Predicting drug–target binding affinity with graph neural networks

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Abstract

Background: The development of new drugs is costly, time consuming, and often accompanied with safety issues. Drug repurposing can avoid the expensive and lengthy process of drug development by finding new uses for already approved drugs. In order to repurpose drugs effectively, it is useful to know which proteins are targeted by which drugs. Computational models that estimate the interaction strength of new drug–target pairs have the potential to expedite drug repurposing. Several models have been proposed for this task. However, these models represent the drugs as strings, which are not a natural way to represent molecules.

Methods: We propose a new model called **GraphDTA** that represents drugs as graphs and uses graph neural networks to predict drug–target affinity. We test 4 graph neural network variants, including GCN, GAT, GIN, and a combined GAT-GCN architecture, for the task of drug–affinity prediction. We benchmark the performance of these models on the Davis and Kiba datasets.

Results: We show that graph neural networks not only predict drug–target affinity better than non-deep learning models, but also outperform competing deep learning methods. Of note, the GIN method performs consistently well for two separate benchmark datasets and for two key performance metrics. In a post-hoc analysis of our model, we find that a graph neural network can learn the importance of known molecular descriptors without any prior knowledge. We also examine the model's performance and find that a handful of drugs contribute disproportionately to the total prediction error.

Conclusions: Our results confirm that deep learning models are appropriate for drug–target binding affinity prediction, and that representing drugs as graphs can lead to further improvements. Although we focus on drug–target affinity prediction, our **GraphDTA** model is a generic solution for any collaborating filtering or recommendation problem where either data input can be represented as a graph.

1 Background

It costs about 2.6 billion US dollars to develop a new drug [1], and can take up to 10–17 years for FDA approval [2, 3]. Finding new uses for already approved drugs avoids the expensive and lengthy process of drug development [2, 4]. In order to repurpose drugs effectively, it is useful to know which proteins are targeted by which drugs. High-throughput screening experiments are used to examine the affinity of a drug toward its targets; however, these experiments are costly and time-consuming [5, 6], and an exhaustive search is infeasible because there are millions of drug-like compounds [7] and hundreds of potential targets [8, 9]. As such, there is a strong motivation to build computational models that can estimate the interaction strength of new drug–target pairs based on previous drug–target experiments.

Several computational approaches have been proposed for drug–target affinity (**DTA**) prediction [10, 11, 12]. One approach uses collaborative filtering. For example, the **SimBoost** model uses the affinity similarities among drugs and among targets to build new features. These features are then used as input in a gradient boosting machine to predict the binding affinity for unknown drug–target pairs [13]. Alternatively, the similarities could come from others sources (rather than the training data affinities). For example, kernel-based methods use kernels built from molecular descriptors of the drugs and targets within a regularized least squares regression (RLS) framework [14, 15]. To speed up model training, the **KronRLS** model computes a pairwise kernel K from the Kronecker product of the drug-by-drug and protein-by-protein kernels [14, 15] (for which any similarity measure can be used).

Another approach uses neural networks trained on 1D representations of the drug and protein sequences. For example, the **DeepDTA** model uses 1D representations and layers of 1D convolutions (with pooling) to capture predictive patterns within the data [16]. The final convolution layers are then concatenated, passed through a number of hidden layers, and regressed with the drug–target affinity scores. The **WideDTA** model is an extension of **DeepDTA** in which the sequences of the drugs and proteins are first summarized as higher-order features [17]. For example, the drugs are represented by the most common sub-structures (the Ligand Maximum Common Substructures (LMCS) [18]), while the proteins are represented by the most conserved sub-sequences (the Protein Domain profiles or Motifs (PDM) from PROSITE [19]). While **WideDTA** [17] and **DeepDTA** [16] learn a latent feature vector for each protein, the **PADME** model [20] uses fixed-rule descriptors to represent proteins, and performs similarly to **DeepDTA** [16].

The deep learning models are among the best performers in DTA prediction [16]. However, these models represent the drugs as strings, which are not a natural way to represent molecules. When using strings, the structural information of the molecule is lost, which could impair the predictive power of a model as well as the functional relevance of the learned latent space. Already, graph convolutional networks have been used in computational drug discovery, including interaction prediction, synthesis prediction, *de novo* molecular design, and quantitative structure prediction [21, 22, 23, 24]. However, graph neural networks have not been used for DTA prediction.

