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THE USE OF MACHINE LEARNING IN PREDICTING DRUG INTERACTIONS

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Abstract

Drug-drug interactions are crucial in drug research. Nevertheless, they may also elicit unfavorable responses in patients, leading to severe repercussions. The manual identification of drug-drug interactions is a laborious and costly process, necessitating the immediate use of computer-based approaches to address this issue. Computers can find medication interactions using two methods: by recognizing established drug interactions and by forecasting undiscovered drug interactions. This study provides an overview of the advancements in machine learning for predicting unfamiliar medication interactions. Out of these techniques, the literature-based method stands out because it integrates the DDI extraction method with the DDI prediction method. Initially, we provide the commonly used databases. Subsequently, we provide a concise description of each approach and conclude by summarizing the merits and drawbacks of several prediction models. Lastly, we will examine the difficulties and potential of machine learning techniques in forecasting medication interactions. This study intends to provide valuable assistance to researchers interested in advancing bioinformatics algorithms for predicting drug-drug interactions (DDI).

1. Introduction

Drug-drug interactions (DDI) may arise when several medicines are administered concurrently (Baxter and Preston, 2010). These interactions may either improve or reduce the effectiveness of pharmaceuticals, leading to adverse drug reactions (ADRs) that can be life-threatening in extreme circumstances (Classen et al., 1997; Agarwal et al., 2020). In certain instances, these interactions can even result in a drug being removed from the market (Lazarou et al., 1998). As to the U.S. Centers for Disease Control and Prevention, over 10% of individuals concurrently use five or more medications. Furthermore, a study conducted by Hohl et al. (2001) revealed that a staggering 20% of older persons use a minimum of 10 medications, significantly amplifying the likelihood of adverse drug reactions (ADRs). The growing number of licensed medications leads to a corresponding rise in the potential for drug interactions (Khori et al., 2011). Hence, the anticipation of DDI beforehand is essential and more challenging in the field of therapeutic treatment.

While in vivo and in vitro tests may aid in the detection of drug-drug interactions (DDI), there are instances when they cannot be conducted owing to constraints in laboratory resources and/or the associated expenses (Safdari et al., 2016). Therefore, it is crucial to develop computational techniques for resolving the challenges associated with discovering Drug-Drug Interactions (DDI). Presently, there are two distinct groups of computational methods used to detect Drug-Drug Interactions (DDI). The process involves extracting drug-drug interaction (DDI) information from many sources such as literature, electronic medical records, and spontaneous reports. Additionally, existing DDI data is used to forecast previously unknown DDI.

2. DDI extraction

Unstructured papers provide a significant amount of Drug-Drug Interaction (DDI) information. However, due to the rapid increase in biomedical literature, it has become very difficult to extract meaningful information from the immense amount of literature and integrate it into drug databases (Rodríguez-Terol et al., 2009; Pathak et al., 2013). The extraction of Drug-Drug Interactions (DDI) may be accomplished using either pattern-based techniques or characteristics-based machine learning methods. The existing pattern-based technique is being gradually discontinued due to its need on domain expertise for the manual classification of DDI. The popularity of the approach for extracting Drug-Drug Interactions (DDI) by machine learning has increased with the introduction of annotated corpus (Segura et al., 2013). In addition, the extraction of Drug-Drug Interactions (DDI) from unstructured text data does not provide an early warning or detect unknown DDI. However, machine learning techniques may accurately predict DDI in advance, as shown by studies conducted by Kanehisa et al. (2010), Chen et al. (2019), and Song et al. (2021).

3. DDI prediction

Only the DDI that is already known may be retrieved from unstructured articles. Nevertheless, if the relevant drug-drug interaction (DDI) can be anticipated prior to the introduction of a medicine onto the market, it becomes possible to identify pharmaceuticals that should not be taken together. These recognized drug-drug interactions may help to avert several medical blunders. Machine learning may be categorized into classic and non-traditional approaches. In the realm of classical machine learning, two main approaches are often employed: similarity-based techniques and classification-based methods. Non-traditional machine learning may be classified into four overarching groups.

Approach based on network propagation. The network propagation-based technique may be categorized into link prediction and graph embedding depending on the various methods used for processing the network. The link prediction approach utilizes biological items as nodes and their intricate relationships as edges in order to forecast unknown relationship interactions and detect erroneous or absent interactions. The graph embedding approach involves converting a given

network (graph) into a lower-dimensional space using an embedding layer, while preserving the network's information.

