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Prediction of drug–target binding affinity using graph neural networks

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Abstract

Background: While the development of new drugs is costly, time consuming, and often accompanied with safety issues, drug repurposing, where old drugs with established safety are used for medical conditions other than originally developed, is an attractive alternative. Then, how the old drugs work on new targets becomes a crucial part of drug repurposing and gains much of interest. Several statistical and machine learning models have been proposed to estimate drug–target binding affinity and deep learning approaches have been shown to be among state-of-the-art methods. However, drugs and targets in these models have been commonly represented in 1D strings, regardless the fact that molecules are by nature formed by the chemical bonding of atoms.

Method: In this work, we propose **GraphDTA** to capture the structural information of drugs, possibly enhancing the predictive power of the affinity. In particular, unlike competing methods, drugs are represented as graphs and graph convolutional networks are used to learn drug–target binding affinity. We trial our method on two benchmark datasets of drug–target binding affinity and compare the performance with state-of-the-art models in the research field.

Results: The results show that our proposed method can not only predict the affinity better than non-deep learning models, but also outperform competing deep learning approaches. This demonstrates the practical advantages of graph-based representation for molecules in providing accurate prediction of drug–target binding affinity. The application may also include any recommendation systems where either or both of the user- and product-like sides can be represented in graphs.

Availability and implementation: The proposed models are implemented in Python. Related data, pre-trained models, and source code are publicly available at https://github.com/thinng/GraphDTA.

Keywords: drug-target binding affinity; graph neural networks; prediction

1 Introduction

It costs 2.6 billion US dollars to develop a *de novo* drug [1] and takes about 10–17 years for the drug to be accepted/rejected by US FDA [2, 3]. Repurposing/repositioning a drug – identifying new use for an existing approved drug [4] – would reduce the time and cost as several phases spent in the development for its original indication could be bypassed [2]. Then, how the old drugs work on new targets – drug-target interaction – becomes an important task for drug repurposing and gains much of interest.

Conventionally, high-throughput screening experiments are used to examine bioactivities between drugs and targets, which lead to a costly and time-consuming

procedure [5, 6]. This is impracticable as there are millions of drug-like compounds [7] and hundreds of potential targets, e.g., 500 protein kinases [8], responsible for the modifications of about 30% of human proteins [9]. Thus, it is an important alternative to use statistical and machine learning models to estimate the strength of the interactions of novel couples of drug-target, based on the interactions already measured in clinical experiments.

Several computational approaches/machine learning methods have been proposed for the purpose [10, 11, 12]. In that trend, deep learning models are among the best performers in the prediction of drug–target binding affinity [13]. However, in these cutting-edge deep learning models, for computing convenience, drugs are represented as strings, which are not a natural representation of compounds, and thus the structural information of molecules is lost.

In this paper we propose **GraphDTA** to predict the drug–target binding affinity. In the model, drugs are represented as graphs where the edges are the bonding of atoms. Then layers of convolutions on graphs of drugs, concatenated with 1D convolution for protein sequences, are together regressed with the affinity of drug-target couples. We test the proposed method on two benchmark datasets and compare the performance with state-of-the-art approaches in the field. The results show that our proposed method gains the best performance in the task of drug–target binding affinity prediction.

2 Related work

2.1 Drug representation

To represent molecules to be readable by computers, SMILES (Simplified Molecular Input Line Entry System) was invented [14], which enables several efficient applications, including fast retrieval and substructure searching. From SMILES codes, drug descriptors, such as the number of heavy atoms or valence electrons, can be inferred and ready to be used as the features to predict the affinity. One can also consider SMILES codes as strings and use natural language processing (NLP) techniques to featurize the drugs. Alternatively, these strings can be seen as in 1D representation, which are input into a convolutional neural network (CNN) to learn a model to predict the affinity. Layers of 1D convolutions and pooling are used to capture hidden patterns in the inputs, which potentially become powerful predictive features of the affinity.

