Implementation of a new detector tool of drug-drug interactions

Bnitir MAROUANE 1*, Konstantin KOSHECHKIN 2

1 Department of Public Health, I.M. Sechenov First Moscow State Medical University, 2-4 Bolshaya Pirogovskaya st., 119991 Moscow, Russia,
Corresponding autor email: Marouane Bnitir mbnitir@gmail.com

SUMMARY

Drug–drug interactions play a vital role in drug research. However, they may also cause adverse reactions in patients more likely with elder people, with serious consequences. So, it is urgent to use computer methods to solve the problem. There are traditional approaches to identify known drug interactions linked to tools including the prediction of unknown drug interactions. This paper aims to provide useful guidance for interested researchers to further promote bioinformatics algorithms to more develop this application.

Introduction

The treatment of complex diseases by taking multiple drugs becomes increasingly popular, and drugs may give rise to the risk of unanticipated adverse effects and unknown toxicity. Taking several drugs at the same time to treat complex illnesses practice (Maher et al., 2013). However, often, when a doctor adds a drug to a patient's prescription, he has no idea of the potential drug interactions. Indeed, the number of possible combinations is such that they cannot be the subject of prior clinical studies (American Cancer Society | Information and Resources About for Cancer: Breast, Colon, Lung, Prostate, Skin, n.d.). It is practically impossible to test a new drug in combination with all the other existing drugs, because, for a single drug, it would require a lot of new experiments, that’s why It has been shown that drug-drug interactions (DDI) are a significant cause of hospital admissions: as much as 4.8% of the admissions in the elderly population (Dechanont et al., 2014). Improved DDI information could help reduce such adverse effects (Feng & Zhang, 2022), drug-drug interactions (DDIs) prediction is one of the most critical issues in drug development and health, and proposing appropriate computational methods for predicting unknown
DDI with high precision is challenging (Stauth, 2022b), we proposed a dynamic filter based for drug-drug prediction.

**Materials and Methods**

Several computational methods have been developed to better understand drug-drug interactions, however, these methods do not provide sufficient details beyond the chance of DDIs occurrence, because it requires details (drug information) often variables for prediction.

Drug-drug interaction (DDI) can occur when two or more drugs are used in a combination (Baxter & Sharp, 2008; Zhou et al., 2013) such interaction may enhance or weaken the efficiency of the drug and cause adverse drug reactions (ADRs) that can be life-threatening in intense cases (Lapham, 2021; Zhou et al., 2013).

*In Vivo* and *in vitro* experiments can facilitate the identification of the DDIs but can’t be performed in some cases due to laboratory limitations and high cost. DDI detection in the wet lab is expensive and time-consuming, that’s why it’s highly recommended to develop computational methods for predicting DDIs, detecting DDIs among a large scale of drug-drug pairs in both in vitro and in Vivo to assist the screening of DDIs.

However, the price of such procedures is relatively high, and testing large numbers of drug combinations is not practical (Zhou et al., 2013). To reduce the number of possible drug combinations, numerous computational approaches have been proposed

Computational approaches have been developed to deduce and indicate drug-drug interactions, one of the approaches than can detect annotated DDIs and can give alerts before a computational treatment is made, this approach is a machine learning based to provide a promising way for downstream experimental validation (Yue-Hua et al., 2020).

Under these conditions, Artificial intelligence (AI), by deep learning and Internet of things improves prediction of Drug-drug interactions (DDIs), it can result in unexpected pharmaceutical effects, including adverse effects with causal mechanism methods have been developed unknown (Lee & Chen, 2020). The machine learning subsystem for the formation of evidence-based medicine knowledge bases is designed to provide specialists (analysts) with diverse thematic reference and methodological information on the data contained in the storage (databases) for decision-making (Lebedev et al., 2020).

Combination drug therapies are becoming a promising approach for several diseases including cancer, hypertension, asthma and AIDS, since they can increase drug efficacy, decrease drug toxicity or reduce drug resistance (He et al., 2016). However, the combination of drugs may result in interactions between drugs (drug-drug interactions, DDIs), which are a major cause of adverse drug events (ADEs) (Vilar et al., 2017; He et al., 2016) It is estimated that DDIs are associated with 30% of all reported ADEs (Vilar et al., 2017).
For predicting unknown ow DDIs using various informative methods, the similar selection and similarity integration parts of NDD have been proposed in previous studies of other problems, our novelty is to give

\[ C_{n,k} = \binom{n}{k} = \frac{n!}{k!(n-k)!} \]

predictions-combined drugs to treat combinations of diseases that are common within old people (Rohani & Eslahchi, 2019).

According to the Centres for Medicare and medicine service common chronic conditions for adults, 80% have at least one chronic condition and 68% have 2 or more chronic conditions (The National Council on Aging, n.d.).

Our computational framework deep DDI gives the drug-drug combinations for two or more diseases or chronic conditions combination of targeted as input to accurately generate a structural response of the drug-drug prediction, the DDIs are important outputs for prescription or the decision of the Drug-drug combinations (up to three drugs).

Multiple drug combinations based on diseases' combination; in the demo application we took into consideration only 5 major common chronic conditions

**Methods**

- Model protein (disease) -drug interactions

The system is based on a massive network that graphically models how common proteins in the human body interact with each other and how active substances in drugs affect these proteins. Each network represents the drug-disease interactions, drug target proteins, and drug-drug interactions, focusing on known side effects.

There are many known side effects and the number of drugs on the market. So it’s almost billions of possible side effects between all possible drug pairs. Most of them have never been prescribed together especially for new diseases, let alone studied systematically.

