IJIREEICE

ISSN (Online) 2321-2004
ISSN (Print) 2321-5526

International Journal of Innovative Research in
Electrical, Electronics, Instrumentation and Control Engineering

Vol. 7, Issue 2, February 2019

Statistical Learning for Predicting Probable Drug-Drug Interactions using Machine Learning Classifiers

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Abstract: Drug-Drug Interaction (DDI) is a change in the effect of a drug when patient takes another drug. Characterizing DDIs is extremely important to avoid potential adverse drug reactions. DDIs are representing as a complex network in which nodes refer to drugs and links refer to their potential interactions. Recently, the problem of link prediction has attracted much consideration in scientific community. The process of link prediction as a binary classification task on networks of potential DDIs are presented. By using link prediction techniques for predicting unknown interactions between drugs in arbitrary chosen large-scale DDI databases namely Two-Sides and Drug bank. The performance of link prediction is estimated using a series of experiments on DDI networks. The link prediction is performed using some of the machine learning classifiers such as random forest; Gradient Boosting .The applied methodology can be used as a tool to help researchers to identify potential DDIs.

Keywords: Random Forest, DNN, Gradient boosting. Pharmacology, Pharmacokinetics

I. INTRODUCTION

Drug–Drug Interactions (DDIs) occur during the co-administration of medication. They are a common cause of Adverse Drug Reactions (ADRs) and lead to increasing health care costs. Empirical evidence reported that the percentage of the U.S. population taking three or more drugs increased for 12% in years 1988-1994 to 21% in years 2007-2010 Drug-drug interactions occur when a drug interacts, or interferes, with another drug. This can alter the way one or both of the drugs act in the body or cause unexpected side effects. The drugs involved can be prescription medications, over-the-counter medicines and even vitamins and herbal products. Drug-Drug Interactions (DDIs) are an important consideration in both development and clinical application, especially for co-administered medications. While it is necessary to identify all possible DDIs during clinical trials, DDIs are frequently reported after the drugs are approved for clinical use and they are a common cause of Adverse Drug Reactions (ADR) and increasing healthcare costs. Computational prediction may assist in identifying potential DDIs during clinical trials. The architecture diagram of this work is shown in figure 1.

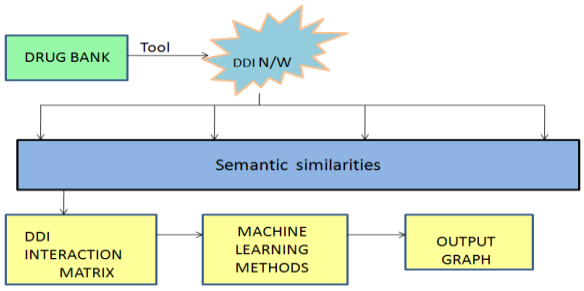

Figure 1: Architecture Diagram

II. LITERATURE SURVEY

Kuhn M, Letunic I, Jensen LJ, Bork P presented their work in SIDER database of drugs and its side effects. Unwanted side effects of drugs are a burden on patients and a severe impediment in the development of new drugs. At the same time, adverse drug reactions (ADRs) recorded during clinical trials are an important source of human phenotypic data. It is therefore essential to combine data on drugs, targets and side effects into a more complete picture of the therapeutic mechanism of actions of drugs and the ways in which they cause adverse reactions. Lu Y, Shen D, Pietsch M, Nagar C, Fadli Z and Huang H presented in a novel algorithm for analyzing drug-drug interactions from MEDLINE

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literature". Drug–Drug interaction (DDI) is becoming a serious clinical safety issue as the use of multiple medications becomes more common. Searching the MEDLINE database for journal articles related to DDI produces over 330,000 results. It is impossible to read and summarize these references manually. Wienkers LC and Heath TG worked on predicting in vivo drug interactions from in vitro drug discovery data. In vitro screening for drugs that inhibit cytochrome P450 enzymes is well established as a means for predicting potential metabolism-mediated drug interactions *in vivo*. Given that these predictions are based on enzyme kinetic parameters observed from *in vitro* experiments, the miscalculation of the inhibitory potency of a compound can lead to an inaccurate prediction of an *in vivo* drug interaction, potentially precluding a safe drug from advancing in development or allowing a potent inhibitor to 'slip' into the patient population.

