Detecting Drug-Drug Interactions using Protein Sequence-Structure Similarity Networks

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Abstract—Adverse drug events represent a key challenge in public health, especially with respect to drug safety profiling and drug surveillance. Drug-drug interactions represent one of the most popular types of adverse drug events. Most computational approaches to this problem have used different types of data, such as drug chemical structure, information about protein targets, side effects, pathways, etc to predict potential interactions between drugs. In this work, we study the question of whether using just genetic information about the drugs can provide significant information about the potential safety profile for a given drug. We propose a novel neural network model to predict adverse drug events using only data about the protein sequence and protein structure associated with the drug targets. We compare the results with those from the state-of-the-art methods on this problem. Our results show that the proposed method is quite competitive, at times outperforming the state-of-the-art.

Index Terms—Drug safety, Drug-Drug Interaction (DDI), Neural Networks, Protein Similarity Network

I. INTRODUCTION

Given the increasing number of medications that are being consumed concurrently by individuals, it is becoming more and more important to know more about the drugs we take. With this increased potential for polypharmacy, there is a corresponding increase in the chance for adverse events involving medications. One key example of adverse drug events is the problem of drug-drug interactions. The sheer number of people taking more than one medication in a given day has made the issue of drug-drug interactions a major public health problem.

Recent advances in biomedical research have generated a large volume of drug-related data. To effectively handle this enormous amount of data, many initiatives have been introduced to help researchers make sense of the massive data sets. As a result, various drug knowledge bases have been constructed, for instance, Drug Bank, SIDER, PDB, STITCH, SMILES, etc. These knowledge bases record various types of information about drugs, including information about genetic sequences, protein structures, drug side-effects, chemical structures, drug indications, etc. Thus, several approaches have been proffered to utilize the information from these different sources to predict potential interactions between drugs [9], [10], [14]–[16]. DrugBank is perhaps one of the most credible databases of known DDIs [4]–[6], and contains information on over 300,000 DDIs. However, the number of drug-drug interactions is less than 1% of the total possible drug pairs that exist in DrugBank. Basically, DDI's are known as the unwanted side effects resulting from the concurrent consumption of two or more drugs [1]–[3]. When a doctor prescribes several drugs simultaneously for a patient, this may cause irreparable side effects. The effects of drugs on each other may lead to other illnesses or even death. These side effects are particularly noticeable in the elderly, or in persons with challenging diseases, such as cancer patients, who take many different drugs daily. Given the relevance of DDI's in an individual's health, and to public health in general, there is a critical need for more accurate and effective computational methods for understanding DDIs and how to predict them.

In this work, we study the problem of DDI prediction from the lens of genetic materials about the drugs. The paper is organized as follows: In the next section, we briefly discuss related work. Section III presents our methodology. Section IV reports on our experiments and results. Discussions are presented in Section V, and Section VI concludes the paper.

II. BACKGROUND AND RELATED WORK

Most existing approaches for DDI prediction are based on different properties of the drug compound, such as its chemical structure, side effects, drug-target relationship, and many more. DDIs can be identified with in vivo models using high-throughput screening [7]. However, the price of such procedures is relatively high, and testing large numbers of drug combinations is not practical [8]. To reduce the number of possible drug combinations, numerous computational approaches have been proposed [9]–[16]. In some of these computational approaches, drug-target networks are constructed, and DDIs are detected by measuring the strength of network connections [13], or by identifying drug pairs that share drug targets or drug pathways, for instance, using the random walk algorithm [14].

Some computational approaches have used the structural similarity and side effect similarities of drug pairs. For example, Gottlieb et al. proposed the Inferring Drug Interactions

(INDI) method, which predicts novel DDIs from chemical and side effect similarities of known DDIs [9]. Vilar et al. used similarities of fingerprints, target genes, and side effects of drug pairs [10], [11]. Cheng et al. constructed features from the Simplified Molecular-Input Line-Entry System (SMILES) data and side effect similarity of drug pairs and applied support vector machines to predict DDIs [12]. Zhang et al. constructed a network of drugs based on structural and side effect similarities and applied a label propagation algorithm to identify DDIs [13]. Recently, Ryu et al. proposed DeepDDI, a computational framework that calculates structural similarity profiles (SSP) of DDIs, reduces features using principal component analysis (PCA), and feeds them to a feed-forward deep neural network [16]. The platform generated 86 labeled pharmacological DDI effects, so DeepDDI [19] is basically a multi-classification (multi-label classification) model.