SMILES as graphs SMILES codes can also be converted back to graphs, and then geometric deep learning techniques can be applied in downstream analysis.

The most popular deep learning approaches to graphs, graph convolutional networks (GCNs), can be adopted for the task of drug–target binding affinity prediction. GCNs are a generalization of convolutional neural networks (CNN) to graph-structured data. GCNs can be divided into two main categories: spectral-based and spatial-based approaches. In the spectral-based approaches, graphs are first represented in spectral domain, then convolutional operation is defined in that domain. Spectral-based GCNs were first proposed in [15], extended by [16, 17, 18].

On the contrary, the spatial-based methods perform learning algorithms directly on graph spatial domain. The learning process includes a neighborhood formulation, then the information of a node is updated by aggregating information from

its neighbor nodes, which is called message passing and followed by a sub-sampling task. Compared to the spectral-based methods which handle the whole graph simultaneously, the spatial approaches can instead process graph nodes in batches and thus can be scalable to large graphs. Recent works on this approach include [19, 20, 21, 22, 23, 24].

GCNs have been used in computational drug discovery [25], including interaction prediction, synthesis prediction, *de novo* molecular design, and especially in quantitative structure activity/property relationship prediction [26, 27, 28]. The problem we explore in this paper, prediction of drug–target binding affinity, belongs to the task of interaction prediction, where the interactions could be among drugs, among proteins, or between drugs and proteins. Examples include Decagon [29], where graph convolutions were used to embed the multi-modal graphs of multiple drugs to predict side effects of drug combinations; or AttSemiGAE/AttTransGAE [30], where attentive multi-view graph auto-encoders were used to measure drug similarity. There are also other approaches in dealing with the problem which this work aims to solve, described as follows.

2.2 Prediction of drug–target binding affinity

2.2.1 Affinity similarity (SimBoost)

Apparently the task of drug–target binding affinity prediction could be considered as a collaborative filtering problem (CF). For example, in movie ratings as in the Nexflix competition[1], the rating for a couple of movie-user is learned, or collaboratively filtered, from the ratings by the movies/users similar to the given movie/user. The lesson from Nexflix competition is that if the number of training user-movie ratings is big enough, external information for users or movies does not make significantly contribution to the recommendation systems. However this is not always the case for drug-target binding prediction problem, where the affinity (as ratings in CF) available is often sparse.

The affinity available in training is also used, accompanied with similarities among drugs as well as among targets, to build features in [31] (**SimBoost**). The features are then the input to gradient boosting machines to predict the binding affinity for unknown drug–target couples.

2.2.2 Kernel based (KronRLS)

Alternatively, the similarity could be built from other sources rather than the affinity in training data. For example, in kernel based approaches, as in [32, 33], kernels for drugs and targets are built from their molecular descriptors, input into a regularized least squares regression model (RLS) to predict the binding affinity.

Given the problem is to predict the affinity for n drugs and m targets, there would be $n*m$ combinations of them and the kernel would be in the size of $(n*m)^2$. To speed up model training, Cichonska et al. [32, 33] (**KronRLS**) suggest to use KronRLS (Kronecker regularized least-squares). In KronRLS, a pairwise kernel K is computed as the Kronecker product of compound kernel of size $n*n$ and protein kernel of size $m*m$.

