

Combining Bottom-up and top-down approaches through graph learning over interaction networks for drug-target-interaction prediction

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Approaches on this rather sophisticated problem can be divided into top-down or network approaches (CITATION), and bottom-up or molecular approaches (CITATION). Top-down approaches take advantage of other data such as diseases (CITATION), side effects, knowledge graphs or ontologies, in order to learn representations for both compound and protein. On the other hand, bottom-up aspirations attempt to learn from chemical properties. For drugs, molecular structure (CITATION GraphDTA), molecular fingerprints, similarity to other drugs (See Bioinf Survey), and other molecular features. On the protein side, secondary structure prediction (CITATION), contact prediction (CITATION), or simply convolution over the amino acid sequences served to obtain a feature for the given proteins. However, both kinds contain and share some problems, that are not

solvable within themselves. Thus, bottom-up approaches share the lack of ability to generalize, which we will show in later sections, and usually focus on engineering sophisticated features for the drugs, while neglecting to formulate meaningful features on the protein side. Top-down approaches lack the ability to spot small differences to cope with small differences within the drug structure and rely heavily on given data for the considered drug-target pair. The latter is not suitable for predictions on novel or unseen compounds, as e.g., data on side effects or its impact on diseases is seldom given for novel drugs.

In order to design such a feature for proteins and drugs, respectively, we make use of the interaction networks for both proteins and compounds. Drug-drug interaction networks were introduced and standardized by Ayvaz *et al.* (2015) and have been used for clinical decision support (Scheife *et al.* (2015)). Drug-drug interaction networks may give a hint on common targeted pathways. As an additional compound feature we will use semantic side effect similarity, which we will discuss later on.

Protein-protein interaction networks have shown great results in . . . (Vazquez *et al.* (2003), Ackerman *et al.* (2019)) in granting context for molecular system biology. However, these contexts were never applied to the problem of drug-target-interaction prediction. Thus we formalized our hypotheses over these interaction graphs and will test them in the following chapters.

2 Approach

2.1 Choosing appropriate train-test splits

As shown, recent work lacks the ability to combine both top-down and bottom-up approaches for their predictions, however performing quite well on their datasets. Drug-target interaction prediction is the task to accurately predict whether for a given drug and a given protein there is a biological interaction within humans. However, when building the train-test split over compound-protein pairs for building the actual model, there are the following three options:

1. Build split over drugs
2. Build split over drug-target pairs
3. Build split over proteins

In general, recent works do perform their split over the drugs or drug-target pairs (Wang and Kurgan (2018), CITATION). The first is more relevant for novel drugs, as it is much more likely to test a new compound than a innovative protein. However, it lies in the very nature of the used datasets, making the prediction for new drugs much easier. Thus, drugs are often built by minor variations of existing drugs, thus leading to no deviations in the functional group of that very compound (CITATION/EXAMPLE). When distributed over both train and test split, the models do not perform inductive inference and generalize, but rather implement transductive inference by just predicting the recently seen structures. Hence, when entirely new molecules are seen, the models perform much worse.

The same applies to splits of drug-target pairs, as all drugs were already seen, and novelty cannot be coped with.

As mentioned in the introduction it is quite difficult to learn suitable features from proteins. In general, attempts search for motifs in the protein sequences under usage of convolutional neural networks and filters, which is more suitable for tasks like protein function prediction, than for drug-target interaction prediction, and lack a more in-depth hypothesis on the protein side, while investing in refined drug features.

Thus, building splitting over proteins is the most challenging of the three options.

2.2 Tested hypotheses

In this work we are testing the following hypotheses:

1. Can we build a model that outperforms state of the art approaches, combining top-down and bottom-up approaches?
2. Are interaction networks sufficient to improve the performance of simple molecular predictors?

We will test the first hypothesis by building a model that takes both top-down and bottom-up features into account. Thus, we propose a novel approach to combine those mutual exclusive attempts, through the usage of interaction networks, similarity and molecular features. Additionally, we test the latter by building a simple molecular DTI predictor and enhance it under usage of the interaction networks.

For the bottom-up approach we build a that only relies only on molecular features, which we will discuss in more detail in the following methods chapter. For the combination of both approaches we now attach the predictions to the protein-protein interaction graph as node features for future graph learning steps. In this graph we tried to find both patterns and regions for each drug that could be of interest through application of different graph convolutional layers, which in return represent the feature for each protein. Representing the drug we take the drug-drug interaction graph and the semantic similarity over side effects which we will explain in the following paragraphs.