Vilar et al. developed a model to predict DDIs based on the Interaction Profile Fingerprint (IPF) [10]. Quite simply, the interaction probability matrix was computed by multiplying the DDI matrix by the IPF matrix. Afterward, Lu et al. proposed a computational framework by applying matrix perturbation, based on the hypothesis that by randomly removing edges from the DDI network, the eigenvectors of the adjacency matrix of the network should not change significantly [17]. These two methods employ no other data about drugs, except known DDIs.

More recently, a new family of similarity-driven methods has followed the assumption that similar drugs should have almost similar interactions. Vilar et al. [18] presented a neighbor recommender method by utilizing substructure similarity of drugs. Relying on Vilar's framework, Zhang et al. constructed a weighted similarity network that is labeled based on interaction with each of the drugs [13] and applied an integrative label propagation method using a random walk model on the network to estimate potential DDIs. This prediction framework only considered three types of similarities for predicting DDI via label propagation, namely substructure-based, side effect-based, and offside effect-based label propagation models [13]. Recently, some methods have also been proposed for adverse event detection using signals from social media [25]–[27].

In this study, we develop a novel DDI prediction method utilizing the protein sequence data from the DrugBank and protein structure data from the Protein Data Bank. We calculate different similarity measures to create the similarity matrices for each feature attribute. Then, we use the generated feature matrices to create a single network fusion to measure the potential for interaction between two drugs. Final decision is performed via the help of a neural network architecture based on multilayer perceptrons. The main novelty of our approach is the focus on only genetic materials (protein sequence and protein structures) associated with the drug targets in developing our prediction model. To our knowledge, this is the first attempt at investigating potential DDI prediction by utilizing only information about the protein sequence and structure to generate the feature space fed to the neural network.

III. METHODOLOGY

We developed a novel neural network model for the prediction of DDIs. The key idea in our approach is the notion that if two drugs have a similar pattern of similarity with other drugs, they are likely to have a similar pattern of interacting partners. To capture the patterns of similarity between drugs, we use information about the protein sequences and protein structures associated with the protein targets for a given drug.

Thus, we construct similarity matrices between drugs based on the protein sequences and protein secondary structures and combine these into one protein sequence-structure similarity matrix using network fusion. Fig. 1 shows a schematic diagram of the general proposed framework. To calculate the similarity matrices we have used cosine distance, Levenshtein distance, Jensen Shannon (JS) divergence, and Euclidean Distance as the similarity measure between a pair of drugs.

A. Distance Matrices

To estimate the similarity between drugs, we compute distance measures (and sometimes similarity measures) between drugs based on their protein sequences and protein structure. We used four such measures as described below.

1) Cosine Similarity (CS): Cosine similarity metric finds the normalized dot product of two vectors. By determining the cosine similarity, we would effectively try to find the cosine of the angle between the two objects, when represented as vectors. The cosine of $0°$ is 1, and it is less than 1 for any other angle. For two n-length vectors A and B, we have:

$$CS(A, B) = \frac{A.B}{\|A\| \|B\|} = \frac{\sum_{i=1}^{n} A_i B_i}{\sqrt{\sum_{i=1}^{n} A_i^2 \sum_{i=1}^{n} B_i^2}} \quad (1)$$

2) Levenshtein Distance (L): The Levenshtein distance is a string metric for measuring the difference between two sequences. The Levenshtein distance between two strings a, b (of lengths $|a|$ and $|b|$, respectively) is given by $L_{a,b}(|a|, |b|)$

$$L_{a,b}(i, j) = \begin{cases} max(i, j) & \text{if min(i,j) = 0} \\ min \begin{cases} L(i-1, j) + 1 \\ L(i, j-1) + 1 \\ L(i-1, j-1) + 1 \end{cases} & \text{otherwise} \end{cases}$$

$$(2)$$

Essentially, $L_{a,b}(i, j)$ is the distance between the first i character of a and the first j character of b.