In this article, we propose **GraphDTA**, a new neural network architecture capable of directly modelling drugs as molecular graphs, and show that this approach outperforms state-of-the-art deep learning models on two drug–target affinity prediction benchmarks. In order to better understand how the graphical model works, we perform an analysis of the model's latent space and find that our graph neural network automatically assigned importance to well-defined chemical features, such as the number of aliphatic OH groups, without any prior knowledge. We also examine the model's performance and find that a handful of drugs contribute disproportionately to the total prediction error, and that these drugs are inliers (i.e., not outliers) in an ordination of the model's latent space. Taken together, our results suggest that graph neural networks are highly accurate, abstract meaningful concepts, and yet fail in predictable ways. We conclude with a discussion about how these insights can feedback into the research cycle.

2 Methods

2.1 Overview of GraphDTA

We propose a novel deep learning model called **GraphDTA** for drug–target affinity (**DTA**) prediction. We frame the DTA prediction problem as a regression task where the input is a drug–target pair and the output is a continuous measurement of binding affinity for that pair. Existing methods represent the input drugs and proteins as 1D sequences. Our approach is different; we represent the drugs as molecular graphs so that the model can directly capture the bonds among atoms.

2.2 Graph representation of drug compounds

2.3 Drug representation

SMILES (Simplified Molecular Input Line Entry System) was invented to represent molecules to be readable by computers [25], enabling several efficient applications, including fast retrieval and substructure searching. From the SMILES code, drug descriptors like the number of heavy atoms or valence electrons can be inferred and readily used as features for affinity prediction. One could also view the SMILES code as a string. Then, one could featurize the strings with natural language processing (NLP) techniques, or use them directly in a convolutional neural network (CNN).

Instead, we view drug compounds as a graph of the interactions between atoms, and build our model around this conceptualization. To describe a node in the graph, we use a set of atomic features adapted from **DeepChem** [26]. Here, each node is a multi-dimensional binary feature vector expressing five pieces of information: the atom symbol, the number of adjacent atoms, the number of adjacent hydrogens, the implicit value of the atom, and whether the atom is in an aromatic structure [26]. We convert the SMILES code to its corresponding molecular graph and extract atomic features using the open-source chemical informatics software **RDKit** [27].