Decomposition of a matrix into its constituent elements. The matrix factorization technique involves breaking down the existing drug interaction matrix into N matrices of lower dimensions using various decomposition techniques. These matrices are then combined to create a matrix that predicts drug interactions. 3) Methods that use ensembles. Ensemble-based techniques aim to improve the accuracy of forecasting medication interactions by combining many methodologies. 4) Methods that rely on literature as a basis. This technique first use Natural Language Processing (NLP) to extract medication interactions from unstructured data, which serves as the data sets. The data that has been retrieved is then used to forecast unfamiliar medication interactions. The next post will provide a comprehensive overview of the database often used in the experiment. The second section presents several techniques for forecasting Drug-Drug Interactions (DDI).

4. Approach based on machine learning

The fundamental principle of conventional similarity-based methods for predicting drug-drug interactions (DDIs) is as follows: if drug A and drug B interact to generate a given effect, then substances similar to drug A (or drug B) are likely to have the same effect when combined with drug B (or drug A). In the context of drug similarity, the prediction of interactions between novel medications is achieved by combining similar features from various pharmaceuticals (Su et al., 2019a; Fu et al., 2020; Mo et al., 2020; Shaker et al., 2021).

In their 2012 study, Vilar et al. introduced a comprehensive method that utilizes molecular similarities to examine the interactions between various medications. These interactions may arise from the inhibition of metabolic enzymes, transporters, and even pharmaceutical targets. In order to measure molecular similarity, the scientists first gathered and manipulated drug molecules. They then transformed the resultant chemical structure into a bit vector, which denoted the presence or absence of particular molecular properties at specified positions. Ultimately, the process of determining similarity and representing it in the form of data is outlined. The Tanimoto coefficient (TC) was used to quantify molecular fingerprints. A value of 0 represents the highest level of dissimilarity, whereas a value of 1 represents the highest level of similarity.

Ferdousi et al. (2017) used the Rus-Rao method to compute the similarity of medication pairings. This method relies on similarity measures derived from 12 binary vectors. As the resemblance increases, the probability of medication interactions also increases. Pharmacokinetic drug-drug interactions (DDIs), as described by Zhang et al. (2009), refer to the influence of one drug on the absorption, distribution, metabolism, or excretion of another drug. On the other hand, pharmacodynamic DDIs, as explained by Imming et al. (2006), involve the interaction of two or more drugs on the same receptor, resulting in either synergistic or harmful effects. Gottlieb et al. (2012) used a logistic classifier to deduce the relationships between pharmacodynamics and

pharmacokinetics, along with their intensity, by merging the similarity measures of seven distinct medicines and constructing classification features.

The conventional classification-based method entails modeling the DDI prediction job as a binary classification issue. DDI pairs and non-DDI pairs are used for constructing classification models. In binary classification, the inputs consist of known interactions, whereas there may be additional drug combinations with interactions that have not been found or seen, and these interactions need to be predicted. Typically, in the field of machine learning, such issues are often transformed into semi-supervised learning tasks (Zhao et al., 2020; Hu et al., 2021a). For the purpose of classifying, a model is often constructed using classifiers such as logistic regression, Bayesian, k-nearest neighbor, random forest, and support vector machines (SVM) in order to make predictions about DDI.

Li et al. (2015) developed a method using a Bayesian network model and similarity algorithm to forecast medication combinations based on molecular and pharmacological properties. In their 2016 study, Jian-Yu et al. introduced a novel semi-supervised fusion approach that utilizes a local classification model and the Dempster-Shafer evidence theory. Using this methodology, it is possible to forecast potential drug-drug interactions (DDIs) by analyzing both the structural and side-effect similarities (Zhao et al., 2019). In their study, Kastrin et al. (2018) approached the prediction of drug-drug interactions (DDI) as a binary classification task. They used a link-prediction technique to predict unknown interactions between randomly selected drugs from five extensive DDI databases. Additionally, they improved the network topology characteristics by incorporating four semantic characteristics.

The traditional method and traditional classification method yield satisfactory results in predicting unknown drug interactions based on similarity. However, these methods fail to effectively integrate the characteristics of drugs and drug interactions from known information, limiting their ability to fully predict drug interactions. Therefore, it is essential to develop more effective computer techniques for forecasting unfamiliar medication interactions.