3) Jensen Shannon (JS) divergence(JSD): The Jensen–Shannon divergence is a method of measuring the similarity between two probability distributions. Given two distributions X and Y, the JS divergence is the average KL divergence of X and Y from their mixture distribution, M:

$$JS(X||Y) = \frac{1}{2} D(X||M) + \frac{1}{2} D(Y||M) \quad (3)$$

where $M = \frac{X+Y}{2}$. and $D(X||M)$ is the KL divergence between X and M.

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B. Protein Sequence and Structure Similarity Matrices

In our work, we use similarity matrices, rather than distance matrices. Thus, for each distance measure, we convert the values into similarity measurement.

Each protein structure could have multiple chains. Moreover, each drug active ingredient could have multiple protein targets. Thus, we could compute the similarity between two drugs (or drug active ingredients) based on the protein chains associated with the respective protein targets for the drugs. For each similarity measure, we record 1) Minimum Similarity 2) Maximum Similarity 3) Average Similarity(AS) 4) Exponential Weighted Average Similarity(EWAS)

Here, we discuss briefly the protein sequence and protein structure similarity matrices used in this work.

1) Protein Sequence Similarity Matrices: In this approach, the protein Sequence information is used directly to compute the similarity matrix. We can compute the Levenshtein distance directly. To compute the cosine, and JS divergence, we will first compute the k-mer profiles for each sequence, and then compute the similarity measure based on the profile. To generate the k-mer profiles, we use the suffix array data structure [22].

2) Protein Structure Similarity Matrices: For protein structure, we first covert the protein 3D structure into a protein string (pString) representation following [24]. The resulting pString is then treated like a sequence of information for structure. The only difference with the protein sequence is that each protein structure could have multiple chains(sequences) of information.

We generalized the similarity calculation which will represent the similarity values between two drug active ingredients (DAIs). We already know that each DAI could have multiple protein targets. Also, though each protein target has just one sequence, it could have multiple chains for its 3D structure. Thus, for a given DAI, we capture its protein structure information as follows:

$$[R_1^1, R_2^1...R_{k_1}^1, R_1^2, R_2^2...R_{k_2}^2...R_1^M, R_2^M, ...R_{k_M}^M]$$

where $R_i's$ represent the the protein targets, M denotes the total number of protein targets in the DAI, and $k_1, k_2...k_M$ represent the number of chains on each protein target.

Now, we can use this generalized DAI representation for similarity calculation between two DAI's. If two DAI's have N and M protein targets and their number of chains are $k_1, k_2, ...k_N$ and $L_1, L_2, ...L_M$ respectively, then the possible number of comparisons would be:

$$P_c = k_1 L_1 + k_1 L_2 + ...k_2 L_1 + ... + k_M L_N \qquad (4)$$

After P_c comparisons at the chain level, we will obtain a vector of similarity values for the two DAI's. We use the vector to calculate the minimum, maximum, average and exponential weighted average similarity between the two DAI's. The exponential weighted average is computed as follows:

$$w_i = \frac{e^{s_i}}{\sum_i (e^{s_i})} \qquad (5)$$

Here w_i represents weights and s_i represents a similarity value.

C. Protein Sequence-Structure Similarity Network

Using the protein sequence, and protein structure similarity matrices, we generate protein sequence based,and protein structured based similarity networks using similarity network fusion approach. Each of these networks can be used independently to analyze potential DDIs between drugs or drug active ingredients. To improve the overall performance, we then integrate the sequence-based similarity network with the protein-based network into one overall similarity network. The result is the protein sequence-structure similarity network (PS3N). Our network integration is based on the technique of Similarity Network Fusion(SNF) [21]. SNF is an approach for combining multiple data sources into a single graph representing sample relationships. The k-nearest neighbors approach is used in the similarity network construction and fusion process to down-weight weaker associations between samples. However, weak relationships that are consistent across data sources are retained during the fusion process. The generated integrated network forms the basis for our analysis of adverse drug events, such as drug-drug interactions.