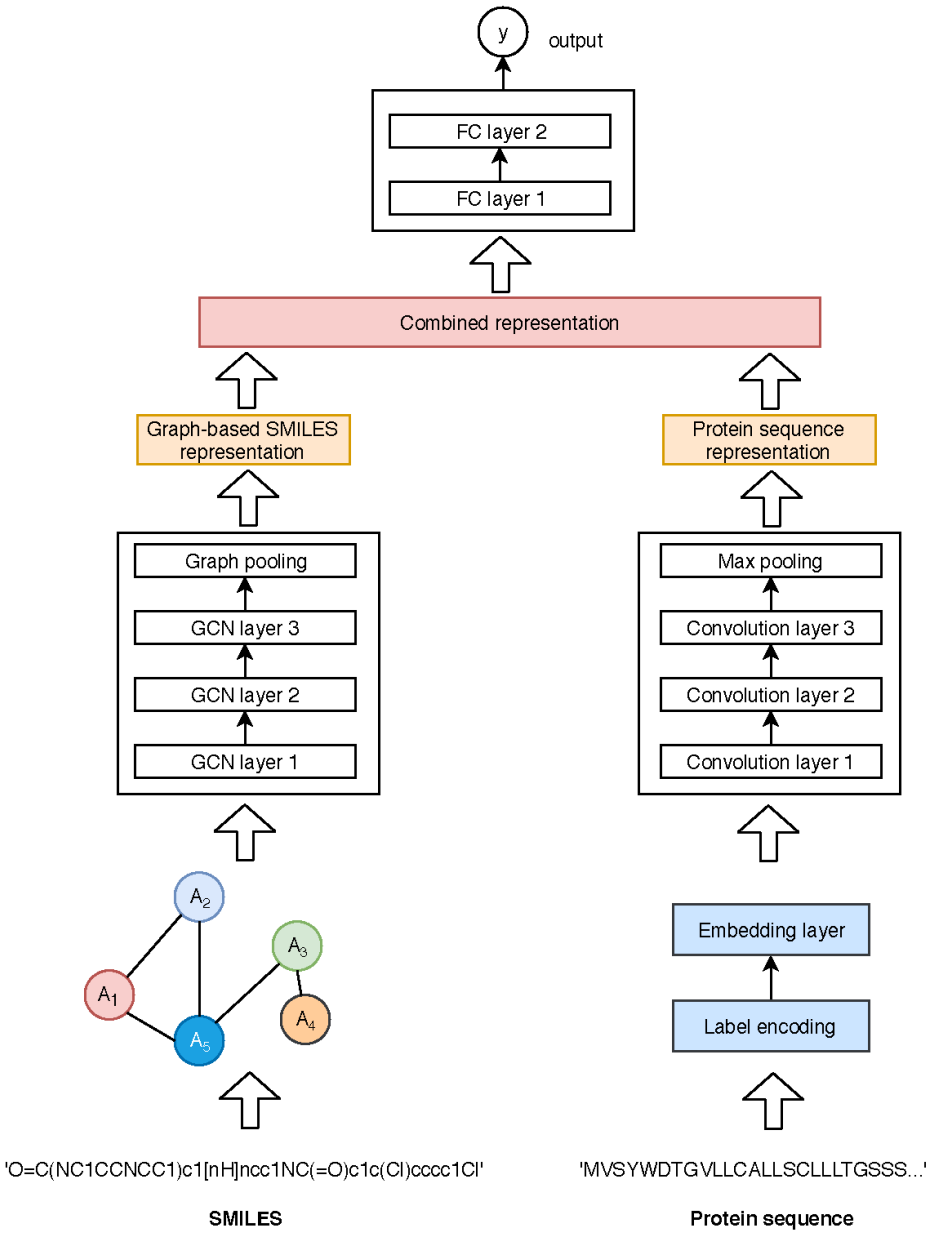

Figure 1: This figure shows the **GraphDTA** architecture. It takes a drug–target pair as the input data, and the pair's affinity as the output data. It works in 3 stages. First, the SMILES code of a drug is converted into a molecular graph, and a deep learning algorithm learns a graph representation. Meanwhile, the protein sequence is encoded and embedded, and several 1D convolutional layers learn a sequence representation. Finally, the two representation vectors are concatenated and passed through several fully connected layers to estimate the output drug–target affinity value.

2.4 Deep learning on molecular graphs

Having the drug compounds represented as graphs, the task now is to design an algorithm that learns effectively from graphical data. The recent success of CNN in computer vision, speech recognition, and natural language processing has encouraged research into graph convolution. A number of works have been proposed to handle two main challenges in generalizing CNN to graphs: (1) the formation of receptive fields in graphs whose data points are not arranged as Euclidean grids, and (2) the pooling operation to down-sample a graph. These new models are called graph neural networks.

In this work, we propose a new DTA prediction model based on a combination of graph neural networks and conventional CNN. Figure 1 shows a schematic of the model. For the proteins, we use a string of ASCII characters and apply several 1D CNN layers over the text to learn a sequence representation vector. Specifically, the protein sequence is first categorically encoded, then an embedding layer is added to the sequence where each (encoded) character is represented by a 128-dimensional 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. This approach is similar to the existing baseline models. For the drugs, we use the molecular graphs and trial 4 graph neural network variants, including GCN [28], GAT [29], GIN [30], and a combined GAT-GCN architecture, all of which we describe below.

2.4.1 Variant 1: GCN-based graph representation learning

The graph convolutional network (**GCN**) model [28] was originally designed for the problem of semi-supervised node classification. This model is able to learn hidden layer representations that capture both the local graph structures and the features of nodes. Formally, we denote a graph for a given drug as $G = (V, E)$, where V is the set of N nodes each is represented by a F-dimensional vector and E is the set of edges represented as an adjacency matrix A. The GCN layer is defined 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 activated by a ReLU function. Then a global max pooling layer is added to obtain the graph representation vector.