[1]https://www.netflixprize.com/rules.html

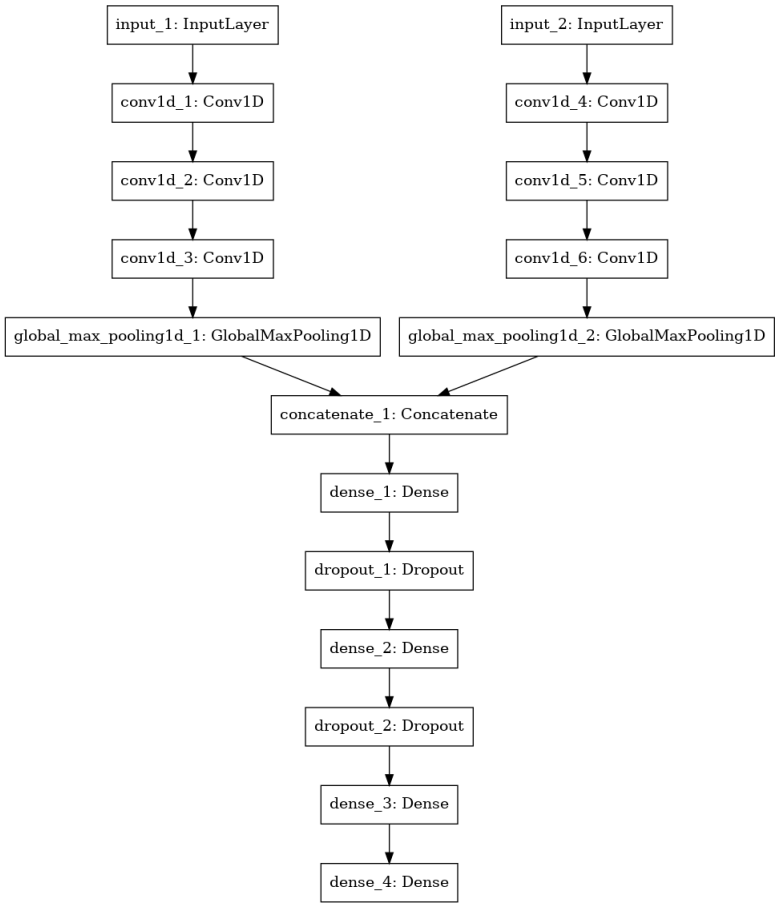

Figure 1 A deep learning model, with drug and targets as strings, to predict the affinity. The strings could be either arrays of characters [36] or arrays of words [36].

To compute the kernels, any similarity measures can be used. For example, in [34], the kernels for drugs were built from Tanimoto-based similarity (*Pubchem-Sim*)[2]; whilst for targets, *Smith-Waterman* score [35] was used as the similarity measure of protein sequences.

2.2.3 Deep learning (DeepDTA & WideDTA)

When 1D representation for drugs (SMILES) and proteins (sequences) is provided, deep learning could be a possible approach to predict the affinity [13] (**DeepDTA**), as shown in Figure 1. In the figure, *input_1* and *input_2* are drugs and targets, respectively. As these are in 1D representation, layers of 1D convolutions and pooling are used to capture potential patterns in the inputs. They are then concatenated, sent through regularized layers of Dropout, and finally regressed with the training affinity.

WideDTA [36] is an extension of DeepDTA [13] where drugs and proteins are represented as words, instead of characters as in DeepDTA. In particular, drugs are described via most common substructures, denoted as Ligand Maximum Common

[2]Provided at http://pubchem.ncbi.nlm.nih.gov

Substructures (LMCS) [37]; and proteins are represented through most conserved sub-sequences, which are Protein Domain profiles or Motifs (PDM), retrieved from PROSITE database [38].

While WideDTA [36] and DeepDTA [13] learned latent feature vectors for the proteins, PADME [39] proposed to use fixed-rule descriptors to represent proteins, such as Protein Sequence Composition (PSC) descriptors [40]. Though, PADME was reported [39] to have similar performance with DeepDTA [13].

