Network Structure Versus Chemical Information in Drug-Drug Interaction Prediction

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Abstract. We apply two embedding mechanisms, node2vec & mol2vec, on the problem of predicting Drug-Drug Interactions (DDIs). These mechanisms, respectively, convert drugs into vectors using the chemical information of the underlying chemical compound and the network information from the graph of drug interactions. Our goal is to compare Single Link Prediction models that are based on each embedding method by exploring the topological features of the drug interactions graph that make each approach more efficient in making correct predictions. We base our experiments on the DrugBank data set and use various computational chemistry tools such RDKit and PubChem, along with NetworkX, in order to create the chemical and structural embeddings for each drug.

Keywords: Drug-drug interaction prediction · DrugBank · Network embeddings · Chemical embeddings · Graph topological features

1 Introduction

The efficacy of a drug can be improved when coadministered with other drugs [4]. Also, it is very common for patients that suffer from comorbidities to follow a multiple drug scheme. Yet, there can be adverse effects in those combinations, which occasionally might be toxic. It is an especially serious problem as the number of drugs that people get for a disease continues to increase [10,19].

While many drug interactions have been discovered, there are potentially new ones that could be predicted with computational methods, before their laboratory confirmation [3]. Thus predicting Drug-Drug Interactions (DDIs) is important for the well-being of patients. The problem of drug interaction prediction with computational methods is usually reduced to the problem of link prediction in a network of interactions. Additional features, such as structural, physicochemical and biochemical characteristics of chemical compounds could

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potentially increase the accuracy of predictions; the usefulness of such properties is already proven in the field of drug discovery [30].

Our work is focused on single link prediction between drugs. We study the embedding of a drug's chemical formula towards vector representations that encapsulate the properties of chemical compounds. We also study the embedding of the network information that we extract when we consider each drug to be a node in a graph of drug interactions; interactions are denoted as edges in this type of graph. We utilize these embedding methods in creating machine learning models that attempt to predict interactions between drugs. Our interest is not just to isolate those methods and separately evaluate their efficacy in creating link prediction systems; we delve into the network of drug interactions and compare the two embedding mechanisms in order to discover which are the network properties that make each approach more efficient than the other when it comes to predicting DDIs. For example, we could assume that a drug for which there is plenty of network information (e.g. a high degree node in our graph) is a good candidate for network embedding methods that n exploit this kind of information. On the other hand, a drug that may seem isolated in the network of drug interactions (perhaps a newly discovered compound with only a few known interactions), may be more suitable for chemical embedding methods. We study various graph properties, such as the degree, core difference and betweenness centrality of nodes and edges in order to discover parts and characteristics of the interactions graph that will help us compare in detail the chemical and the structural methods of embedding drug information.

Contribution In this work we make the following contributions:

- Comparison of two drug interaction prediction methods. One based on network information and another on chemical information. The node2vec and mol2vec were used for embedding network and chemical information respectively.
- In-depth study of topological features that influence the accuracy of the two link prediction models. In particular, when is chemical information more useful than network information when it comes to drug interaction discovery.
- Experimental evaluation of the link prediction models on a graph created from DrugBank's [25] drug interactions.

The rest of the paper is structured as follows: In Sect. 2 we refer to methods of link prediction. Section 3 describes the embedding processes, the prediction, and the topological features that were used. A presentation of the dataset we extracted from DrugBank is provided in Sect. 4. The experimental results are discussed in Sect. 5 and conclusions and future work suggestions are drawn in Sect. 6.

2 Literature Review

Link prediction in graphs is a well researched area [26], with many applications in social networks analysis [22,27] and drug interaction prediction [21], to name

just two prominent ones. Link prediction can be based on graph features, upon which matrix and tensor factorization can be applied [18,22]. Such methods have also been applied to graphs that evolve in time [5]. Node and edge embedding methods are widely used to create features for classification [12]. Lately graph neural networks have become popular in link prediction [17,28].

