Representation learning of drug and disease terms for drug repositioning

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Abstract—Drug repositioning (DR) refers to identification of novel indications for the approved drugs. The requirement of huge investment of time as well as money and risk of failure in clinical trials have led to surge in interest in drug repositioning. DR exploits two major aspects associated with drugs and diseases: existence of similarity among drugs and among diseases due to their shared involved genes or pathways or common biological effects. Existing methods of identifying drug-disease association majorly rely on the information available in the structured databases only. On the other hand, abundant information available in form of free texts in biomedical research articles are not being fully exploited. Word-embedding or obtaining vector representation of words from a large corpora of free texts using neural network methods have been shown to give significant performance for several natural language processing tasks. In this work we propose a novel way of representation learning to obtain features of drugs and diseases by combining complementary information available in unstructured texts and structured datasets. Next we use matrix completion approach on these feature vectors to learn projection matrix between drug and disease vector spaces. The proposed method has shown competitive performance with state-of-the-art methods. Further, the case studies on Alzheimer’s and Hypertension diseases have shown that the predicted associations are matching with the existing knowledge.

Keywords—Representation Learning, Vector Representation, Drug repositioning, Word vector, Heterogeneous Inference

I. INTRODUCTION

Development of new drugs is associated with huge investment of time and money, and risk of failure in clinical trials. It has been estimated that on an average, drug development process takes 15 years [1] and associated cost is approximately $1 billion [2]. Finding novel indications for approved drugs, referred as drug repositioning or drug repurposing (DR), has attracted researchers and pharmaceutical industry as a cost-effective and faster alternative to overcome this challenge [3]. The candidates for drug repositioning are drugs which are already in market or which have been discontinued due to various reasons other than safety issues. As per the estimate in [3], DR allows a significant reduction in time from 10-17 years to 3-12 years in novel drug discovery. According to [4], among all the drugs which have been approved by the US Food and Drug Administration (FDA), approximately 30% of them were the result of drug repositioning. Significant examples of drug repositioning includes Aspirin (regular use as analgesic and now also being widely adapted to treat heart related disease [5]), Plerixafor (initially developed to treat HIV but later being used as a drug to mobilize stem cells [6]), and Thalidomide (initially developed to treat nausea but after drug repositioning research, being used to treat dermatological issues and the myelome disease [7]).

There have been significant number of methods developed for the drug repositioning problem including machine learning methods. We summarize the prominent methods in the section[V]. Working principle of all methods rely on two important aspects related to drugs and diseases. First, drugs often bind to multiple targets resulting into various biological effects including side-effects [8]. Second, a biological target of a drug which is relevant to a particular disease, may also be directly or indirectly associated with other diseases. In other words, overlapping pathways or common associated targets between various diseases are important factors and thereby making it possible that an approved drug for one disease may be useful in treating a similar disease [9].

Existing methods of identifying drug-disease association majorly rely on the information available in the structured databases only. However these databases are unable to keep pace with the exponential growth of information appearing in research articles. In this paper, our primary aim is to develop a method which can exploit information present in free texts as well as in structured databases. In recent years, vector representation of words, learned using neural network based methods from a large corpora of free texts, have been shown to give significant performance for several natural language processing tasks. Word vectors thus obtained are also shown to capture syntactic and semantic properties. We employ a novel method to learn representation of each drug and disease terms which then are projected on a common vector space to obtain similarity between drugs and diseases. Towards this end, first we learn vector representation of drugs and diseases by using the knowledge present in literature. Next, these vectors are updated to accommodate various similarity measures of drugs and diseases respectively. The resultant drug and disease vector representation are not necessarily in the same vector-space. So we employ matrix completion approach [10] to learn a projection matrix between drug and disease vector space. We evaluate the performance of our method using ten fold cross validation and top k rank threshold methods and compare it with 3 other competitive methods. We further perform case studies on Alzheimer’s disease and Hypertension and verify our predictions for these diseases from literature. Our study shows that all our top ten drugs predicted for
Alzheimer’s disease are approved to treat neurodegenerative diseases. Similarly 7 out 10 drugs predicted for Hypertension are approved and 2 out of remaining 3 are used to treat Ocular Hypertension.

