RESEARCH

Predicting Comperhensive Drug - Drug Interaction via Similarity Network Fusion and Convolutional Neural Networks

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Abstract

Background: Drug-drug interactions (DDIs) always cause unexpected and even adverse drug reactions. It is important to identify DDIs before drugs are used in the market.However, preclinical identification of DDIs requires much money and time. Computational approaches have exhibited their abilities to predict potential DDIs on a large scale by utilizing premarket drug properties. Nevertheless, most of them only predict whether or not one drug interacts with another, but neglect their enhancive (positive) and depressive (negative) changes of pharmacological effects. Moreover, these comprehensive DDIs do not occur at random, and derived from the structural features of the graph of DDIs. Revealing such a relationship is very important, because it is able to help understand how DDIs occur. Both the prediction of comprehensive DDIs and the discovery of structural relationship among them play an important guidance when making a co-prescription.

Results: In this work, treating a set of comprehensive DDIs as a signed network, we design a novel model (SNF-CNN) for the prediction of enhancive and degressive DDIs based on similarity network fusion and convolutional neural networks. SNF-CNN achieves the depressive DDI prediction ($AUC = 0/9747 \pm 0/0033$ and $AUPR = 0/9666 \pm 0/0045$), enhancive DDI prediction ($AUC = 0/9686 \pm 0/0028$ and $AUPR = 0/8221 \pm 0/0184$) and the Unknown DDI prediction ($AUC = 0/9714 \pm 0/0040$ and $AUPR = 0/9480 \pm 0/0083$). Compared with three state-of-the-art approaches, SNF-CNN shows it superiority.

Conclusions: This new approach is not only able to predict comprehensive DDI, but also predicts non-DDI.

Keywords: Drug-Drug Interaction; Drug Similarity; Drug Similarity Integration; Feature Selection; Recommender System

Introduction

When two or more drugs are taken together, drugs' effects or behaviors are unexpectedly influenced by each other [1]. This kind of influence is termed as Drug-Drug interaction (DDI), which would reduce drug efficacy, increase unexpected toxicity, or induce other adverse drug reactions between the co-prescribed drugs. As the number of approved drugs increases, the number of drug-unidentified DDIs is rapidly increasing, such that among approved small molecular drugs in Drug Bank, on average, 15 out of every 100 drug pairs have DDIs [2]. The DDIs would put patients who are treated with multiple drugs in an unsafe situation [3, 4, 5, 6]. Understanding DDI is the first step in drug combinations, which becomes one of the most promising

solutions for the treatment of multifactorial complex diseases [7]. Therefore, there is an urgent need for screening and analysis of DDIs before clinical co-medications are administered. However, traditional DDI identification approaches (e.g., testing Cytochrome P450 [8] or transporter-associated interactions [9]) face challenges, such as high costs, long duration, animal welfare considerations [10], the very limited number of participants in the trial, and the great number of drug combinations under screening in clinical trials. As a result, only a few DDIs have been identified during drug development production (usually in the clinical trial phase). Some of them have been reported after drugs approved, and many have been found in post-marketing surveillance.

Computational approaches are a promising alternative to discovering potential DDIs on a large scale, and they have gained attention from academy and industry recently [11, 12]. Data mining-based computational approaches have been developed to detect DDIs from various sources [10] , such as scientific literature [13, 14] , electronic medical records [15] , and the Adverse Event Reporting System of FDA (http://www.fda.gov). These approaches rely on post-market clinical evidence. So, they cannot provide alerts of potential DDIs before clinical medications are administered. In contrast, machine learning-based computational approaches (e.g. Naïve Similarity-Based Approach [16] , Network Recommendation-Based [10] , Classification-Based [17]) can provide such alerts by utilizing pre-marketed or post-marketed drug attributes, such as drug features or similarities [18]. These methods use different drug features to predict DDIs, such as chemical structures [16] , targets [19] , hierarchical classification codes [17] , side effects, and off-label side effects [10, 20].

Most of these existing machine learning approaches are designed to predict the typical two-class problem, which only indicates how likely a pair of drugs is a DDI. However, two interacting drugs may change their own pharmacological behaviors or effects (e.g., increasing or decreasing serum concentration) in vivo. For example, the serum concentration of Flunisolide (DrugBank Id: DB00180) decreases when it is taken with Mitotane (DrugBank Id: DB00648), whereas its serum concentration increases when taken with Roxithromycin (DrugBank Id: DB00778). For short, the first case is degressive DDI, and the second case is enhancive DDI, which contains drug changes in terms of pharmacological effects. It is more important to know exactly whether the interaction increases or decreases the drug's pharmaceutical behaviors, especially when making optimal patient care, establishing drug dosage, designing prophylactic drug therapy, or finding the resistance to therapy with a drug [21].

On the other hand, the occurrence of both enhancive and degressive DDIs is not random, but most current approaches have not yet exploited this structural property and have been developed only for conventional two-classes DDIs. Furthermore, revealing such a structural relationship is very important because it can help us understand how DDIs occur. It is one of the most important steps for treating complex diseases and guides physicians in preparing safer prescriptions to high-order drug interaction. The proposed algorithms for predicting three-classes DDIs are introduced in the following. And how they work are briefly described. All three introduced algorithms use matrix factorization methods, which is a network recommender-based

approach. The matrix factorization approach, with slightly modifying, is a suitable solution for the subject of predicting DDI that has received much attention from researchers.

In this paper, we firstly introduce data and features. Then, a novel algorithm (SNF-CNN) based on the integration of drug similarities and deep learning recommendation systems for predicting DDI is presented in a comprehensive three-class model. This algorithm is called Predicting Comprehensive Drug-Drug Interaction via Similarity Network Fusion and Convolutional Neural Networks.