2.4.2 Variant 2: GAT-based graph representation learning

Unlike graph convolution, the graph attention network (**GAT**) [29] 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 as input, and applies a linear transformation to every node by a weigh matrix $\mathbf{W}$. For each 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

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

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 the graph representation vector. For the first GAT layer, *multi-head-attentions* are applied with the number of heads set to 10, and the number of output features set to the number of input features. The number of output features of the second GAT is set to 128.

Method	Protein rep.	Compound rep.	CI	MSE
Baseline models				
DeepDTA [16]	Smith-Waterman	Pubchem-Sim	0.790	0.608
DeepDTA [16]	Smith-Waterman	1D	*0.886*	0.420
DeepDTA [16]	1D	Pubchem-Sim	0.835	0.419
KronRLS [14, 15]	Smith-Waterman	Pubchem-Sim	0.871	0.379
SimBoost [13]	Smith-Waterman	Pubchem-Sim	0.872	0.282
DeepDTA [16]	1D	1D	0.878	*0.261*
WideDTA [17]	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 the Davis dataset, sorted by MSE. Baseline results are from [16, 17]. We compare 4 graph neural network variants: GIN [30], GAT [29], GCN [28], and combined GAT-GCN [29, 28]. Italics: best for baseline models, bold: better than baselines.

Method	Protein rep.	Compound rep.	CI	MSE
Baseline models				
DeepDTA [16]	1D	Pubchem-Sim	0.718	0.571
DeepDTA [16]	Smith-Waterman	Pubchem-Sim	0.710	0.502
KronRLS [14, 15]	Smith-Waterman	Pubchem-Sim	0.782	0.411
SimBoost [13]	Smith-Waterman	Pubchem-Sim	0.836	0.222
DeepDTA [16]	Smith-Waterman	1D	0.854	0.204
DeepDTA [16]	1D	1D	0.863	0.194
WideDTA [17]	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 the Kiba dataset, sorted by MSE. Baseline results are from [16, 17]. We compare 4 graph neural network variants: GIN [30], GAT [29], GCN [28], and combined GAT-GCN [29, 28]. Italics: best for baseline models, bold: better than baselines.

2.4.3 Variant 3: Graph Isomorphism Network (GIN)

The graph isomorphism network (**GIN**) [30] is newer method that supposedly achieves maximum discriminative power among graph neural networks. 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 neighboring *i*.

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

2.4.4 Variant 4: GAT-GCN combined graph neural network

We also investigate a combined **GAT-GCN** model. Here, the graph neural network begins with a GAT layer that takes the graph as input, then passes a convolved feature matrix to the subsequent GCN layer. Each layer is activated by a ReLU function. The final graph representation vector is then computed by concatenating the global max pooling and global mean pooling layers from the GCN layer output.

2.5 Benchmark

To compare our model with the state-of-the-art **DeepDTA** [16] and **WideDTA** [17] models, we use the same 2 datasets from the [16, 17] benchmarks:

- **Davis** contains the binding affinities for all pairs of 72 drugs and 442 targets, measured as K_d constants and ranging from 5.0 to 10.8 [31].
- **Kiba** contains the binding affinities for 2,116 drugs and 229 targets, measured as KIBA scores and ranging from 0.0 to 17.2 [32].

To make the comparison as fair as possible, we use the exact same train/test data splits from [16, 17] (i.e., 80% used for training and 20% for testing), as well as the same performance metrics: Mean Square Error (**MSE**, the smaller the better) and Concordance Index (**CI**, the larger the better). For all baseline methods, we report the performance metrics as originally published in [16, 17].

2.6 Model interpretation

The activation of nodes within layers of a deep neural network are called latent variables, and can be analyzed directly to understand how a model's performance relates to domain knowledge [33]. We obtained the 128 latent variables from the graph neural network layer, and analyzed them directly through a redundancy analysis. This multivariable statistical method allows us to measure the percent of the total variance within the latent variables that can be explained by an external data source. In our case, the external data source is a matrix of 38 molecular JoeLib features/descriptors [34] for each drug (available from ChemMine Tools [35]).