Link prediction has also been used for drug interactions, with methods varying from predicting the presence or absence of interactions, to methods that predict the type of an interaction in a multi-relational network [1,11]. Moreover, many methods have been proposed that employ additional features apart from graph based features, for instance the usage of chemical information has been proposed in [14]. Also a hybrid method that combines multiple types of information, including network information has been proposed in [28]. For multi-relational link prediction there are approaches based on graph neural networks [31]. A rather recent approach focused explicitly on chemical information to predict drug-drug interaction types [20]. Essentially, the authors performed multi-relation link prediction, where the links are the adverse side effects of drugs. This study went further into predicting alternative drug interactions that are not toxic.

This paper focuses on the difference between chemical and network information in DDIs prediction, and in particular how the graph topological features could render one of these types of information more useful for discovering new interactions.

3 Methodology

For each drug, we created two embedding vectors: a network and a chemical based representation. Next, we used three neural network classifiers to predict DDIs: a classifier based on node embeddings, another classifier for chemical embeddings, and a hybrid classifier that is based on both network and chemical embeddings. We evaluated the performance of each classifier, and proceeded to compare their DDI prediction behavior against various topological features on the network of drug interactions.

Mol2vec encodes chemical compounds as vectors with an unsupervised machine learning approach on a corpus of compounds that consists of all available chemical matter [9]. The vector representations of molecular substructures are close for chemically related substructures. In the experiments a pre-trained mol2vec model was used to produce the chemical embeddings of the drugs.[1]

Node2vec is a machine learning algorithm for producing node embeddings, by mapping the nodes of a graph to a low-dimensional space of features that maximizes the likelihood of preserving their network neighborhoods [7]. After harvesting DrugBank's drug interaction graph and then extracting a sample subgraph (see Sect. 4), we trained a node2vec model on the sampled graph and used it to produce the structural embeddings of the drugs.

[1] https://github.com/samoturk/mol2vec/tree/master/examples/models.

Training Samples The experiments focus on predicting drug interactions, we consider two categories of samples: positive and negative. Positive samples refer to observed interactions between drugs, and negative samples refer to interactions that have not been observed so far, i.e. a closed world assumption. The input to a classifier is pair of drugs represented as a vector, both for the mol2vec and the node2vec embeddings. The output is the presence or absence of an interaction. Figure 1 displays the logic of the classifiers for drugs v_i and v_j.

Note that each DDI leads to two different vector concatenations depending on the order the concatenation is done; in the following experiments we included both options to generate positive samples. Acquisition of positive samples was straightforward. However, to create negative interactions it was assumed that unobserved interactions do not exist, and thus the graph was sampled for pairs of nodes that do not form edges.

In order to have a balanced data-set for the experiments, we produced a set of negative samples equal in size to the set of positive samples.

We evaluated three classifiers based on the same neural network architecture of a feed forward model with two hidden layers: A *mol2vec* classifier based on mol2vec embeddings, a *node2vec* classifier based on node2vec embeddings, a *hybrid* classifier based on both mol2vec and node2vec embeddings. The aim was to compare chemical and structural information when used for DDI prediction. For this purpose, along with commonly used metrics in classification, we also used network topological features such as node degree, k-core values and betweenness centrality, in order to identify which topology characteristics make each approach more efficient in the problem of link prediction.

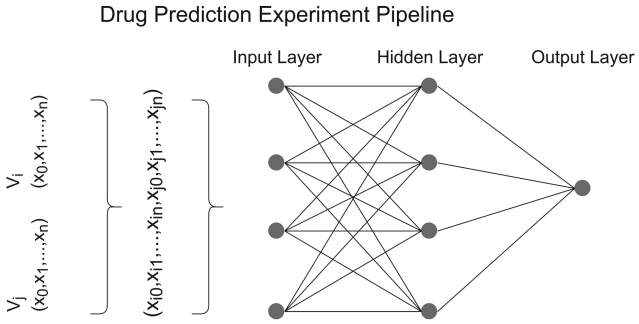


Fig. 1. DDIs, in the form of concatenated vectors of drug embeddings, are used as training samples for our classifiers.