The application of the AI remains in the calling of the deep learning by making connections and filters of the possible combinations (drug-disease interactions) the machine learning will establish every time systematically the combination during the prescription of the drug. The step of the IoT application remains in the implantation of a mini cloud or a cloud (depending on the area of using), a network that can support all devices, storage, database, related and confirmed.

The deep learning algorithm to be employed is algorithm type 1 because is the: Artificial Neural Network: because the drug-disease interactions are done based on a database (Drug bank). So no need for a complex network.

Calculations to be performed for drug and diseases combination.

Combinations are selections of objects, without repetition, order does not matter.

The number of k-element combinations (2 or/and 3) of n objects (depending on the number of elements), without repetition is:
Combinations Formula:

\[ C(n, k) = \frac{n!}{k!(n-k)!} \]  For \( n \geq k \geq 0 \). Also referred to as \( k \)-combination or "n choose k" or the binomial coefficient

Extraction of DDIs

Many of DDI are contained in unstructured articles, but with the explosion of biomedical literature, it has become a huge challenge to identify useful information from the vast literature and synchronize it within drug databases, our approach in this implementation will be the traditional approach (Han et al., 2022).

Steps of DDI Extractions.

Extraction of DDI is achieved by a classified traditional approach and characteristics-based machine learning. More and more popular. In our implementation the method employed for data Extraction is a literature-based approach (Lo et al., 2013).

in which the prediction of DDI consists of two steps: first, extraction of the reasonable relationship between drugs from unstructured data sources (drug bank in our case.) with a statistical or text-mining method, followed by use of natural language processing technique; second, prediction of unknown DDI from extracted information about the interactions between drugs using machine learning (from the drug-drug interactions filter of the drug bank website. Predicted DDI by combining text mining and reasoning (Lo et al., 2013).

Results

The application of the formula can predict the number of combinations of diseases : \( C(8,2) = \frac{8!}{2!(8-2)!} = 28 \). Because this demo is a simple overview of eight major diseases that elder population is suffering from so in this case \( n=8 \), and \( k=2 \) because the dynamic filter is for pair combinations (Drug-Drug /Disease-Disease). Number of combinations possible for disease-disease is 28 combination without repetition.

And as next step, the prediction of the drug pairs combination, and with the application of the filters based on the Drug bank base (https://go.drugbank.com/)can remind on the degree of severity of the majority of drug combinations pairs which can be double pairs or triple pairs (Stauth, 2022b; Wishart et al., 2017).

The drug interactions in our study is based on the manual research using the database of drug bank

- Parameters

The dynamics filters are linked to the drug-drug pair combinations, disease-disease pair combinations, the drug interaction severity and to the prescribing decision.
The interaction severity is calculated by the application of the statistics formula: total of Drug-drug combinations.

**Figure 2: Application of the Dynamic filter**

(with / without interactions / the total of Drug-drug with specific severity); The mentioned severity probability of the drug-drug interactions is related to the interaction severity of the majority or the total of the drugs' combination, drugs without reactions are not take in consideration in the case of majority has a significant risk or severity.

The Numerical symbols (i.e. 1-2 2-3,.... ) in the drug-drug pair combinations in linked and refer to the drug list that was fully analyzed and entered to the drug bank interactions filter.

- Application demo
- Steps to work in the application

**Figure 3: Key-number for disease-drugs**

First, we write a keyword of the disease to be treated (figure 1).

Secondly, we search in results the exact combination (disease pairs) (figure 2).

Finally, we use the drug-disease key-number and the table to find the drug-drug pairs to be prescribed (figure 3 and 4).

**Figure 4: drugs list**

The dynamics filter demo is giving traditional prediction of interaction severity of different drug-drug pairs prescribed in the treatment of some important disease-disease pairs within the elder people, as already mentioned below.

The harm caused by DDI will be greatly reduced if traditional methods based on machine learning can be used to efficiently predict DDI. To this end, it is urgent to develop better-performing machine learning approaches. This article describes a new dynamic filter for understanding and better-controlling patient safety, especially for elders. In the past 10 years, the traditional literature approach has been widely applied in bioinformatics and healthcare generally.
Discussion

The dynamics filter could help doctors to minimize the adverse effects during the prescription of a combined treatment for patients, and with the simplicity of the method employed, many healthcare professionals can use it.

Description of the drug combinations with notable severity or risk:

- Pulmonary disease-diabetes (moderate risk): it may increase the central nervous system activities of glycopyrronium
- Arthritis-diabetes: (moderate risk), it may increase some excretion of the rate which could result in a lower serum level and potentially a reduction in efficacy
- Diabetes-heart failure (major risk): the metabolism of certain drugs can be decreased with combined with the other drug of the same combination
- Diabetes-alzheimer: (moderate risk): it may increase some excretion of the rate which could result in a lower serum level and potentially a reduction in efficacy
- High cholesterol chronic kidney disease (minor risk): The risk of severity of adverse effects can be increased when some drugs and combined with other drugs of the same combination of diseases

The application needs hard effort during the parametrizing process, because of the huge number of drug-drug pairs interactions

The dynamic filter can be also applied on triple combinations (Drug-Drug-Drug) or even more.

Conclusion

The occurrence of new traditional method related to drug-drug interactions affect the treatment of patients and also become a concrete solution for many problems for patient safety and drug management. The harm caused by DDI will be greatly reduced if traditional methods based on machine learning can be used to efficiently predict DDI. To this end, it is urgent to develop better-performing machine learning approaches. This article describes a new dynamic filter for understanding and better controlling the patient's safety, especially elders. In the past 10 years, traditional literature approach has been widely applied in bioinformatic and healthcare generally.

Conflicts of Interest:

Authors declare no conflicts of interest exist for this publication.

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References