We also compare the value of the principal components from these latent variables with the per-drug test set error. Here, the per-drug (or per-protein) error refers to the median of the absolute error between the predicted DTA and the ground-truth DTA for all test set pairs containing that drug (or that protein). For these analyses, we focus on the GIN model [30] (because of its superior performance) and the Kiba dataset [32] (because of its larger drug catalog).

3 Results and Discussion

3.1 Graphical models outperform the state-of-the-art

Table 1 compares the performance of 4 variant **GraphDTA** models with the existing baseline models for the Davis dataset. Here, all 4 variants had the lowest MSE. The best variant had an MSE of 0.229 which is 12.3% lower than the best baseline of 0.261. The improvement is less obvious according to the CI metric, where only 2 of the 4 variants had the highest CI. The best CI for a baseline model was 0.886. By comparison, the GAT and GIN models achieved a CI of 0.892 and 0.893, respectively.

Table 2 compares the performance of the **GraphDTA** models with the existing baseline models for the Kiba dataset. Here, 3 of the 4 variants had the lowest MSE and the highest CI, including GIN, GCN, and GAT-GCN. Of note, the best MSE here is 0.139, which is 22.3% lower than the best baseline. Of all variants tested, GIN is the only one that had the best performance for both datasets and for both performance measures. For this reason, we focus on the GIN in all post-hoc analyses.

3.2 Graphical models discover known drug properties

A graph neural network works by abstracting the molecular graph of each drug into a new feature vector of *latent variables*. In our model, there are 128 latent variables which together characterise the structural properties of the drug. Since the latent variables are learned during the DTA prediction task, we assume that they represent graphical features that contribute meaningfully to DTA.

Unfortunately, it is not straightforward to determine the molecular sub-structures to which each latent variable corresponds. However, we can regress the learned latent space with a matrix of known molecular descriptors to look for overlap. Figure 2 shows a redundancy analysis of the 128 latent variables regressed with 38 molecular descriptors [34] (available from ChemMine Tools [35]). From this, we find that 20.19% of the latent space is explained by the known descriptors, with the "Number of aliphatic OH groups" contributing most to the explained variance. Indeed, two latent variables correlate strongly with this descriptor: hidden nodes V58 and V14 both tend to have high activation when the number of aliphatic OH groups is

large. This finding provides some insight into how the graphical model might "see" the drugs as a set of molecular sub-structures, though most of the latent space is orthogonal to the known molecular descriptors.