D. Neural Network Model

The model we propose for our problem is entirely reliant on the datasets we're working with. That means the neural network's performance will be influenced by the number of medications used in the dataset. In our neural network model, we used no more than four hidden layers. We use Rectified Linear activation function (ReLU) as the activation function where the dropout rate for each layer would vary from 0.3 to 0.5. Each of the hidden layers is followed by a dropout layer to avoid over-fitting problems during the training of the model. The output of each neuron in a layer is a nonlinear function f of all nodes in the previous layer. f is the ReLU, which is defined as the positive part of its arguments $f(x) = x^* = \max\{x, 0\}$ The final output layer is calculated using the sigmoid function: $Sigmoid(x) = \frac{1}{1+e^{-x}}$

For each layer, we used Xavier weight initialization, batch size of 100, and 20 - 50 epochs, with binary cross-entropy loss and stochastic gradient descent (SGD) for optimization. The momentum parameter was set at 0.9.

E. Performance Evaluation

To evaluate the performance of the proposed method, we compared it with machine learning approaches such as KNN (K Nearest Neighbor), RF (Random Forest), Logistic Regression, LDA (Linear Discriminant Analysis), and Support Vector Machine. We also compared our results with state of the art methods proposed in [20], [10], [13], [23]. We evaluated the competitiveness of our models using different
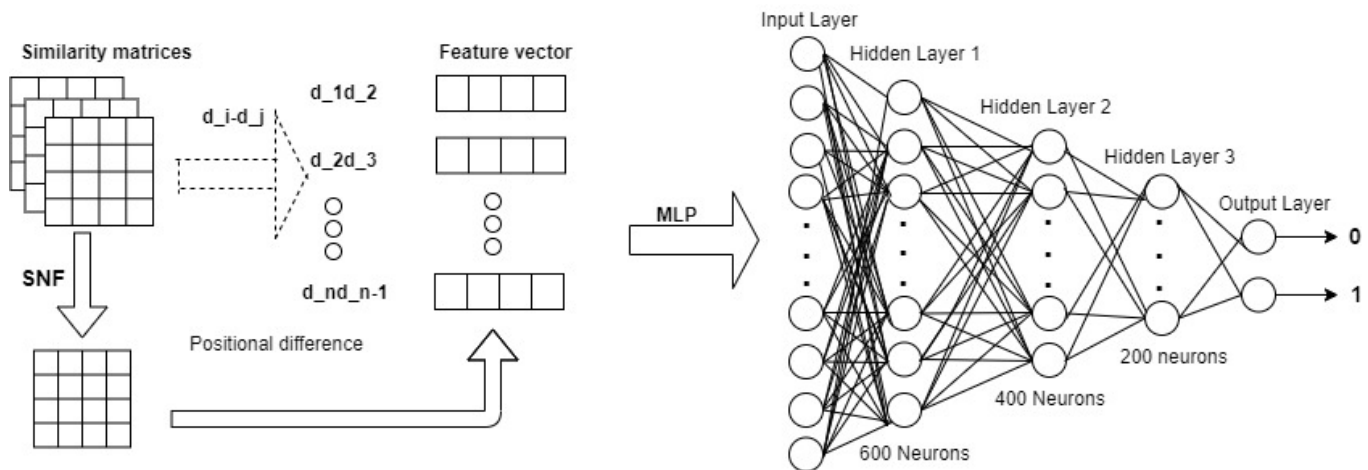
Fig. 1. Proposed Protein Sequence-Structure Similarity Network (PS3N) model for predicting adverse drug events. Using the method of Similarity Network Fusion (SNF) we create a single $N \times N$ fusion matrix for N drugs. From the fusion matrix, we compute the feature vectors for each pair of drugs. In this way we will have possible $\binom{N}{2}$ rows, and each row will have N columns as features. These feature vectors are then fed into a multi-layer perceptron model. For protein sequence similarity network, the number of hidden layers would reduce to 3 since we have less number of drugs.

performance metrics such as Precision, Recall, F1, Area under Curve (AUC), and AUPR.