II. MATERIALS AND METHODS

In this study we describe the datasets used. Later we explain our method which includes learning the feature vector and learning the projection matrix between drug and disease vector space.

A. Dataset

This section discusses all datasets and their sources used in this work.

1) Drug-Disease Association Data-
We use the same drug-disease association data as used in PREDICT [11]. Data is made available as the supplementary material of the corresponding paper [11]. It contains 1933 drug-disease associations between 593 drugs and 313 diseases. All 593 drugs are registered in DrugBank [12] and all 313 diseases are listed in OMIM [13] database. As we have mentioned earlier that the proposed method rely on obtaining word embedding for each drug and disease from a huge corpus of biomedical articles, we discarded some drugs and diseases which we were not present in the corpus. Finally we consider 584 drugs, 294 diseases and 1854 drug-disease associations known between them.

2) SIDER: Drug Side Effect Data- We obtain the list of side effects corresponding to all 584 drugs from the SIDER [14] database.

3) Chemical Fingerprint of Drugs- Chemical fingerprint of a drug corresponds to the record of component fragment present in their chemical structure. For each drug their chemical fingerprint was obtained from the DrugBank [12].

4) DrugBank- Similar to the chemical fingerprint of drugs, drug targets are obtained from the DrugBank. Drug targets one or more cellular molecules such as metabolites or proteins for desired effects. A list of targets corresponding to all 584 drugs are obtained.

5) DisGeNet: Disease Associated Genes- We collect genes associated with disease from DisGeNET [15].

B. Construction of similarity measures

We calculate three types of similarity for drugs which are based upon side-effects, chemical structure and target proteins. Two similarities are calculated for each disease pair based upon the disease phenotypes and associated genes.

1) Drug Similarity measures:

I Side effect similarity : A side effect is an undesired consequence of a drug. Drugs cause side-effects when they bind to off-target apart from their desired on-targets. Under the assumption that if 2 drugs share side-effects and hence off-targets, there is a possibility that they might share on-targets which can be used to cure diseases. Studies [16] show that drugs sharing off targets might also share on targets. For each drug pair \((d_i, d_j)\), this similarity is:

\[
Sim(d_i, d_j) = \frac{|SE(d_i) \cap SE(d_j)|}{|SE(d_i) \cup SE(d_j)|}
\]

where \(SE(d)\) is the set of side-effects related to drug \(d\).

II Chemical Similarity : Similarity of two chemicals is based upon comparing their chemical fingerprint. A fingerprint is a record of component fragment present in a chemical structure. It has been shown in [17] that Tanimoto coefficient can be an effective measure to calculate similarity between two chemicals based on their structures. Pairwise similarity between two drugs was calculated as Tanimoto score of their fingerprint using RDKit [18] library of Python.

III Drug-Target Similarity : A biological target is the protein in the body which is either up regulated or down regulated due to the action of a particular drug on it. If two drugs share same targets, the probability of them causing the similar effect may also increase. Pairwise drug-target similarity between drugs \(d_i\) and \(d_j\) is calculated as:

\[
Sim(d_i, d_j) = \frac{1}{|P(d_i)||P(d_j)|} \sum_{i=1}^{P(d_i)} \sum_{j=1}^{P(d_j)} SW(P(d_i), P(d_j))
\]

where \(P(d)\) denotes the set of genes associated to drug \(d\) and \(SW\) is the Smith-Waterman Sequence alignment score [19].

2) Disease Similarity measures:

I Phenotypic similarity : A phenotypic feature is an observable biological or clinical characteristic of a disease. It is a amalgamation of gene expression as well as influence of external environmental factors. The similarity is collected from MIMMiner Tool [20]. The tool measures disease similarity by computing similarity between MeSH terms [21] that appear in the medical description of diseases in the OMIM database.

II Gene Similarity : Disease causing or associated genes are collected from DisGeNET [15]. Pairwise gene similarity between disease \(d_i\) and \(d_j\) is calculated as:

\[
Sim(d_i, d_j) = \frac{1}{|P(d_i)||P(d_j)|} \sum_{i=1}^{P(d_i)} \sum_{j=1}^{P(d_j)} SW(P(d_i), P(d_j))
\]

where \(P(d)\) denotes the set of genes associated to disease \(d\) and \(SW\) is the Smith-Waterman Sequence alignment score [19].