5. Ensemble-Based Approach

The ensemble-based technique utilizes a combination of various approaches to accurately forecast unknown drug-drug interactions (DDI). Zhang P et al. (2015) suggested that the computational load of multi-label situations might be decreased by choosing suitable information dimensions based on the shared features and side effects of medications. The use of genetic algorithms in conjunction with the multi-label k-nearest neighbor approach allows for the determination of the most favorable characteristic size and facilitates the creation of prediction models. The suggested technique, FS-MLKNN, is a unique approach that combines function selection with the K-nearest adjacency method. It is capable of concurrently determining important feature sizes and constructing accurate multi-label prediction models. FS-MLKNN employs a two-step process to establish the correlation between characteristic vectors and side effects. Initially, the selection of information dimensions is based on the mutual information

between functional dimensions and side effects. This is done to minimize the computing load of multi-label learning. Subsequently, the genetic algorithm (GA) and multi-label K-nearest neighbor point approach (MLKNN) were integrated to ascertain the most favorable feature size and construct a predictive model.

Zhang et al. (2017) developed a prediction model that utilizes neighbor-recommendation, random walk, and matrix disturbance techniques to integrate several models with unique ensemble rules. The model is based on the features of medications and known data concerning drug-drug interactions (DDI). Deepika and Geetha (2018) used positive-unlabeled (PU) learning (Elkan and Keith, 2008) and meta-learning (Lemke et al., 2015) to predict drug-drug interactions (DDI). They also introduced a learning framework for semi-supervised classifiers using support vector machines (SVM). The PU-based classifier was used to derive meta-knowledge from the network, while the meta-classifier was specifically created to forecast the likelihood of DDI based on the obtained meta-knowledge.

6. Approach based on literature

Literature-based prediction of drug-drug interactions (DDI) involves two main steps. The first step is to extract the relevant relationship between drugs from unstructured data sources such as literature, electronic medical records, and spontaneous reports. This is done using statistical or text-mining methods, along with natural language processing techniques. The second step is to predict unknown DDI based on the extracted information about the interactions between drugs, using machine learning.

Tari et al. (2010) used a combination of text mining and reasoning to make predictions about drug-drug interactions (DDI). The approach consisted of two stages: natural language extraction and reasoning. The scientists used a parsing tree to identify diverse interactions and employed logical principles to forecast interactions based on the recovered interactions between novel and preexisting medications. Tatonetti et al. (2012b) categorized the FAERS dataset into two subsets: reports that included a single medication and reports that involved two medicines. They then developed eight adverse event models that were considered to be of significant clinical importance.

Each model utilized drug information extracted from FAERS to provide an overview of the frequency of adverse events. A logistic regression classifier was employed to differentiate drugs that caused significant clinical adverse events from those that did not. Prediction was made based on the drug combination for each model. Kolchinsky et al. (2013) assessed the effectiveness of several classifiers, including logistical regression, SVM, and discriminating analysis, in differentiating between relevant abstracts and PubMed articles that provide evidence for pharmacodynamic drug-drug interactions (DDI). Importantly, this technique is also beneficial for connecting causative processes to probable drug-drug interactions (DDI).

7. Conclusion

The presence of drug-drug interactions (DDI) has a significant impact on patient treatment and has emerged as a critical issue for patient safety and medication administration. Utilizing machine learning to accurately forecast DDI may significantly mitigate its detrimental effects. In order to achieve this objective, it is essential to enhance the effectiveness of machine learning methods. This article discusses the current machine learning methods used to forecast drug-drug interactions (DDI). Over the last decade, machine learning has been extensively used in the field of bioinformatics and has shown significant success. In the majority of current methods, drug similarity is considered to be the primary factor in improving the prediction of drug-drug interactions (DDIs), along with the use of several additional techniques. Nevertheless, the majority of existing DDI predictions is constrained to the interactions involving just two medications. In future research, it is essential to not only prioritize the precision of forecasting the likelihood of drug-drug interactions, but also to prioritize the capacity to reliably forecast the specific categories of drug-drug interactions. Given the growing prevalence of using several medications in clinical medicine, it is essential to develop strategies for predicting interactions between these treatments.

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