We note that if the interaction between two drugs is assigned to zero, it simply implies that no evidence of their interaction has been found yet. The two may still interact, but the features we have we have used so far are not able to detect that.

IV. EXPERIMENTS & RESULTS

For our training experiment, we split each dataset into training, validation,and test sets according to a $70\% - 10\% - 20\%$ random split. For each dataset, networks were trained on the training set for a total of 100 epochs with a batch size of 100 for the proposed neural network method.

A. DataSets

In this work, we use two different protein datasets of which one is the protein sequence data with a relationship with drugs. This sequence dataset is extracted from the DrugBank. The second is the protein structure dataset retrieved from RCSB Protein Data Bank (https://www.rcsb.org). Protein chains are extracted from each PDB file using biopython libraries. We combined these for a dataset of 905 drugs (active ingredients) in DrugBank with information on both protein structure and protein sequences. We also evaluated our methods using the DS1 and DS2 datasets reported in [20].

B. Results

First, we evaluated our model on the single feature matrices to identify the contribution of specific features to the performance of the model. We used the average and exponential weighted average similarity measures to generate the similarity matrices. Table I shows the performance of the proposed model using protein sequences. Table II shows results using protein structure.

We then compared our model performance with other state-of-the-art methods using the datasets from Drug Bank and

TABLE I
PERFORMANCE OF PS3N USING SIMILARITY MATRICES BASED ON PROTEIN SEQUENCES

Feature name	Precision	Recall	F-measure	AUC	Accuracy
L AS	0.9199	0.9419	0.9308	0.9673	0.9081
JSD AS	0.8837	0.8667	0.8751	0.9181	0.8377
CS AS	0.8799	0.9093	0.8943	0.9315	0.8590
L EWAS	0.9499	0.9638	0.9568	0.9832	0.9429
JSD EWAS	0.9406	0.8835	0.9112	0.9559	0.8870
CS EWAS	0.9523	0.9632	0.9578	0.9833	0.9443

*L = Levenshtein, JSD = JS Divergence, CS = Cosine, AS = Average Similarity, EWAS = Exponential Weighted Average Similarity

TABLE II
PERFORMANCE OF PS3N USING SIMILARITY MATRICES BASED ON PROTEIN STRUCTURE.

Feature name	Precision	Recall	F-measure	AUC	Accuracy
JSD AS	0.8796	0.9279	0.90313	0.9171	0.8564
CS AS	0.9037	0.9469	0.9248	0.9499	0.8889
JSD EWAS	0.9762	0.9650	0.9706	0.9895	0.9578
CS EWAS	0.9743	0.9738	0.9741	0.9910	0.9627

*L = Levenshtein, JSD = JS Divergence, CS = Cosine, AS = Average Similarity, EWAS = Exponential Weighted Average Similarity

Protein Data Bank. The constructed protein sequence and structure similarity matrices from the datasets we Showed proved a clear performance improvement. Table III shows that our PS3N outperforms the state-of-the-art methods. We also use datasets from [20] to evaluate the competitiveness with other state-of-the-art. However, the Table showed generally improved results for all learning models and the impact of data imbalance is evident, especially considering the recall and F-measures.