C. Method

The proposed method has three major steps. In the first step we obtain vector representation of drugs and diseases using neural embedding method [22]. We update these representations using similarity scores calculated from the various structured datasets. And in the last step, we learn a projection matrix between the two vector-spaces so that a final association score between drug-disease pair can be obtained. It is noteworthy
to mention here again that there is no requirement of negative datasets. Figure 1 summarizes the proposed method.

1) Word vectors for drugs and diseases: To capture the information present in literature, we obtain the word vector representation of drugs and diseases. We use Pubmed open access set as our corpus. Each disease is mapped to its OMIM id. As diseases can appear under various names in Pubmed corpus, each disease in the corpus is mapped to a Concept Unique Identifier (CUI) by using UMLS Meta thesaurus [24]. If a disease (OMIM indication) has multiple concept names associated to it, then the resultant vector is taken as the simple average of all the vectors associated to that OMIM indication. The concept names for each OMIM indication is obtained from Supplementary Information of PREDICT [11]. Word vector representation of each drug and disease is obtained by training Pubmed Corpus using word2Vec [25] Python library. To train vectors, we set window size to 5. We have experimented using various vector dimensions ranging from 100 to 200.

2) Learning vector representation by combining similarity measures: Let \( N_d \) be the number of drugs and \( N_s \) be the number of diseases. Each drug word vector is denoted as \( \tilde{d}_i \in \mathbb{R}^N \), where \( i \) ranges from 1 to \( N_d \). Each disease word vector is denoted as \( \tilde{s}_i \in \mathbb{R}^N \), where \( i \) ranges from 1 to \( N_s \). Let the updated drug vector (feature vector) for \( i^{th} \) drug be denoted as \( \tilde{d}_i \), which is initialized to \( \tilde{d}_i \). Let the updated disease vector (feature vector) for \( i^{th} \) disease be denoted as \( \tilde{s}_i \), which is initialized to \( s_i \). Let \( \text{Sim}_k(i, j) \) denote the \( k^{th} \) similarity between drug \( i \) and drug \( j \) or disease \( i \) and disease \( j \).

Let \( M \) be the number of drug similarity measures and \( L \) be the number of disease similarity measures. The motive is to obtain a feature vector for each drug and disease by combining the above mentioned similarities and updating the word vectors. For each drug \( i \) ( \( i \) varies from 1 to \( N_d \)), \( \tilde{d}_i \) is updated when the below objective ( \( J_1 \) ) is minimized:

\[
J_1 = \sum_{i=1}^{N_d} \sum_{j=1}^{M} \left( \frac{\tilde{d}_i \cdot \tilde{d}_j}{||\tilde{d}_i|| ||\tilde{d}_j||} - \text{Sim}_k(i, j) \right)^2
\]

where \( ||\tilde{d}_i|| \) denote the length of the vector \( \tilde{d}_i \).

Each drug word vector is updated using all the other drug vectors and for each similarity measure. The updated set of drug vectors (called feature vectors) is denoted as \( D = [\tilde{d}_1, \tilde{d}_2, ..., \tilde{d}_{N_d}] \), where each \( \tilde{d}_i \in \mathbb{R}^N \).

Similar kind of objective ( \( J_2 \) ) is minimized for all disease \( \tilde{s}_i \), where \( i \) varies from 1 to \( N_s \).

\[
J_2 = \sum_{j=1}^{N_s} \sum_{k=1}^{L} \left( \frac{\tilde{s}_i \cdot \tilde{s}_j}{||\tilde{s}_i|| ||\tilde{s}_j||} - \text{Sim}_k(i, j) \right)^2
\]

where \( ||\tilde{s}_i|| \) denote the length of the vector \( \tilde{s}_i \).

Each disease word vector is updated using all the other disease vectors and for each similarity measure. The updated set of disease vectors (called feature vectors) is denoted as \( S = [\tilde{s}_1, \tilde{s}_2, ..., \tilde{s}_{N_s}] \), where each \( \tilde{s}_i \in \mathbb{R}^N \).

The optimization problem is solved using Theano library of Python. We have obtained a drug vector space and a disease vector space where each vector is of dimension \( \mathbb{R}^N \).