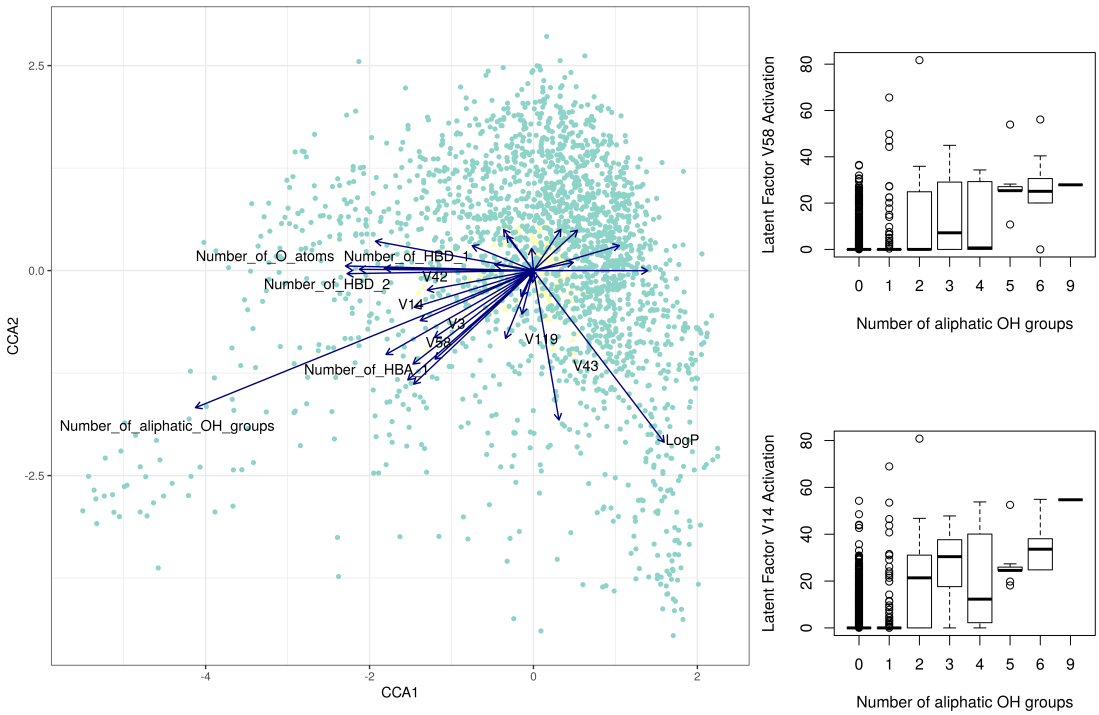

Figure 2: The left panel of the figure shows a redundancy analysis triplot for the 128 drug latent variables regressed with 38 JoeLib molecular descriptors [34]. The blue dots represent drugs, the yellow dots represent latent variables (with the top 6 labelled explicitly), and the arrows represent molecular descriptors (with the top 5 labelled explicitly). The right panel of the figure shows the activation of two latent variables plotted against the number of aliphatic OH groups in that drug. These results suggest that the graph convolutional network can abstract known molecular descriptors without any prior knowledge.

3.3 A few drugs contribute disproportionately to total error

Although the **GraphDTA** model outperforms its competitors, we wanted to know more about why its predictions sometimes failed. For this, we averaged the prediction error for each drug (and each protein), for both the Davis and Kiba test sets. Figures 3 and 4 show the median of the absolute error (MAE) for affinity prediction, sorted from smallest to largest. Interestingly, we see that a handful of drugs (and a handful of proteins) contribute disproportionately to the overall error. Of note, CHEMBL1779202 (an ALK inhibitor), CHEMBL1765740 (a PDK1 inhibitor) and the protein CSNK1E all had an MAE above 2.

We examined the latent space with regard to the prediction error, but could not find any obvious pattern that separated hard-to-predict drugs from easy-to-predict drugs. The only trend we could find is that the easy-to-predict drugs are more likely to appear as outliers in a PCA of the latent space. Supplemental Figure 6 shows the median errors plotted against the first 6 principal components, where we see that the hard-to-predict drugs usually appear close to the origin. We interpret this to mean that drugs with unique molecular sub-structures are always easy to predict. On the other hand, the hard-to-predict drugs tend to lack unique structures, though this is apparently true for many easy-to-predict drugs too.

