

System Biology

SG-DTA: Stacked Graph Drug-Target binding Affinity prediction

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Abstract

Motivation: The development of new pharmaceuticals is expensive, time-consuming, and sometimes fraught with safety concerns. By identifying new uses for existing authorized pharmaceuticals, medication repurposing can circumvent the costly and time-consuming process of drug development. To efficiently repurpose pharmaceuticals, it is necessary to understand which proteins are targeted by specific medications. Computational models that predict the intensity of interactions between novel drug–target pairings have the potential to accelerate drug repurposing. For this goal, several models have been presented with various types of input, from the sequences of string to graphs. Previous papers agreed that using graphs will increase the accuracy due to the detail feature extracted from the input. In this paper, we propose the Stacked Graph DTA (SG-DTA) that not only pushes the use of graph methods to the limit when using the stacking of both graph-representation and node-representation but also renders the higher accuracy compared with the base model. Our result demonstrates that using graph embedding of input will be better than any other input representation, specifically in the DTA task.

Results: We provide an end-to-end pair-wise input neural network, Stacked Graph Drug-Target Affinity (SG-DTA) algorithm, to leverage the relationship between drug and target. Our method achieves the remarkable result on both Davis and Kiba dataset when compares with the state-of-the-art methods. Moreover, the features generated from our method include the information of each neighbor and make a strong assumption that many drug’s effects on a target might have relevant information and vice versa.

Availability: Source code is available at <https://github.com/CuongVoThanh/SGDTI>

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1 Introduction

As all of us know, the process of developing a new drug is time-consuming, this is more than ten years from target identification to drug approval (Rifaoglu *et al.*, 2019), and it costs billions of US Dollars (Mullard, 2014). Clearly, we need to compress the time as every problem in biomedical becomes more complex with high intensity as in the moment, for example, the COVID-19 pandemic.

Fortunately, the exploding digitization of data, which can be retrieved from a variety of sources ranging from clinical pharmacology to cheminformatics-driven databases, has reshaped biomedical discovery. This “big data” approach has been accelerating the process of new research as well as improving and filling the gap that the previous study could not

solve. Based on these advances, lots of methods have been studied in order to quicken the progress of drug development, such as de novo drug design and drug repurposing, etc.

At the moment, several computational techniques for drug-protein affinity prediction have been developed such as molecular docking method, non-parametric machine learning algorithms such as Random Forest (Ballester and Mitchell, 2010; Li *et al.*, 2015; Shar *et al.*, 2016), etc. In addition, collaborative filtering is another approach, the affinity similarities between medicines and targets might be attributed to other sources, for example, the Kernel-based techniques employ kernels constructed from molecular descriptors of medicines and targets inside a regularized least squares regression (RLS) framework (Cichonska *et al.*, 2017, 2018). The KronRLS model computes a pairwise kernel K from the Kronecker product of the drug-by-drug and protein-by-protein kernels to accelerate model

training (Cichonska *et al.*, 2017, 2018). However, these methods have some disadvantages on the input or features selection. Specifically, although the molecular docking technique is instructive, it requires information and concrete knowledge of the crystalline structure of proteins, which may not be available. Or in the Random Forest algorithm, features such as atom-pair co-occurrence oversimplified the description of the protein–ligand complex and resulted in the loss of information (Öztürk *et al.*, 2018).

Along with the explosion of data, deep learning step by step became a popular architecture recently, supported by high-capacity computing devices that challenged existing machine learning approaches. Deep learning methods are currently being used extensively in many other research fields, including bioinformatics such as genomics studies (K.K.Leung *et al.*, 2014; Y.Xiong *et al.*, 2015) and quantitative structure-activity relationship (QSAR) studies in drug discovery, inspired by the remarkable success rate in image processing and speech recognition (Ma *et al.*, 2015). The main advantage of deep learning architectures is that they offer improved representations of raw data through non-linear modifications in each layer (LeCun *et al.*, 2015), making it easier to understand the underlying patterns in the data. A few researches have previously been conducted utilizing Deep Neural Networks (DNN) for DTI binary class prediction utilizing multiple input models for proteins and medicines, in addition to some researches that use stacked auto-encoders (Wang *et al.*, 2018) and deep-belief networks (Wen *et al.*, 2017). Similarly, stacked auto-encoder models incorporating Recurrent Neural Networks (RNNs) and Convolutional Neural Networks (CNNs) were used to describe chemical and genomic structures in real-valued vector forms (Gómez-Bombarelli *et al.*, 2018; Jastrzębski *et al.*, 2016). Deep learning algorithms have also been applied to protein-ligand interaction scores, with CNNs learning from the 3D structures of protein-ligand complexes being a frequent use (Gomes *et al.*, 2017; Ragoza *et al.*, 2017; Wallach *et al.*, 2015). This technique, however, is confined to known protein-ligand complex structures, with only 25000 ligands described in PDB (W.Rose *et al.*, 2016).