3) Learning projection from drug vector space to disease vector space: Our motive is to learn a projection matrix from drug vector space to disease vector space which will help us in predicting drug-disease association scores. The projection matrix should be such that the projected drug vectors are geometrically close to vectors of their well known disease vectors. The drugs that are in proximity in the directions of their feature vectors may share diseases and vice-versa. Let \( I \in \mathbb{R}^{N_d \times N_s} \) be called the association matrix where \( I_{ij} = 1 \) if drug \( i \) treats disease \( j \) else 0. The projection matrix is denoted as \( Z \in \mathbb{R}^{N \times N} \).

To learn this projection matrix we use inductive matrix completion approach [10, 27] which minimizes the following objective function:

\[
\min_{G,H} \sum_{i,j} ||I_{ij} - \tilde{d}_i G H^T \tilde{s}_j^T||^2 + \frac{\lambda}{2} (||G||^2 + ||H||^2)
\]

where the projection matrix \( Z = GH^T \), where \( G \in \mathbb{R}^{N \times K} \) and \( H \in \mathbb{R}^{N \times K} \). The score of a drug \( i \) and disease \( j \) pair is calculated as:

\[
\text{score}(i,j) = \tilde{d}_i Z \tilde{s}_j^T
\]

Higher the score, greater is the possibility of drug \( i \) treating disease \( j \).

III. Experiments

We conduct 10-fold cross-validation experiments to evaluate the performance of all methods. We use AUC, ROC and top-rank thresholds as evaluation metrics. In the top-rank threshold measure, a well known drug-disease association is considered as correctly predicted if its rank based on the predicted score is within the specified rank threshold.
A. Baseline Methods

We compare the proposed method with three other methods, MBIRW \[28\], HGBI \[29\] and TP-NRWH \[30\]. We briefly summarize each of the three methods for the sake of completeness.

The HGBI method creates a heterogeneous network of two different type of nodes. One set of nodes are representing different drugs and another set of nodes represent targets. Edges exist between within same node types as well as between two different node types. Existence of edge depends on drug-drug similarities, target-target similarities and drug-target interactions. The edge weights of the network are updated in an iterative fashion by incorporating all the paths between the drug-target pair.

The MBIRW method constructs two separate networks on drugs and diseases. Both similarity networks were created using novel similarity measure which takes into account correlation between different similarities. Further MBIRW performs bi-directional random walk on these two networks to get scores for drug disease associations.

TP-NRWH again uses random walk method but on single heterogeneous drug-disease network. This network is similar to the network used in the the HGBI method and integrates all the similarity measures (drug-drug and disease-disease) and well known drug-disease associations. This is in contrast to the MBIRW method which creates two separate networks on drugs and diseases.

We use default parameter settings for all the three methods. Parameters of TP-NRWRH are set as \((\alpha = 0.3, \lambda = 0.8, \eta = 0.4)\). For MBIRW \(\alpha\) is set to default 0.3 and max iterations for right and left random walk is set to 2. For HGBI, restart probability \(\alpha\) is set to default 0.4 and cut off was set to 0.3.

IV. RESULTS

A. Vector representation

First we analyze the performance of our method with respect to varying length of feature vectors between 100 and 200. Fig 2 shows AUC obtained by using different size of drugs and disease vectors. Although increasing dimension generally led to improved AUC score but improvement was not really significant. Next we analyze the importance of updating the word vectors based on similarity scores. We obtain an AUC score of 0.77 when word-vectors obtained using word2vec method on biomedical copora are not updated. On the other hand an AUC score of 0.86 is obtained when updated word-vectors are used. The relative improvement of 10% clearly indicates that the vectors learned through our method captured the similarity of drugs and diseases in better manner.

B. Comparison with existing methods

Fig 3 shows the AUC values and the ROC of 10-fold cross-validation experiments. Although the proposed method has obtained AUC value of 0.86 which is better than the one obtained by HGBI (0.79) but the other two methods were best performing methods. Similar observations are made based on the top-rank threshold metric. The number of correctly predicted associations by our method is greater than that of HGBI for every top rank thresholds as shown in the Fig 4.