3 Proposed method (GraphDTA)

Motivated by bringing nature representation for drugs into modeling of drug-target interaction, we propose a novel deep learning model, **GraphDTA**, for drug-target affinity prediction. Then the DTA prediction problem is cast as a regression task, where the input is a pair of protein and drug representations and the output is a continuous value reflecting the affinity binding score of the pair. In existing methods, the input proteins and drugs are treated as sequence representations. Specifically, drugs are represented as SMILES strings – describing the chemical structure in short ASCII strings; and similarly, protein sequences are represented as strings of ASCII letters, which are the amino acids. Having the inputs as strings of text, one conventional approach is to apply various 1D CNN layers to learn latent features on those sequences, similar to natural language processing techniques. Our approach is different, we instead investigate the use of input compounds' representation in the form of graphs, which are capable of capturing bonds among the atoms.

3.1 Graph representation of drug compounds

The drug compounds can be described as graphs of interactions between atoms. Therefore, handling input compounds in the form of graph representation, and subsequently applying learning algorithms on graphs may fit well the task. To this end, for each input compound string (SMILES), we construct a corresponding molecular graph reflecting interactions between the atoms inside the compound. The graph construction and the process of atom feature extraction are conducted by using the RDKit – an open-source chemical informatics software [41].

To describe a node in the graph, we adopt an atom feature design from DeepChem [42][3]. In details, the node feature vector is constituted of five types of atom features: atom symbol, atom degree – number of bonded neighbors plus number of Hydrogen, total number of Hydrogen, implicit value of atom, and aromatic or not. These atom properties constitute a multi-dimensional binary feature vector.

An edge is set to a pair of atoms if there exists a bond between them. As a result, an indirect, binary graph with attributed nodes is built for each input SMILES string.

3.2 Deep learning on molecular graphs

Having the drug compounds represented in the form of graphs, the problem is to employ an algorithm that enables learning effectively from graph structured data. Recent success of deep convolutional neural networks in computer vision, speech recognition, and natural language processing has led to the idea of extending the

[3]https://github.com/deepchem/deepchem

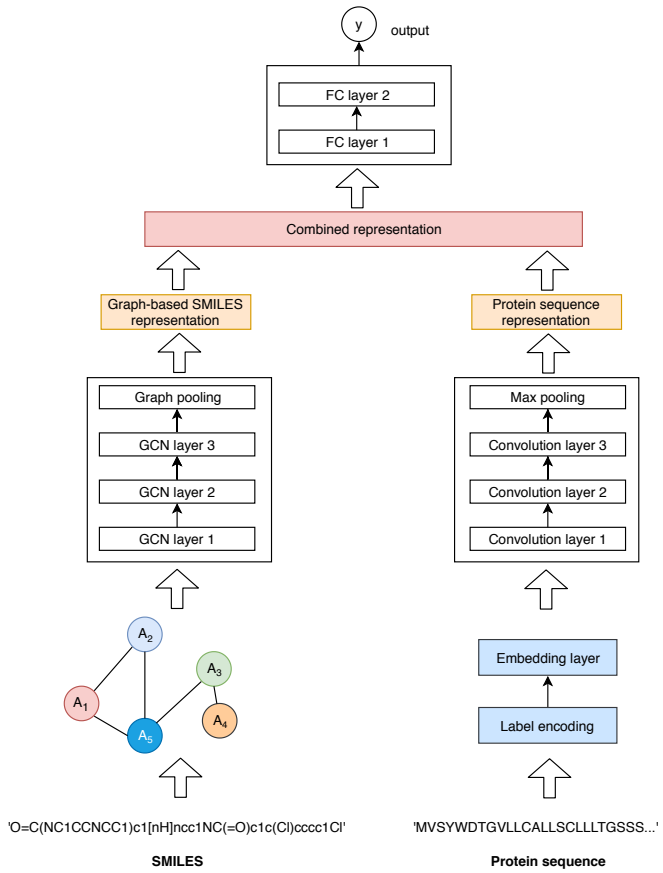

Figure 2 GraphDTA model illustration. Compound SMILES is first converted to a molecular graph, then a deep learning algorithm is adopted on the graph to learn graph representation. Protein sequence is first encoded and embedded, then several 1D CNN layers are applied to learn sequence representation. The two representation vectors are then concatenated and undergo various fully connected layers, ended by a regression layer to estimate the output as the drug-target affinity value.

convolution operation to graph structures. A number of works have been proposed to handle two main challenges of generalizing CNN to graphs, that are, the formation of receptive fields in graphs whose data points are not arranged as Euclidean grids, and the pooling operation to down-sample a graph.