Another method is to train neural networks on 1D representations of drug and protein sequences. For example, the DeepDTA model captures predictive patterns in data using 1D representations and layers of 1D convolutions with pooling (Öztürk *et al.*, 2018). The final convolution layers are then concatenated, processed through many hidden layers, and regressed with drug–target affinity ratings. The WideDTA model is an expansion of the DeepDTA model in which the drug and protein sequences are first summarized as higher-order characteristics (Öztürk *et al.*, 2019). Drugs, for example, are represented by the most common sub-structures (the Ligand Maximum Common Substructures (LMCS) (Woźniak *et al.*, 2018), whereas proteins are represented by the most conserved sub-sequences (the Protein Domain profiles or Motifs (PDM) from PROSITE (J.A.Sigrist *et al.*, 2009)). The conducting of a latent feature vector for each protein is . While WideDTA (Öztürk *et al.*, 2019) and DeepDTA (Öztürk *et al.*, 2018) develop a latent feature vector for each protein, the PADME model (Feng *et al.*, 2018) represents proteins using fixed-rule descriptors and outperforms DeepDTA (Öztürk *et al.*, 2018).

However, the 1D representation has its own disadvantage when it might lead to the loss of information about ligand and protein structure. Besides, the traditional alignment between these two objects would not depict in the right way how molecules and protein are combined. Previously, Thin *et al.* (Nguyen *et al.*, 2020a) improved the 1D input of the drug by embedding the SMILES structure into the graph, then learning the molecule’s features using the graph-embedding method. By using this way, the characteristic of the drug will not be lost when aligning the drug structure matrix with the learned feature of the embedded protein. The model might not be stable for further use because the 1D protein is kept for later fusion between them. Some other approaches such as the early fusion of the GEFA architecture (Nguyen *et al.*, 2020b), tried to fill the gaps of target representation by using

the 2D protein contact maps then pushing the combination of embedding features and the maps to the layers of GCN for extracting the protein characteristic before aligning to the given molecules. Compared to the GraphDTA, it seems to have better intuition and the way proteins are represented, but it cannot maintain the accuracy of the task (on CI measure metric).

In this paper, we proposed an upgrade version by exploiting the better use of graph representation for increasing the accuracy of the previous model GraphDTA by Thin *et al.* (Nguyen *et al.*, 2020a), meanwhile maintaining the dynamic of any combination drug-protein. As compared with the base model, our architecture has already outperformed due to the combination method. Instead of the traditional alignment, we propose the extension of node-embedding to capture as much as possible the characteristics of the connection between molecule and protein target. In the next section, we discuss the data representation as well as the model architectures and their complements that will be implemented. The third section is our experiment on parameter setting, model training and evaluation metrics. In the fourth section, the model result and comparison will be discussed.

To summarize, our main contributions in this work are:

- We propose an end-to-end SG-DTA method on drug-target affinity tasks. SG-DTA exposes the relationship between drug and target. While previous methods (Öztürk *et al.*, 2018; Nguyen *et al.*, 2020a,b; Jiang *et al.*, 2020; Nguyen *et al.*, 2021) apply only to combine features.
- Our method yields better accurate predictions. We compare the performance against several previous state-of-the-art methods (Jiang *et al.*, 2020). SG-DTA considerably outperforms those methods.
- We public an open-source code for SG-DTA, which is easy to custom and flexible design. Our implementation and data are publicly available at <https://github.com/CuongVoThanh/SGDTI>.