4 Data Harvesting and Processing

Interactions Graph Data were harvested from DrugBank [25] (version 5.1.9), a drug interactions repository that is human curated. The data included 14,624

drug entries and 1,389,184 unique DDIs. Only the drugs that have at least one known interaction were kept, and we also excluded some drugs that have chemical compounds that are incompatible with the tools (i.e. PubChem) that we used . After the data cleaning, a set was obtained that comprised of 3,753 nodes and 1,207,953 edges, and it will be referred as the *full graph*.

When we refer to structural (or network) information regarding DDIs, it is critical to make a distinction between direct edges between drugs, which denote drug interactions, and information that derives from the rest of the graph properties that two interacting drugs (nodes) share. There is no point in creating node2vec embeddings over a graph that holds all the direct edges between interacting drugs, because that information—which is essentially the train and test set of the following experiments—will infiltrate in the structural embeddings. What we do instead, is take a small sample of the *full graph* that contains the same number of nodes and only 1% of its edges. We will refer to the result of this process as *sampled graph*. We train the node2vec model on the *sampled graph* and then use it to create the structural embeddings for our experiments.

Graph Sampling Sampling 1% of the edges of the *full graph*, serves two purposes. First, it showcases the ability of node2vec to capture graph properties of the original graph, from a subset of edges that is smaller by two orders of magnitude; this fact is presented in detail in Sect. 5. The second and most important purpose is to have node embeddings that capture information beyond the one-hop neighbours, thus minimizing the effect of direct links between the corresponding nodes.

Closeness centrality in Table 2 confirms that the sampled graph has been stripped off most of the direct edges, raising the average distance between nodes of the graph and, therefore, setting a level of difficulty for our model to identify interacting drugs through graph information that does not include the direct edges. Figure 3a provides a more detailed view on closeness centrality [6] for both graphs; in the case of more than one connected components we use the Wasserman and Faust formula [23].

Table 1. Basic properties for full graph and sampled graph.

Graph	Nodes	Edges	Avg. degree	Clustering Co.	Conn. components	Diameter
Full	3753	1,207,953	643.73	0.621	1	5
Sampled	3753	12,080	6.44	0.005	799	∞

Table 1 depicts some basic properties for the full and the sampled graph, and Table 2 contains the average centrality measures. Also, DrugBank labels drugs with the categories shown in Table 3; note that some drugs belong to more than one category. Interestingly, drugs that belong to different categories also seem to differentiate on a graph/topological perspective (avg. node degrees and std. of node degrees).

Table 2. Average centrality measures for full graph and sampled graph.

Graph	Degree C.	Eigenvector C.	Closeness C.	Betweenness C.
Full	0.1715	0.012	0.5030	0.00027
Sampled	0.0017	0.011	0.1556	0.00049

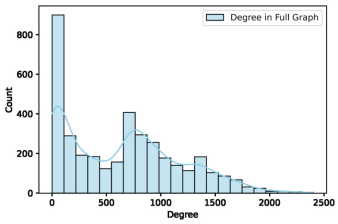


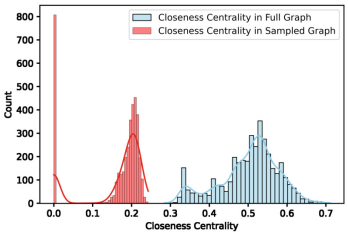
Fig. 2. Histogram and KDE for node degrees in *full graph.*

The average node degree of the *full graph* reflects a high density of drug-interactions, thus an average drugs interacts with 600 other drugs. Also, Fig. 2 reveals that there is a considerable number of drugs that have only few known interactions, as well as many drugs with thousands of identified interactions.