In Table IV and V we compare our results with the existing state-of-the-art algorithms and found significant improvements in terms of AUC, Precision, and Recall. We considered DS1 and DS2 datasets from [20] to compare the performance

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Method	Precision	Recall	F-measure	AUC	Accuracy
PS3N	0.9800	0.9818	0.9809	0.9946	0.9725
RF	0.7812	0.7241	0.7516	0.8089	0.8354
SVM	0.5507	0.2076	0.3015	0.5711	0.7320
LR	0.5169	0.1586	0.2427	0.5506	0.7243
LDA	0.5302	0.1740	0.2620	0.5572	0.7269
KNN	0.5470	0.6196	0.5810	0.7107	0.7510
Decision Tree	0.7134	0.7008	0.7071	0.7961	0.8382
NDD	0.5646	0.1927	0.2874	0.7366	0.7311

of existing methodologies. From the two datasets, we could generate the protein sequence and structure metrics for a subset of drugs. We used the newly generated feature space in our model to check the performance and showed significant improvement in both cases. From Table IV, we can see that the PS3N showed better performance when compared to the other methods. However, it showed similar results on the datasets based on sequence, structure, or both information. This also holds in Table V which was created from the DS2 dataset.

C. Impact of algorithmic parameters

Table VI shows the impact of different hyperparameters on the performance of the proposed model. From the table, Adam Optimizer with a learning rate of 0.01 produced the best overall result. SGD Optimizer for learning rate 0.05, 0.01 and 0.10 showed almost similar accuracy level as we got for Adam optimizer. In our proposed neural network model, the number of hidden layers will vary based on the number of drug active ingredients (DAI's) on the datasets. Normally, for protein sequence dataset, it will not more than 4. For Protein structure or the combination of both, it will be between 3 to 5.

V. DISCUSSION

The main objective of this work is to propose a new computational model for DDI prediction utilizing the genetic information about drug protein targets. Our work has given a promising direction for addressing DDI prediction problems. We showed different ways of creating the feature space to identify the interaction between a pair of drugs. Roughly, we identified drugs with information on protein structures, and drugs with information on the protein sequence. We created the labeled feature space by utilizing the interaction information available in DrugBank. The combination of the structure and sequence information resulted in 904 drugs. Unlike previous methodologies, we considered only protein sequence and structure similarity networks for the first time to predict drug interactions. In addition, our similarity network computation technique allows extracting important protein features in terms of different distance measures.

The major drawback of our work is the lack of availability of protein structure level and sequence level information of the same drugs. As we mainly focused on Drugbank and Protein Data Bank (PDB). It was a challenge to find the commonality

between the two different datasets. Moreover, the datasets have significantly more unknown interactions than known interactions. Thus, this creates a problem of data imbalance, especially if we do not consider appropriate thresholds for the unknowns. However, the time and space complexity for feature space generation is significant which will need to be addressed in the future.

VI. CONCLUSION

In this study, we proposed a novel drug-drug interaction detection mechanism. The proposed model is divided into three major chunks. The first is focused on building the similarity profiles from Drug Bank and PDB. The second is the creation of an integrated similarity network (PS3N) about drugs, using information about their protein targets, namely, the protein sequences and protein structures of such targets. The third component is how information from the integrated network is used to develop a deep neural network model for improved prediction of the potential drug interactions. We compare the results produced using the proposed PS3N in a deep learning framework with results from other recent machine learning-based approaches. The comparisons showed that our proposed methodology is quite competitive with respect to the state-of-the-art, at times outperforming the state-of-the-art methods. Though the computational complexity is high for the pre-processing, there are still opportunities to improve the performance of the model and also improve the datasets as well.

In our proposed methodology, we showed a new approach to dealing with the DDI prediction problem, by exploit only genetic information about the drug protein targets, in particular, information about their protein sequence and protein structure. Potential future work will be to study how the general approach could be extended to other adverse drug events, beyond DDIs. Another would be to see if the general approach can be adapted to use other types of feature attributes about the medications, or about interacting drugs.

REFERENCES

[1] Lazarou, J., Pomeranz, B. H. and Corey, P. N. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. Jama 279, 1200–1205 (1998).

[2] Prueksaritanont, T. et al. Drug–drug interaction studies: regulatory guidance and an industry perspective. The AAPS journal 15,629–645 (2013

[3] Kusuhara, H. How far should we go? Perspective of drug-drug interaction studies in drug development. Drug metabolism pharmacokinetics 29, 227–228 (2014).