III. MATERIALS AND METHODS

We represent DDIs as a complex network in which nodes refer to drugs and links refer to their potential interactions. We form a heterogeneous network of DDI's for predicting unknown interactions between drugs using arbitrary chosen large-scale DDI databases, namely drugbank, Twosides.

A. *Construction of a DDI Network*

Sample Network drawn and shown in figure 2.

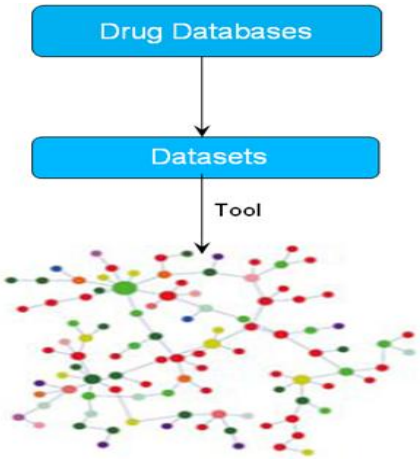

Figure 2: Sample Network

DrugBank: DrugBank is an encyclopedic Web repository containing complete biochemical and pharmacological data about drugs, including biological mechanisms and targets information.

Twosides: Twosides is a comprehensive source of poly-pharmacy ADRs for combinations of drugs. Interactions in Twosides database are restricted to only those that cannot be unambiguously ascribed to either drug alone.

Semantic features: we consider four types of semantic similarity features i.e., phenotypic, therapeutic, chemical and genomic which is used to form a similarity matrix and then the machine learning algorithms are applied.

B. *General steps in analysis of DDI's*

Basically we collect the dataset from different drug bank and give to a tool known as Cytoscape. We obtain a DDI network for the known interaction between drugs. A. Collection of a comprehensive DDI dataset from the Drug Bank and two sides' database and construction of a DDI network. B. Calculation of four drug–drug pair similarities. Phenotypic similarity is based on a comprehensive drug–adverse drug reaction network, therapeutic similarity is based on the drug Anatomical Therapeutic Chemical (ATC) classification system, structural similarity is derived from chemical structural data, and genomic similarity is based on a large drug–target interaction network from DrugBank and the Therapeutic Target Database. The drug phenotypic, therapeutic, and structural similarities were calculated using a previously published method. C. Construction and evaluation of machine learning-based HNAI models. The following figures 3a, 3b and 3c describes steps in the analysis of DDI.