In this work, we propose a new DTA prediction model based on a combination of graph neural network and conventional CNN. As illustrated in Figure 2, our model takes two inputs – SMILES sequences and protein sequences – and feed them -forward in parallel to learn a representation vector for each, then the two latent feature vectors are concatenated and undergo several dense layers, ended by a regression layer to estimate the affinity value.

For protein sequence input, similar to existing methods, our model takes the sequence as a string of ASCII chars and applies several 1D CNN layers over the text to learn a sequence representation vector. More specifically, the protein sequence is first categorically encoded, then an embedding layer is added to the sequence, each (encoded) character is represented by a 128-dimentional vector. Next, three 1D convolutional layers are used to learn different levels of abstract features from

the input. Finally, a max pooling layer is applied to get a representation vector of the input protein sequence.

On the other hand, our model takes the SMILES input as a graph which has been constructed as previously described, then applies a graph convolutional algorithm to learn a representation vector. In order to evaluate the effectiveness of graph-based methods, we investigate several graph neural network models, including GCN [17], GAT [22], GIN [24], and a combined GAT-GCN architecture. The details of each GCN architecture are described as follows.

3.2.1 GCN-based graph representation learning

GCN model [17] was originally designed for the problem of semi-supervised node classification. The model enables to learn hidden layer representations that capture both local graph structures and features of nodes. This fits well our constructed indirect, node attributed graphs. Formally, denote a graph for a given drug as $G = (V, E)$, where V is the set of N nodes each represented by a F-dimentional vector and E is the set of edges represented as an adjacency matrix A. The GCN layer is defined by [17] as

$$\tilde{D}^{-\frac{1}{2}}\tilde{A}\tilde{D}^{-\frac{1}{2}}X\Theta \tag{1}$$

where $\tilde{A}$ is the graph adjacency matrix with added self loop, $\tilde{D}$ is the graph diagonal degree matrix, X is the node feature matrix, and Θ is the trainable parameter matrix.

To make the GCN applicable to the task of learning a representation vector of the whole graph, we add a global max pooling layer right after the last GCN layer. In our GCN-based model, we use three consecutive GCN layers each is activated by a ReLU function. Then a global max pooling layer is added to aggregate the whole graph representation.

3.2.2 GAT-based graph representation learning

We adopt graph attention network (**GAT**) [22] in our model. Unlike graph convolution techniques, this method proposes an attention-based architecture to learn hidden representations of nodes in a graph by applying a self-attention mechanism. The building block of a GAT architecture is a *graph attention layer*. The GAT layer takes the set of nodes of a graph, the node feature vector $\mathbf{x}$, as input, applies a linear transformation to every node by a weigh matrix $\mathbf{W}$. At the input node i in the graph, the *attention coefficients* between i and its first-order neighbors are computed as

$$a(\mathbf{W}\mathbf{x}_i, \mathbf{W}\mathbf{x}_j) \tag{2}$$

This value indicates the importance of node j to node i. These *attention coefficients* are then normalized by applying a soft-max function, then used to compute the output features for nodes as