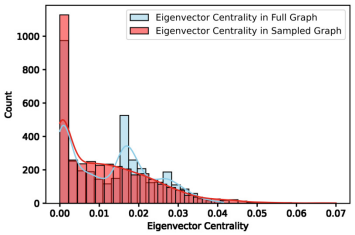
Although reducing closeness centrality in the *sampled graph* is one of our goals in order to exclude most of the direct edges' influence from our node2vec embeddings, we also need to keep enough edges of the *full graph* to maintain its core characteristics and, therefore, produce useful vectors that will efficiently train the node2vec classifier. Thus we considered the eigenvector centrality of the *full graph* and the *sampled graph.* Edges originating from high-scoring nodes contribute more to the score of a node than connections from low-scoring nodes. A high eigenvector score means that a node is connected to many nodes who themselves have high scores [2], denoting the transitive influence of nodes. Figure 3b shows that sampling the *full graph* did not result in a big difference at the *sampled graph's* eigenvector centrality distribution. We can say that nodes in the *full*

Table 3. *Full graph's* drug categories.

Category	Frequency	Degree (Mean, std.)
Approved	2179	787.54 ± 540.90
Investigational	1585	635.09 ± 541.51
Experimental	853	480.82 ± 447.84
Vet Approved	309	731.11 ± 578.32
Withdrawn	190	871.08 ± 492.24
Illicit	123	870.91 ± 503.60
Nutraceutical	63	282.95 ± 337.05



(a) Histogram and KDE of Closeness Centrality in *Full graph* and *Sampled graph*.



(b) Histogram and KDE of Eigenvector Centrality in *Full Graph* and *Sampled Graph*.

Fig. 3. Closeness centrality and eigenvector centrality.

graph that not only have many connections to other nodes, but are also connected with other nodes of importance—in the sense of eigenvector centrality—continue to hold this characteristic in the *sampled graph*.

Sampling a greater percentage than 1% of edges of the *full graph* to create the *sampled graph* leads to similar closeness centrality distributions between the two graphs, and sampling less than that causes great differences in their eigenvector centrality distributions. This is the reason behind the choice to sample 1% of the *full graph's* edges before training the node2vec model and producing the network embedding for each drug.

Data pre-processing Starting from DrugBank's drug IDs, we used various tools in order to obtain the chemical and the structural embeddings (see Fig. 4). With the NetworkX library [8] a graph data structure was created out of DrugBank data, and it was also used to create the *sampled graph*. We trained node2vec on the *sampled graph*, setting the algorithm to embed nodes to vectors of 128 dimensions. Once node2vec [7] was trained, we applied it on each drug (node) to produce the corresponding node2vec (structural) embedding.

To compute the mol2vec (chemical) embeddings, first we used PubChem's services and acquired the isomeric SMILES (Simplified Molecular Input Line Entry System) notation for each drug [13]. SMILES is a chemical notation system based on molecular graph theory [24]. Then, we used RDKit [16] to convert each SMILES to a MOL data structure [29], a widely-used chemical structure file format in which adjacent lists and adjacent matrices are used to describe a chemical compound's structure. Finally, mol2vec [9] was applied on the MOL structures, using a pre-trained model to embed drugs to vectors of 300 dimensions.

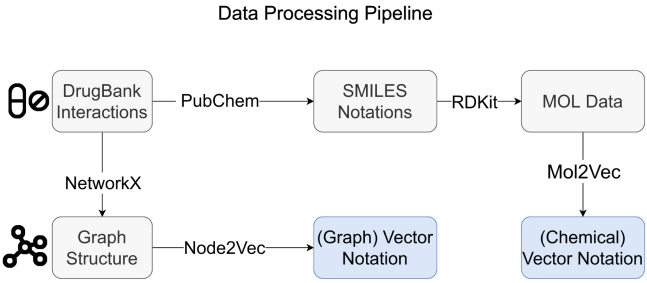


Fig. 4. Data processing pipeline: steps between DrugBank data and final embeddings for each drug.