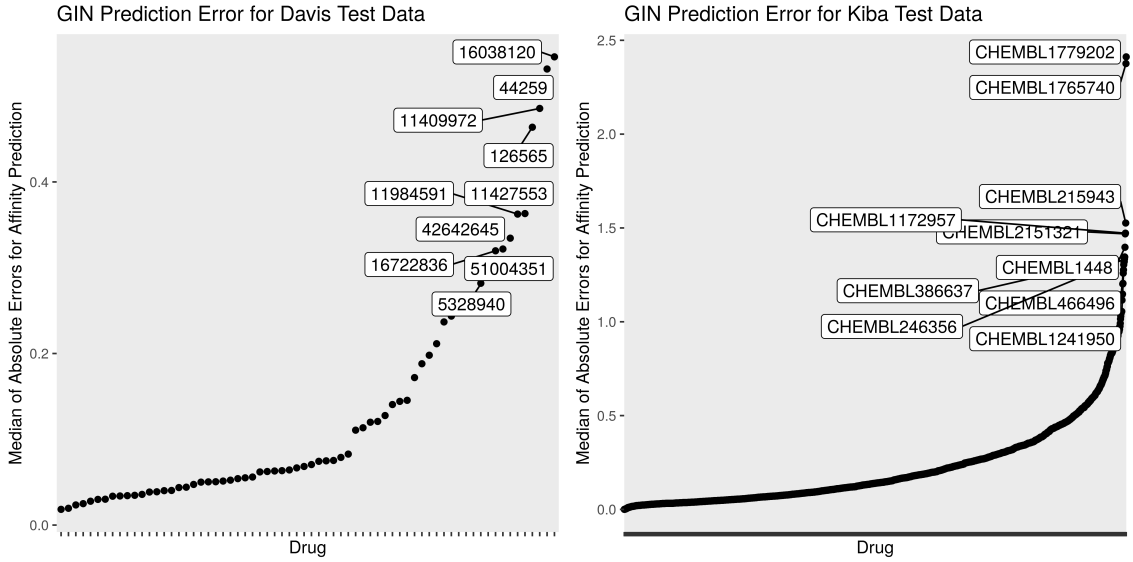

Figure 3: This figure shows the median of the absolute error for each drug, sorted in increasing order, for the Davis and Kiba test sets. Here, we see that the errors are not distributed evenly across the drugs. It is harder to predict the target affinities for some drugs than others.

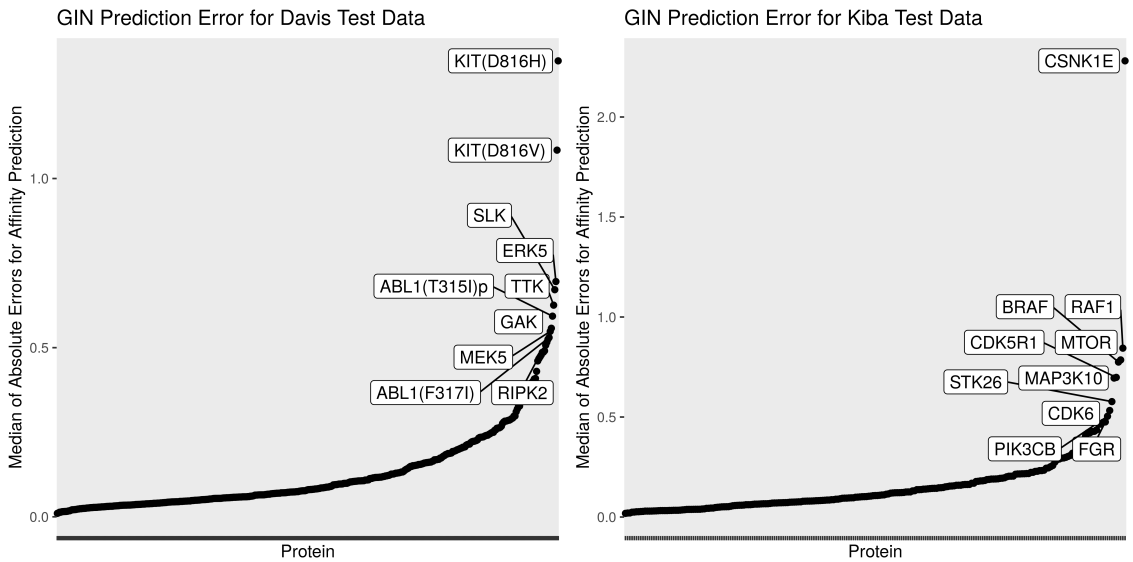

Figure 4: This figure shows the median of the absolute error for each protein, sorted in increasing order, for the Davis and Kiba test sets. Here, we see that the errors are not distributed evenly across the proteins. It is harder to predict the target affinities for some proteins than others.

3.4 Model interpretation and the research cycle

Knowing how a model works and when a model fails can feedback into the research cycle. In the post-hoc analysis of our model, we find that a graph neural network can learn the importance of known molecular descriptors without any prior knowledge. However, most of the learned latent variables remain unexplained by the available descriptors. Yet, the model's performance implies that these learned representations are *useful* in affinity prediction. This suggests that there are both similarities and differences in how machines "see" chemicals versus how human experts see them. Understanding this distinction may further improve model performance or reveal new mechanisms behind drug–target interactions.

Meanwhile, the distribution of the test set errors suggest that there are "problem drugs" (and "problem proteins") for which prediction is especially difficult. One could action this insight either by collecting more training data for these drugs (or proteins), or by using domain-knowledge to engineer features that

complement the molecular graphs. Indeed, knowing that the PCA outliers are the easiest to predict suggests that some additional feature input may be needed to differentiate between drugs that lack distinct molecular sub-graphs. Although 2D graphs contain more information than 1D strings, our model still neglects the stereochemistry of the molecules. Future experiments could test whether representing drugs in 3D (or proteins in 2D) further improves model performance.