$$\sigma(\sum_{j\in\mathcal{N}(i)} \alpha_{ij}\mathbf{W}\mathbf{x}_j) \tag{3}$$

Method	Protein rep.	Compound rep.	CI	MSE
Baseline models				
DeepDTA [13]	Smith-Waterman	Pubchem-Sim	0.790	0.608
DeepDTA [13]	Smith-Waterman	1D	*0.886*	0.420
DeepDTA [13]	1D	Pubchem-Sim	0.835	0.419
KronRLS [32, 33]	Smith-Waterman	Pubchem-Sim	0.871	0.379
SimBoost [31]	Smith-Waterman	Pubchem-Sim	0.872	0.282
DeepDTA [13]	1D	1D	0.878	*0.261*
WideDTA [36]	1D + PDM	1D + LMCS	*0.886*	0.262
Proposed method - **GraphDTA**				
GCN	1D	Graph	0.880	**0.254**
GAT_GCN	1D	Graph	0.881	**0.245**
GAT	1D	Graph	**0.892**	**0.232**
GIN	1D	Graph	**0.893**	**0.229**

Table 1 Prediction performance on Davis dataset, sorted by MSE. Baseline results are from [13, 36]. Proposed graph-based method is tested with different graph neural networks: GIN [24], GAT [22], GCN [17], and combined GAT-GCN [22, 17]. Italics: best for baseline models, bold: better than baselines.

where $\sigma(.)$ is a non-linear activation function and α_{ij} are the normalized *attention coefficients*.

In our model, the GAT-based graph learning architecture includes two GAT layers, activated by a ReLU function, then followed a global max pooling layer to obtain graph representation vector. In details, for the first GAT layer, *multi-head-attentions* are applied with the number of heads is set to 10, and the number of output features are set identical with the number of input features. The number of output features of the second GAT are set to 128.

3.2.3 Graph Isomorphism Network

We integrate a recently proposed graph learning method, namely Graph Isomorphism Network (**GIN**) [24]. This model is theoretically proven that it achieves maximum discriminative power among GNNs [24]. Specifically, GIN uses a multi-layer perceptron (MLP) model to update the node features as

$$MLP((1+\epsilon)\mathbf{x}_i + \sum_{j \in B(i)} \mathbf{x}_i) \tag{4}$$

where ϵ is either a learnable parameter or a fixed scalar, $\mathbf{x}$ is the node feature vector, and $B(i)$ is the set of nodes neighbor to i.

In our model, the GIN-based graph neural net consists of five GIN layers, each is followed by a batch normalization layer. Finally, a global max pooling layer is added to aggregate a graph representation vector.

3.2.4 GAT-GCN combined graph neural network

We investigate a combination of **GAT-GCN** [22, 17] for learning on graphs in our proposed GraphDTA model. In detail, the graph neural network starts by a GAT layer which takes graphs as input and returns the convolved feature matrix to a GCN layer. Each layer is activated by a ReLU function. The graph representation vector is then computed by concatenating the global max pooling and global mean pooling layers from GCN layer output.

Method	Protein rep.	Compound rep.	CI	MSE
Baseline models				
DeepDTA [13]	1D	Pubchem-Sim	0.718	0.571
DeepDTA [13]	Smith-Waterman	Pubchem-Sim	0.710	0.502
KronRLS [32, 33]	Smith-Waterman	Pubchem-Sim	0.782	0.411
SimBoost [31]	Smith-Waterman	Pubchem-Sim	0.836	0.222
DeepDTA [13]	Smith-Waterman	1D	0.854	0.204
DeepDTA [13]	1D	1D	0.863	0.194
WideDTA [36]	1D + PDM	1D + LMCS	*0.875*	*0.179*
Proposed method - **GraphDTA**				
GAT	1D	Graph	0.866	0.179
GIN	1D	Graph	**0.882**	**0.147**
GCN	1D	Graph	**0.889**	**0.139**
GAT_GCN	1D	Graph	**0.891**	**0.139**

Table 2 Prediction performance on Kiba dataset, sorted by MSE. Baseline results are from [13, 36]. Proposed graph-based method is tested with different graph neural networks: GIN [24], GAT [22], GCN [17], and combined GAT-GCN [22, 17]. Italics: best for baseline models, bold: better than baselines.