5 Experimental Results

Classifier Evaluation Figure 5 displays the classification report of the three models on the test set; negative interactions are denoted by class 0 and positive interactions are denoted by class 1. We used a 65/5/30 split on all samples (positive and negative) of the *full graph* for training, validation and testing—we applied a random split, with the exception that all of the edges in the *sampled graph* (which are also present in the *full graph*) ended up on the training set. Also, both variations of an interaction sample (regarding the order of the concatenation of the corresponding drug embeddings) are always included in the same set (i.e., train, validation or test). Figure 8 compares the average value of useful graph properties of the test samples, and Fig. 8 provides a comparison between the Kullback-Leibler divergence of the distributions of test sample properties for the correct and false predictions of mol2vec and node2vec classifiers. *Average mean degree* refers to the average of all means of the node degrees of the test samples; similarly *average min degree* denotes the average of all minimum degrees between all test interactions, and *average max degree* denotes the average maximum degree. Also, *betweenness* centrality in this section is calculated only for positive samples, and refers to the corresponding edge betweenness centrality (and not the node betweenness centrality that is reported in Sect. 4).

The higher performance of the hybrid classifier compared to the other models in the classification report suggests that there is knowledge on DDIs that is unique for both the chemical and the structural embedding methods. Combining the embeddings to train the hybrid model—trading this abundance of information with higher vector dimensions that are known to hinder the learning capabilities of neural networks—leads to a better predictor. The only exception here is the higher precision on positive interactions for the node2vec classifier; hinting that the node2vec classifier shows a greater ability to identify negative interactions properly and maintain a lower number of false positives choices through the evaluation phase. Figure 6a confirms our assumption that drugs with few known interactions (possibly newly discovered compounds) make better candidates for chemical based predictors when recall is more important than accuracy; iden-

tifying more true interactions by trading some false positives may be a good trade off for a chemical researcher. The figure even sets a threshold value at a *min degree* of 350 where node2vec begins to perform better than mol2vec in terms of recall. Figures 6b and 7b show that for low core difference values[2] of sample interactions the node2vec classifier performs as well as the hybrid classifier in terms of recall and accuracy. The fact that node2vec classifier reaches hybrid model's efficiency means that chemical embeddings, when it comes for test interactions with low core difference, show no unique knowledge to add to structure embeddings' learning capabilities. Also, all models seem to perform better for lower values of core difference.

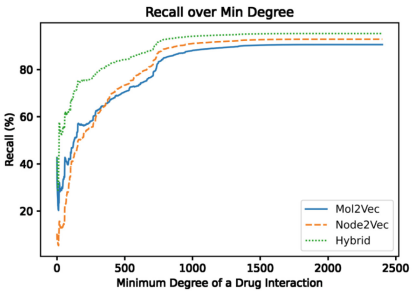
Class	Classifier	Precision	Recall	F1 Score
Negative Samples (Class 0)	mol2vec	0.91	0.89	0.90
	node2vec	0.90	0.94	0.92
	Hybrid	**0.96**	**0.94**	**0.95**
Positive Samples (Class 1)	mol2vec	0.88	0.91	0.89
	node2vec	**0.96**	0.93	0.94
	Hybrid	0.93	**0.95**	**0.94**

(a) Classification Report.

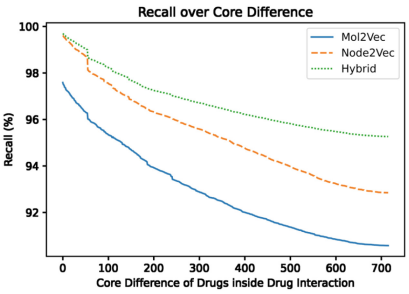
Category	mol2vec	node2vec	Hybrid
Experimental	87	94	96
Approved	85	93	94
Investigational	87	94	95
Vet Approved	88	94	97
Withdrawn	87	96	97
Illicit	87	95	96
Nutraceutical	91	90	97

(b) Accuracy percentage comparison for each drug category.