The paper is organized as follows. In the first section, the data preparation process is explained. The recommendation system is then designed and trained on enhancive and degressive, which detects pairs of non-interacting drugs with high probability. Next, the previous recommender system, based on a convolutional neural network, is trained on incremental and decremental interaction data without interaction (detected in the previous step).In section Results and Discussions, we investigate the results of SNF-CNN in the 10-fold cross-validation process(10-fold CV).

It should be noted that the proposed method of this research is a recommender-based on deep neural networks and has no structural similarities with matrix factorization methods. The only reason for mentioning these methods is the limited number of articles that have used three-class data in their work.

Methods

Dataset and features

In this study, we use the data set presented in paper of [22]. This set contains 568 approved small molecule drugs, each of them has at least one interaction with the other drugs in the set. In total, the interactions between these 568 drugs contain 21,351 DDIs, including 16,757 enhancive DDIs and 4,594 degressive DDIs.In addition, each drug represented as an 881-dimensional feature vector F_{str} based on PubChem chemical structure descriptor and also a 9149-dimensional feature vector F_{se} according to the off-label side effects provided by OFFSIDES.

Problem formulation

Without loss of generality, let $D = \{d_i\}$, $i = 1, 2, .., m$ be a set of m approved drugs. Their interactions can be accordingly represented as an $m \times m$ symmetric interaction matrix $A_{m\times m} = \{a_{ij}\}$. For the conventional DDIs, $a_{ij} = 1$ if d_i interacts with d_j, and $a_{ij} = 0$ otherwise. For the comprehensive DDIs, $a_{ij}\{1, 0, +1\}$. Again, if d_i and d_j do not interact with each other, $a_{ij} = 0$. When there is an enhancive DDI or a degressive DDI between d_i and d_j , $a_{ij} = +1$ or $a_{ij} = 1$ respectively.

In addition, each drug d_i in the D is represented as a p-dimension feature vector $f_i = [f_1, f_2, .., f_k, .., f_p]$, which $f_k = 1$ indicates the K-th specific chemical structure fragment or occurs an off-label side effect, and $f_k = 0$ otherwise. Because each drug has two chemical structure feature vectors and off-label side effects, there are two feature matrices of F with dimensions of m×p (amount of p depends on kind of feature). Matrices of F_{str} and F_{se} are, respectively, the feature matrix of the chemical structure and the feature matrix of off-label side effects.

Data preparing

Since the new drugs are isolated nodes in the interaction network, we cannot infer their possible interaction from topological information alone. Therefore, additional information (such as chemical structure or off-label side effects) is needed, which is called a drug feature in terms of machine learning. First, we prepare the features based on our model, and then we teach a deep learning model of interaction prediction.

Similarity matrix calculation

A common method of calculating similarity called Cosine Similarity is used in machine learning articles such as Articles [23, 24]. If we name feature vectors of the drug of d_i and d_j as x_i and x_j,Cosine Similarity between x_i and x_j is defined as follows:

$$S_{Cos}(x_i, x_j) = \frac{x_i.x_j}{||x_i||_2||x_j||_2} \tag{1}$$

Where $||.||_2$ is the Euclidean Norm and $x_i.x_j$ is inner product of two vectors.

It was observed that the values of the feature matrices are discrete, and also the dimensions of the matrices are large. The chemical structure and the off-label side effect have 881 and 9149 dimensions, respectively. On the other hand, machine learning algorithms do not work properly with high-dimensional data and discrete data. As a result, they do not get good results on these kinds of data. Therefore, by exploiting the cosine similarity, that was described above, drug similarity matrices based on chemical structure and off-label side effects are calculated. These matrices are S_{str} and S_{se}, respectively. The dimensions of these two matrices are $m \times m$, where $s_{i,j}$ is an element of similarity matrices that shows similarity value between drugs of di and d_j. Each element of S has a continuous value between zero and one.

Integration drug similarity matrices

Similarity Network Fusion (SNF)[25] is a new computational method for data integration. Briefly, SNF combines many different types of features (such as chemical structure and off-label side effect, and more - clinical data, questionnaires, image data, etc.) for a given set of samples (e.g., drugs). SNF first constructs a sample similarity network for each of the data types and then iteratively integrates these networks using a novel network fusion method. Working in the sample network space allows SNF to avoid dealing with different scales, collection bias, and noise in different data types. Integrating data in a non-linear fashion allows SNF to take advantage of the common and complementary information in different data types. Figure 1 is a good visualization of SNF processes that has been used in our method structure.

SNF

Figure 1 SNF processes [25]

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$$E\big[Z_1(vT_x)\big] = \int_0^{v\wedge 1} Z_0(uT_x)\exp(\lambda_1)\,du.$$

If we assume that sensitive cells follow a deterministic decay $Z_0(t) = xe^{\lambda_0 t}$ and approximate their extinction time as $T_x \approx -\frac{1}{\lambda_0}\log x$, then we can heuristically estimate the expected value as

$$\begin{aligned} &E\big[Z_1(vT_x)\big] \\ &\quad = \frac{\mu}{r}\log x \int_0^{v\wedge 1} x^{1-u}x^{(\lambda_1/r)(v-u)}\,du. \end{aligned} \tag{2}$$

Appendix
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Abbreviations
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Availability of data and materials
the code and data is available at GitHub page of SNF-CNN code and data

Ethics approval and consent to participate
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Figures

Figure 2 Sample figure title

Figure 3 Sample figure title

Tables

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A2	...	..	.
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