whether a given drug-target interaction was positive or not according to the gold standard dataset. Finally, Support Vector Machine (SVM) was used as a classifier to train the new deep representations.

Results

The experimental results are presented in Table 1. We use 5-fold cross-validation, where each fold leaves out 20% of the positive and negative samples for testing. At present, many studies are proposed for predicting the synergistic drug combinations. We further considered several important studies of feature-based and network-based models which have been implemented in the prediction of synergistic drug combinations. We selected three studies to include two feature-based machine learning approaches (Ensemble model and SVM) and a method using the drug similarity network. When we compared the the DSDC score using these methods against the best AUROC scores, DSDC performed better.

Table 1– The average AUROC of proposed DSDC, NLLSS, Ensemble model, original SVM

Methods	NLLSS [10]	Ensemble model[9]	SVM	DSDC
AUROC	0.783	0.801	0.652	0.825

Conclusions

This study shows that the network integration method can effectively use the network representation of various properties to predict the potential SDC. In the context of clinical treatment, providers can quickly identify which drugs play an auxiliary role according to the prescribed primary drug. In the future, if we further combine the personal information of patients with the properties of drugs, we hope to provide more reliable synergistic drug combinations.

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