Fig. 5. Classification report and accuracy comparison per drug category.



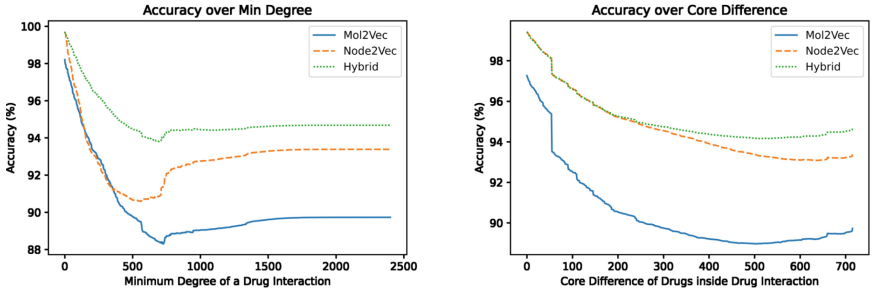
(a) Recall over Min Degree.



(b) Recall over Core Difference.

Fig. 6. Recall plots for mol2vec, node2vec and hybrid classifiers.

[2] We consider the core difference of a sample interaction as the absolute difference of the k-core values of two nodes that are connected by the corresponding graph edge.



(a) Accuracy over Min Degree.

(b) Accuracy over Core Difference.

Fig. 7. Accuracy plots for mol2vec, node2vec and hybrid classifiers.

	Metric	mol2vec	node2vec	Hybrid
False Prediction	Average Min Degree	518.06	470.07	517.01
	Average Max Degree	1137.02	1143.09	1163.44
	Average Mean Degree	827.54	806.58	840.22
	Average Core Difference	237.17	266.10	242.34
	Average Betweenness Centrality	4.57e-06	6.99e-06	6.76e-06
Correct Prediction	Average Min Degree	519.66	593.45	512.09
	Average Max Degree	1083.25	1143.96	1078.67
	Average Mean Degree	801.45	868.713	795.38
	Average Core Difference	228.50	196.01	231.80
	Average Betweenness Centrality	1.39e-06	1.29e-06	1.44e-06

(a) Comparison of average graph properties of interactions grouped by each model's prediction.

Classifier	Correct	False
Average Degree	0.018	0.047
Min Degree	0.019	**0.199**
Max Degree	0.010	**0.110**
Core Difference	0.013	**0.103**
Betweenness C.	**0.109**	0.071

(b) KL Divergence between mol2vec and node2vec sample distributions (values over 0.1 in bold).

Fig. 8. Result metrics by classifier choice (Correct or false).

6 Conclusions and Future Work

Regarding the prediction of presence or absence of edges/interactions we have observed the following results. Recall for the min-degree criterion is better for mol2vec up to a certain threshold, after that node2vec takes over. Also regarding the core-differences criterion, node2vec is always better than mol2vec. Moreover, the distribution of the betweeness centralities of the pairs of nodes for which the presence or absence of edges were correctly predicted, were very different for the mol2vec and the node2vec model.

We have also shown that low core differences between a pair of nodes make structural information based models a better candidate to predict interactions achieving the same accuracy and recall even with the hybrid approach. But for higher core differences, chemical information can boost the information that is provided by structural information and thus enhance the performance of interaction prediction.

By and large the hybrid model that combines structural and chemical information of drugs leads to more efficient predictors of DDIs than using either of the models.

After comparing structural and chemical approaches for predicting simple interactions between drugs, a question arises about what conclusions we would reach if we expanded our research on the broader field of predicting multi-labeled drug interactions. We can also expand the graph to include other types of nodes besides drugs (e.g. proteins).

Further study on techniques for negative samples generation could improve the quality of the training set and, possibly, allow for better predictors. When it comes to multi-relational link prediction, [15] provides a notable analysis on the importance of negative sampling, as well as useful methods for negative sample generation, such as the "corruption of positive samples" or "nearest neighbor sampling".

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