[4] Wishart, D. S. et al. Drugbank 5.0: a major update to the drugbank database for 2018. Nucleic acids research 46, D1074–D1082 (2017). 740–741, August 1987 [Digests 9th Annual Conf. Magnetics Japan, p. 301, 1982].

[5] Knox, C. et al. Drugbank 3.0: a comprehensive resource for omics research on drugs. Nucleic acids research 39, D1035–D1041 (2010)

TABLE IV

PERFORMANCE COMPARISON OF DIFFERENT METHODS ON DS1 FROM [20]. WE OBTAINED INFORMATION ON 469 DRUGS FOR PROTEIN SEQUENCES, AND ON 414 DRUGS FOR PROTEIN STRUCTURE. THE FIRST SIX ROWS ARE FROM [20] TO COMPARE THE RESULTS FROM OUR MODEL

Method	AUC	AUPR	F-measure	Recall	Precision
Substructure-based label propagation model [13]	0.937	0.901	0.804	0.797	0.811
Side-effect-based label propagation model [13]	0.936	0.903	0.806	0.793	0.820
Offside-effect-based label propagation model [13]	0.937	0.904	0.809	0.795	0.823
Vilar's substructure-based model [10]	0.936	0.902	0.804	0.797	0.812
Classifier ensemble method [23]	0.956	0.928	0.836	0.827	0.843
Weighted average ensemble method [23]	0.948	0.919	0.831	0.835	0.826
NDD [20]	0.954	0.922	0.835	0.836	0.833
PS3N (Protein Sequence)	**0.974**	0.948	0.916	0.925	**0.906**
PS3N (Protein Structure)	0.972	**0.949**	0.917	**0.932**	0.903
PS3N (Sequence + Structure)	0.972	0.948	0.917	0.931	0.903

TABLE V

PERFORMANCE COMPARISON OF DIFFERENT METHODS ON THE DS2 DATASET FROM [20]. WE OBTAINED INFORMATION ON 585 DRUGS FOR PROTEIN SEQUENCES, AND ON 504 DRUGS FOR PROTEIN STRUCTURE. THE FIRST SIX ROWS ARE FROM [20] TO COMPARE THE RESULTS FROM OUR MODEL

Method	AUC	AUPR	F-measure	Recall	Precision
Substructure-based label propagation model [13]	0.788	0.208	0.294	0.537	0.197
Vilar's substructure-based model [10]	0.810	0.244	0.312	0.479	0.232
Classifier ensemble method [23]	0.936	0.487	0.553	0.689	0.462
Weighted average ensemble method [23]	0.646	0.440	0.15	0.226	0.118
NDD [20]	0.994	0.890	0.825	0.804	0.847
PS3N (Protein Sequence)	**0.998**	**0.975**	0.978	0.987	**0.972**
PS3N (Protein Structure)	0.997	**0.975**	0.978	**0.992**	0.964
PS3N (Sequence + Structure)	0.997	0.970	0.977	0.987	0.970

TABLE VI

RESULTS OF PS3N WITH VARIATION ON ALGORITHMIC PARAMETERS.

Optimizer	Learning rate	Accuracy
Adam optimizer	0.05	0.7200
Adam optimizer	0.10	0.7213
Adam optimizer	**0.01**	**0.9710**
SGD	0.05	0.9646
SGD	0.10	0.9644
SGD	0.01	0.9637
RMSProp	0.01	0.7210

[6] Law, V.et al. Drugbank 4.0: shedding new light on drug metabolism. Nucleic acids research 42, D1091–1097 (2013)

[7] Gao H, Korn JM, Ferretti S, Monahan JE, Wang Y, Singh M, Zhang C, Schnell C, Yang G, Zhang Y. High-throughput screening using patient-derived tumor xenografts to predict clinical trial drug response. Nat Med. 2015; 21(11):1318.