3 Methods

3.1 Data

The data for the different parts of this model were obtained from different sources. Starting with the protein-protein interactions, we fetched 11.574 proteins with over 170.000 links from STRING (Szklarczyk *et al.* (2014)). As STRING provides statistical scores for each association, we filtered them as advised by a threshold of 700. For the drug-drug interaction we retrieved the drugs from Ayvaz *et al.* (2015). Side effects were obtained from MedDRA database (Mozzicato (2009)) that hierarchically orders side effects. Links between drugs and side effects were fetched from *SIDER* (Kuhn *et al.* (2015)) side effects database. The intersection between these sources yielded 641 common drugs for usage in our data. For the drug-target interactions themselves, we fetched 137.000 links from STITCH database (Szklarczyk *et al.* (2015)). We provide links and methods to and for the necessary data in the provided Github repository.

3.2 Models

The used model consists of two separate models, that help to fuse together the two methods:

1. The molecular predictor
2. The interaction network based predictor

We build the molecular predictor by using pretrained, molecular fingerprints models for both drugs and proteins. Regarding proteins, we used the pretrained feature generator from *DeepGoPlus* ((Kulmanov and Hoehndorf, 2019)) that was originally designed for protein function prediction and is regarded as state of the art for this purpose. For drugs we used a pretrained fingerprint model from SMILES transformer (Honda *et al.* (2019)), that provides a simple and fast method to compute fingerprints through autoencoder models. The encodings from these two models were funneled into a simple deep neural network (see Figure 1) with few fully connected.

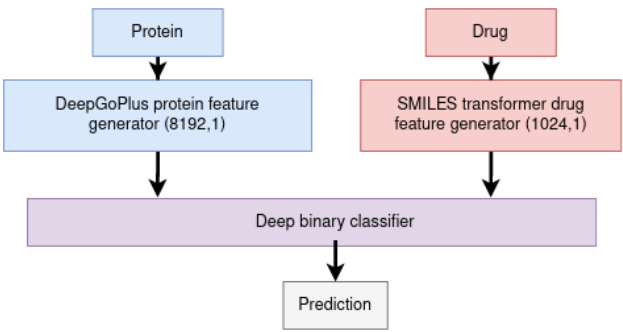


Figure 1. Molecular predictor based on the generated features from DeepGoPlus and SMILES transformer.

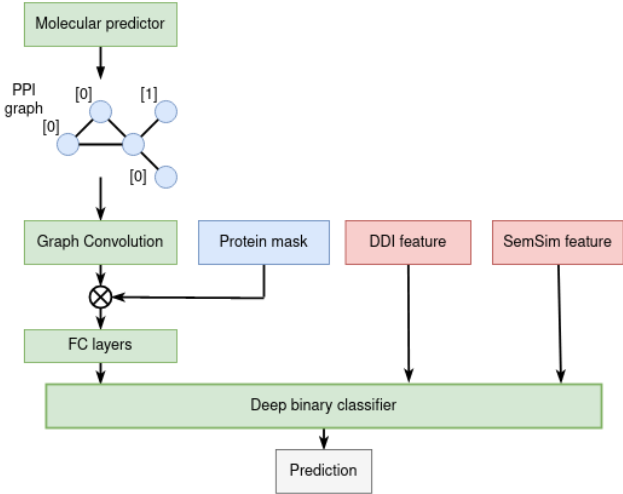


Figure 2. Deep neural network that predicts based on drug-drug interaction features and semantic similarity features over side effects for drugs, and graph convolution over protein-protein interaction networks for proteins. Protein and drug features are represented by blue and red, respectively.

The results of that prediction flow into the annotation of the protein-protein interaction (PPI) graph as depicted in (IMAGE). Hereby, the predictions of the molecular predictor are used as node features for the graph, with respect to the given drug. Thus, given a compound-target pair, the nodes of the PPI graph now hold bottom-up features, which can now be processed by the graph learning algorithms.

The PPI graph is processed by different graph convolutional layers, that may underline the importance of either patterns or regions within the graph, to obtain a feature vector for the wanted node. In contrast to learning over whole graphs we perform node classification within the graph.