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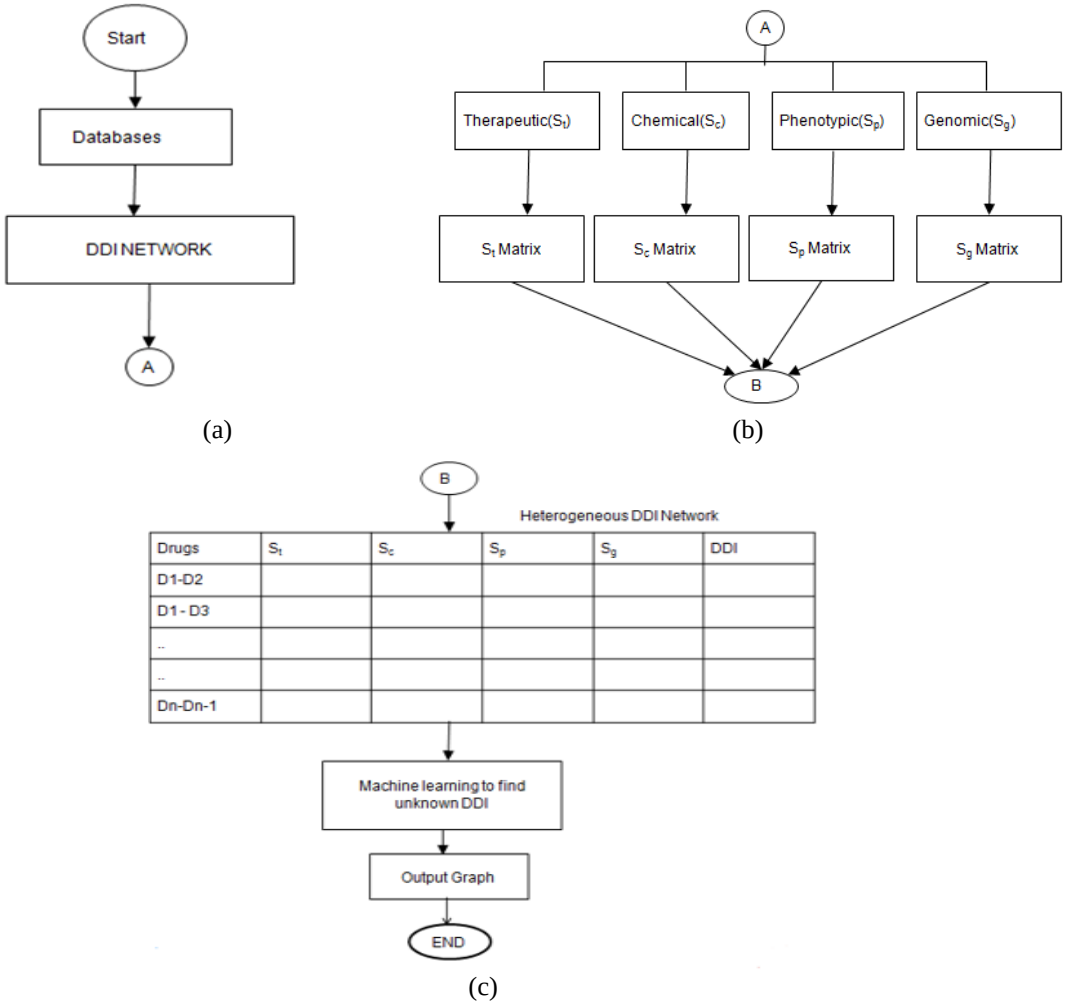

Figure 3a, 3b, 3c: Steps in analysis of DDI

IV. ALGORITHMS

A. Random Forest

RF is a statistical learning methodology that performs ensemble learning for classification. Ensemble consists of multiple classification trees. We split each node using the best among a randomly selected subset of given features. Next, we combined class labels predicted by each tree in the forest. Majority vote is finally used to create final prediction.

B. Gradient Boosting

GBM also provides ensemble learning, but the base learners in a GBM are weak learners. The trees in GBM are not grown to the maximum possible extent as in RF. The GBM starts with an imperfect model (i.e., the base learner that is not grown maximally) and generates a new model by successively fitting the residuals of the current model, using the same class of base learners as the initial imperfect model.

C. DNN

Deep learning (also known as deep structured learning or hierarchical learning) is part of a broader family of machine learning methods based on learning data representations, as opposed to task-specific algorithms. Deep learning architectures such as deep neural networks can be applied to fields including bioinformatics, drug design where they have produced results comparable to and in some cases superior to human experts.DNN uses various algorithms for classification such as KNN and the values. The tensor flow package of python is also used.

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CONCLUSION

Link prediction is a promising methodological framework for studying complex systems in different scientific disciplines, including pharmacology. We evaluate an approach to potential DDIs prediction using link prediction methodology. We study the prediction performance link prediction algorithms on several large-scale DDI networks. From the knowledge we gained by referring multiple project reports and survey papers belonging to the domain of Random Forest, gradient boosting and DNN, we conclude that these algorithms approach for predicting unknown DDI's is best suited for training the model when there is availability of data.

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