C. Case Studies

After finding the performance of our model, we conducted leave-disease-out experiment. For this, first we select a disease and train our model only with the remaining data after excluding all known associations related to it. Then scores are calculated for the held out disease and top scoring drugs are reported. We perform the case studies on two diseases, Alzheimer and Hypertension.

1) Alzheimer’s Disease: Table I shows the top scoring
TABLE I. TOP 10 PREDICTED DRUGS FOR ALZHEIMER’S DISEASE BY OUR METHOD

| Rank | Drug Name     | Predicted Score | Clinical Evidence | Mean Score |
|------|---------------|-----------------|-------------------|------------|
| 1    | Rivastigmine  | 0.31898         | Yes               | 0.57096    |
| 2    | Galantamine   | 0.21839         | Yes               | 0.60274    |
| 3    | Donepezil     | 0.20712         | Yes               | 0.60969    |
| 4    | Memantine     | 0.19311         | Yes               | 0.60871    |
| 5    | Ropinirole    | 0.15378         | No                | 0.31309    |
| 6    | Tacrine       | 0.14715         | Yes               | 0.61930    |
| 7    | Entacapone    | 0.14210         | No                | 0.60625    |
| 8    | Valproic Acid | 0.14009         | Yes               | 0.61276    |
| 9    | Pramipexole   | 0.12957         | No                | -0.00299   |
| 10   | Carbipoda     | 0.12401         | No                | 0.60282    |

Out of the top 10 drugs predicted by our method, 6 drugs namely Rivastigmine, Galantamine, Donepezil, Memantine, Tacrine and Valproic Acid have been approved for Alzheimer’s disease. Other drugs namely Ropinirole, Entacapone, Pramipexole and Carbipoda have been used to treat Parkinson’s disease. Although there is a difference in pathogenesis of Parkinson’s disease and Alzheimer’s disease, but both of them are neuro-degenerative disease associated with aging. Pramipexole has been under Phase 2 of Clinical trials (NCT01388478) for the treatment of Alzheimer’s disease. The above results have been verified from PREDICT [11] and DrugBank [12].

TABLE II. TOP 10 PREDICTED DRUGS FOR HYPERTENSION BY OUR METHOD

| Rank | Drug Name     | Predicted Score | Clinical Evidence | Mean Score |
|------|---------------|-----------------|-------------------|------------|
| 1    | Dyphylline    | 0.33169         | No                | 0.13141    |
| 2    | Trandolapril  | 0.30106         | Yes               | 0.13025    |
| 3    | Prazosin      | 0.27290         | Yes               | 0.13750    |
| 4    | Mecamylamine  | 0.26114         | Yes               | 0.13784    |
| 5    | Brinzolamide  | 0.26103         | No                | 0.13185    |
| 6    | Tramoprost    | 0.25957         | No                | 0.09937    |
| 7    | Labetalol     | 0.25241         | Yes               | 0.12682    |
| 8    | Captopril     | 0.25222         | Yes               | 0.12211    |
| 9    | Lisinipril    | 0.25189         | Yes               | 0.07150    |
| 10   | Valsartan     | 0.24950         | Yes               | 0.00656    |

Out of the top 10 drugs predicted by our method, 6 drugs namely Trandolapril, Prazosin, Mecamylamine, Labelotol, Captopril, Losartan and Valsartan are approved drugs for hypertension. Brinzolamide and Tramoprost have been used for treating ocular hypertension. The scores of these top predicted drugs for treating Hypertension and Alzheimer’s disease are much higher than the mean score of these drugs for all diseases.

VI. CONCLUSION

In this paper we have presented a novel representation learning method to obtain vector representation of drugs and diseases. These representations are then utilized to obtain association score between drug-disease pairs. The main contribution of this work is combining complementary information available in unstructured texts and structured datasets. Heterogeneous information was combined and feature vectors were learned for drugs and diseases. Prediction using updated feature vectors gave better results than using the original word vectors. Case studies on Hypertension and Alzheimer’s disease indicate that predictions made by our method can be used for biomedical research. We compared our method with existing methods on drug repositioning. Our results are fairly comparable to those methods in terms of AUC and top k rank threshold scoring mechanism.
ACKNOWLEDGMENT

The authors would like to thank Shubhakar Reddy (Former bachelor’s student at Indian Institute of Technology Guwahati) for providing us the disease to CUI mapping tool developed by him.

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