4 Summary

In this work, we propose a novel method for estimating drug–target binding affinity, called **GraphDTA**. We show that graph neural networks not only predict drug–target affinity better than non-deep learning models, but also outperform competing deep learning methods. In particular, the GIN method performs consistently well for two separate benchmark datasets and for two key performance metrics. Our results confirm that deep learning models are appropriate for drug–target binding affinity prediction, and that representing drugs as graphs can lead to further improvements. Although we focus on drug–target affinity prediction, our **GraphDTA** model is a generic solution for any collaborating filtering or recommendation problem where either data input can be represented as a graph.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publish

Not applicable.

Availability of data and materials

The proposed models are implemented in Python. Related data, pre-trained models, and source code are publicly available at https://github.com/thinng/GraphDTA. All scripts and data needed to reproduce the post-hoc analysis are available from https://doi.org/10.5281/zenodo.3603523.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Author's contributions

TN, SV conceived the idea of this work. TN, HL, TL, SV refined the idea. TN, HL designed and performed the experiments. TPQ interpreted the model. TN, HL, TPQ, TL drafted the manuscript. All authors revised the manuscript and approved the final version.

Acknowledgements

Not applicable.

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Supplemental Figures

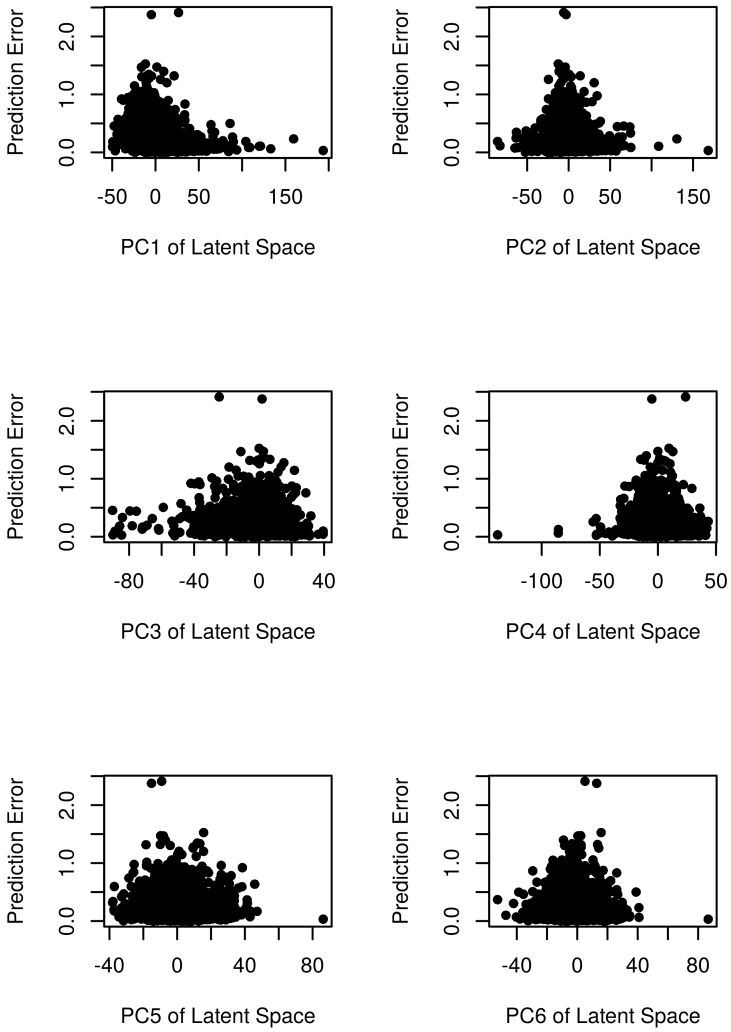

Figure 5: This figure shows the per-drug median errors plotted against the first 6 principal components, where we see that the hard-to-predict drugs usually appear close to the origin. We interpret this to mean that drugs with unique molecular sub-structures are always easy to predict.