4 Experiments and Results

4.1 Experimental setting

To compare with the state of the art performers DeepDTA [13] and WideDTA [36], we ran our proposed method on the same datasets used in these works. In particular, two datasets were used to evaluate the models:

- **Davis** dataset: contains binding affinities observed for all pairs of 72 drugs and 442 targets, measured by Kd value (kinase dissociation constant) [43]. The affinity value ranges from 5.0 to 10.8.

- **Kiba** dataset: contains binding affinities for 2,116 drugs and 229 targets [44]. The affinity value ranges from 0.0 to 17.2.

For these two datasets, same train/test splits with [13] (DeepDTA) and [36] (WideDTA) were used in the experiments, making the comparison as fair as possible. That is, 80% of data instances were used for training and 20% were for testing the models. For the same purpose, same measures used in [13, 36] were also employed to evaluate the performance of all the methods: Mean Square Error (MSE, the smaller the better) and Concordance Index (CI, the larger the better). For DeepDTA [13], WideDTA [36] and all the referenced methods, reported results in relevant papers were shown.

4.2 Results and Discussion

Tables 1&2 present the performance, in MSE or CI measures, for different approaches to predict the affinity for Davis and Kiba datasets.

For Davis dataset (Table 1), the best MSE for baseline is *0.261*, gained by DeepDTA [13], when both drugs and proteins are represented as 1D strings. In comparison, all of our proposed graph convolution models achieved better MSE. The best MSE our methods gained is **0.229**, a reduction of **12.3%** over the best baselines.

Meanwhile, on CI measure, there is a slight improvement by the proposed methods. In details, the best CI a baselines could achieve is *0.886*, by DeepDTA [13], when drugs are represented as 1D strings and proteins in Smith-Waterman, and by WideDTA [36], when the both parties are presented as 'words'. In comparison, two graph-based methods, GAT and GIN outperformed the best baselines in CI measures, at **0.892** and **0.893**, respectively.

Similar performance is observed for Kiba dataset (Table 2). In particular, WideDTA [36] is the best baseline in both measures, CI, at *0.875*, and MSE, at *0.179*, when both drugs and proteins are represented as 'words'. In comparison, three of our four proposed models outperformed the best baseline in both of MSE and CI measures. Noticeably, the best MSE the proposed methods gained is **0.139**, a reduction of **22.3%** over the best baseline. Whilst, on CI measure, the proposed methods achieved **0.891**, versus *0.875* by the best baseline, which is not a substantial gain.

Of all the graph convolution models experimented, GIN [24] outperformed the best baselines in both the datasets and both the performance measures. This shows the potential of GIN in graph discrimination/representation, partly supporting the claim in [24] that Graph Isomorphism Network (GIN) is among most powerful GNNs.

5 Conclusion

In this work, we propose a novel method for estimating drug–target binding affinity, called GraphDTA, which represents drugs as graphs. Using deep convolution networks on graphs of drugs, we show that GraphDTA can not only predict the affinity of drugs–targets better than non-deep learning models, but also outperform competing deep learning methods. In particular, GraphDTA performs consistently well across two separate benchmark databases in all the evaluation measures. The result suggests that representing molecules as graphs can improve the performance considerably. Also, it confirms that deep learning models are appropriate for drug–target binding affinity problems. In addition to tackling drug–target binding affinity problems, our method could be applied to any collaborating filtering problems / recommendation systems where either or both of user- or product-like sides can be represented in graph structures.

Ethics approval and consent to participate
Not applicable.

Consent to publish
Not applicable.

Availability of data and materials
GraphDTA is implemented in Python. Related data, pre-trained models, and source code are publicly available at https://github.com/thinng/GraphDTA.

Competing interests
The authors declare that they have no competing interests.

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Author's contributions
TN and SV conceived the idea of this work. TN, HL, TL, SV refined the idea. TN, HL designed and performed the experiments. TN, HL, TL drafted the manuscript. All authors revised, read and approved the manuscript.

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