The drug-drug interaction features are retrieved by choosing the corresponding row in the adjacency matrix of the graph, thus leading to quite simple features.

For the semantic similarity feature, that once again represents a top-down

attribute, we artificially link each drug to its corresponding side effects in the MedDRA hierarchy. Concerning this hierarchy, drug-drug similarity is computed by the Resnik similarity (Resnik (1995)). For the given compound we take the corresponding row of this symmetric similarity matrix.

Thereby, we concatenate these three features together and funnel them into another deep neural network as depicted in figure 2.

4 Discussion

5 Conclusion
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References

Ackerman, E. E., Alcorn, J. F., Hase, T., and Shoemaker, J. E. (2019). A dual controllability analysis of influenza virus-host protein-protein interaction networks for antiviral drug target discovery. *BMC Bioinformatics*, **20**(1).

Ayvaz, S., Horn, J., Hassanzadeh, O., Zhu, Q., Stan, J., Tatonetti, N. P., Vilar, S., Brochhausen, M., Samwald, M., Rastegar-Mojarad, M., Dumontier, M., and Boyce, R. D. (2015). Toward a complete dataset of drug–drug interaction information from publicly available sources. *Journal of Biomedical Informatics*, **55**, 206–217.

Bianchi, F. M., Grattarola, D., Alippi, C., and Livi, L. (2019). Graph neural networks with convolutional arma filters.

Defferrard, M., Bresson, X., and Vandergheynst, P. (2016). Convolutional neural networks on graphs with fast localized spectral filtering.

Hamilton, W. L., Ying, R., and Leskovec, J. (2017). Inductive representation learning on large graphs.

Honda, S., Shi, S., and Ueda, H. R. (2019). Smiles transformer: Pre-trained molecular fingerprint for low data drug discovery.

Kipf, T. N. and Welling, M. (2016). Semi-supervised classification with graph convolutional networks.

Klicpera, J., Bojchevski, A., and Günnemann, S. (2018). Predict then propagate: Graph neural networks meet personalized pagerank.

Kuhn, M., Letunic, I., Jensen, L. J., and Bork, P. (2015). The SIDER database of drugs and side effects. *Nucleic Acids Research*, **44**(D1), D1075–D1079.

Kulmanov, M. and Hoehndorf, R. (2019). DeepGOPlus: improved protein function prediction from sequence. *Bioinformatics*.

Mozzicato, P. (2009). MedDRA. *Pharmaceutical Medicine*, **23**(2), 65–75.

Resnik, P. (1995). Using information content to evaluate semantic similarity in a taxonomy.

Scheife, R. T., Hines, L. E., Boyce, R. D., Chung, S. P., Momper, J. D., Sommer, C. D., Abernethy, D. R., Horn, J. R., Sklar, S. J., Wong, S. K., Jones, G., Brown, M. L., Grizzle, A. J., Comes, S., Wilkins, T. L., Borst, C., Wittie, M. A., and Malone, D. C. (2015). Consensus recommendations for systematic evaluation of drug–drug interaction evidence for clinical decision support. *Drug Safety*, **38**(2), 197–206.

Szklarczyk, D., Franceschini, A., Wyder, S., Forslund, K., Heller, D., Huerta-Cepas, J., Simonovic, M., Roth, A., Santos, A., Tsafou, K. P., Kuhn, M., Bork, P., Jensen, L. J., and von Mering, C. (2014). STRING v10: protein–protein interaction networks, integrated over the tree of life. *Nucleic Acids Research*, **43**(D1), D447–D452.

Szklarczyk, D., Santos, A., von Mering, C., Jensen, L. J., Bork, P., and Kuhn, M. (2015). STITCH 5: augmenting protein–chemical interaction networks with tissue and affinity data. *Nucleic Acids Research*, **44**(D1), D380–D384.

Vazquez, A., Flammini, A., Maritan, A., and Vespignani, A. (2003). Global protein function prediction from protein-protein interaction networks. *Nature Biotechnology*, **21**(6), 697–700.

Veličković, P., Cucurull, G., Casanova, A., Romero, A., Liò, P., and Bengio, Y. (2017). Graph attention networks.

Wang, C. and Kurgan, L. (2018). Review and comparative assessment of similarity-based methods for prediction of drug–protein interactions in the druggable human proteome. *Briefings in Bioinformatics*, **20**(6), 2066–2087.