[8] Fang H-B, Chen X, Pei X-Y, Grant S, Tan M. Experimental design and statistical analysis for three-drug combination studies. Stat Methods Med Res. 2017;26(3):1261–80.

[9] Gottlieb A, Stein GY, Oron Y, Ruppin E, Sharan R. INDI: a computational framework for inferring drug interactions and their associated recommendations. Mol Syst Biol. 2012;8(1):592.

[10] Vilar S, Uriarte E, Santana L, Tatonetti NP, Friedman C. Detection of drug-drug interactions by modeling interaction profile fingerprints. PLoS One. 2013;8(3):e58321.

[11] Vilar S, Uriarte E, Santana L, Lorberbaum T, Hripcsak G, Friedman C, Tatonetti NP. Similarity-based modeling in large-scale prediction of drug-drug interactions. Nat Protoc. 2014;9(9):2147.

[12] Cheng F, Zhao Z. Machine learning-based prediction of drug–drug interactions by integrating drug phenotypic, therapeutic, chemical, and genomic properties. J Am Med Inform Assoc. 2014;21(e2):e278–86.

[13] Zhang P, Wang F, Hu J, Sorrentino R. Label propagation prediction of drugdrug interactions based on clinical side effects. Sci Rep. 2015;5:12339.

[14] Huang J, Niu C, Green CD, Yang L, Mei H, Han J-DJ. Systematic prediction of pharmacodynamic drug-drug interactions through protein-proteininteraction network. PLoS Comput Biol. 2013;9(3):e1002998.

[15] Park K, Kim D, Ha S, Lee D. Predicting pharmacodynamic drug-drug interactions through signaling propagation interference on protein-protein interaction networks. PLoS One. 2015;10(10):e0140816.

[16] Ryu JY, Kim HU, Lee SY. Deep learning improves prediction of drug–drug and drug–food interactions. Proc Natl Acad Sci. 2018;115(18):E4304–11.

[17] Lü, L., Pan, L., Zhou, T., Zhang, Y.-C. & Stanley, H. E. Toward link predictability of complex networks. Proc. Natl. Acad. Sci. 112, 2325–2330 (2015).

[18] Vilar, S. et al. Drug-drug interaction through molecular structure similarity analysis. J. Am. Med. Informatics Assoc. 19, 1066–1074 (2012).

[19] Geonhee Lee, Chihyun Park and Jaegyoon Ahn. Novel deep learning model for more accurate prediction of drug-drug interaction effects. BMC Bioinformatics(2019) 20:415

[20] Narjes Rohani & Changiz Esahchi. Drug-Drug interaction predicting by neural network Using integrated Similarity. Scientific Reports volume 9, Article number: 13645 (2019).

[21] Wang, B. et al. Similarity network fusion for aggregating data types on a genomic scale. Nat. methods 11, 333 (2014).

[22] Adjeroh Donald, Timothy C.Bell, Amar Mukherjee. The Burrows-Wheeler Transform: Data Compression, Suffix Arrays, and Pattern Matching. Springer, 2008.

[23] Zhang, W. et al. Predicting potential drug-drug interactions by integrating chemical, biological, phenotypic and network data. BMC bioinformatics 18, 18 (2017)

[24] Jun Tan and Donald A. Adjeroh. Protein family structure signature for multidomain proteins. International Journal of data Mining and Bioinformatics 20(4)pages285-302(2018)

[25] A. Abbasi and D. Adjeroh, "Social media analytics for smart health," IEEE Intelligent Systems, 29(2): 60-64, 2014.

[26] D. Adjeroh, R. Beal, A. Abbasi, W. Zheng, A. Abate, and A. Ross. "Signal fusion for social media analysis of adverse drug events," IEEE Intelligent Systems, 29(2): 74-80, 2014.

[27] Faizan A, Abbasi A, Kitchens B, Adjeroh D, and Zeng D, "Deep learning for adverse event detection from web search", IEEE Transactions on Knowledge and Data Engineering (TKDE), Accepted (Aug. 10, 2020), (in press). Published Online Aug 2020.