2 Background on Graph Neural Networks

Graph Neural Networks (GNNs) is one of the most powerful frameworks for representation learning of graphs. Graphs could both learn the elements of a system and their relationship through a set of nodes and edges. The features output of GNNs methods aggregates by the neighbors of this element. It turns out to be dependencies across instances and beyond the independent and identically distributed assumption. Let $\mathcal{G} = (\mathcal{V}, \mathcal{A}, \mathcal{X})$ is represented as a graph in common where \mathcal{V} is a set of N nodes concerning node feature vectors $\mathcal{X}_v \in \mathbb{R}^{N \times D}$ (D is the dimension of features each node) and adjacency matrix \mathcal{A} indicates the connection of nodes in the graph. Learning a representation vector of a node v or the entire graph \mathcal{G} can be utilized the graph structure and node features \mathcal{X}_v in GNNs. Following a neighborhood aggregation strategy, the information of a node is iteratively updated in several steps. Assume that we choose l iterations to aggregate information, a node’s representation captures the l -hop network neighborhood structural information. There are several ways to exploit and aggregate the relationship between each node. In this work, we briefly introduce four regular mechanisms in graph research as follows.

2.1 Graph Convolution Neural Network

Graph Convolution Neural Network (GCN) was first proposed in (Kipf and Welling, 2017), which endeavors to mimic the convolution network scheme in the Computer Vision area. All of the neighbors and themselves are aggregated and combined as the formula below.

$$h_v^{(l+1)} = \sigma(W \cdot \text{Mean}(h_u^{(l)}, \forall u \in N(v) \cup \{v\})). \quad (1)$$

where σ is any non-linear activation function, such as the *ReLU* while W is the trainable weight matrix. Concretely, in the first step we initialize

$h_v^{(0)} = \mathcal{X}_v$. Then, k-hop layer-wise convolution operation is established as follows

$$H^{(l+1)} = \sigma(\tilde{D}^{-\frac{1}{2}} \tilde{\mathcal{A}} \tilde{D}^{-\frac{1}{2}} H^{(l)} W^{(l)}). \quad (2)$$

The term $\tilde{D}^{-\frac{1}{2}} \tilde{\mathcal{A}} \tilde{D}^{-\frac{1}{2}}$ is completely equivalent to *Mean* aggregation method (Eq. 2) between neighbors and itself where $\tilde{\mathcal{A}} = \mathcal{A} + I_N$ is the adjacency matrix \mathcal{A} of bi-directed graph \mathcal{G} with self-connection identity matrix I_N . $\tilde{D}_{ii} = \sum_j \tilde{\mathcal{A}}_{ij}$ is the degree matrix of \mathcal{A} . Finally, the encoding node embedding feature is the last layer-wise: $Z = H^L$ where L is the number of layers of the model. However, the limitation of this approach is based on the assumption that equal importance of self-connections vs edges to neighboring nodes while it is not true for graphs when there are relationships that are more important than others.

2.2 Graph Attention Network

Attention mechanisms (Bahdanau *et al.*, 2015) have become the most successful standard in both Computer Vision and Nature Language Processing fields. When an attention mechanism utilizes to compute a representation of data (such as an image or a sequence), it is usually known as self-attention or intra-attention. Self-attention is not only useful for learning sentence representations (Lin *et al.*, 2017; Vaswani *et al.*, 2017) or learning image representations (Dosovitskiy *et al.*, 2020) but also for learning graph representation (Veličković *et al.*, 2018). The main factor that makes GAT more outstanding than previous approaches is that not all node’s neighbors are equally important. That leads to a change of Eq. 1 a new formula.

$$h_v^{(l+1)} = \sigma\left(\sum_{u \in N(v)} \alpha_{vu} W^{(l+1)} h_u^{(l)}\right). \quad (3)$$

In terms of attention α_{vu} , concentrates on the important parts of the input data and fades out the rest. When explicitly defining $\alpha_{vu} = \frac{1}{|N(v)|}$, all neighbors $u \in N(v)$ are equally important to node v . We need a new implicitly definition for α_{vu} (such as a neural network) to specify arbitrary importance to different neighbors. A weight matrix $W \in \mathbb{R}^{D' \times D}$ is applied to every node to extract high-level features of node input features. Then an attention mechanism functions a (such as a neural network) maps $\mathbb{R}^{D' \times D'} \mapsto \mathbb{R}$ shows the importance of node u to node v .

$$e_{vu} = a(W^{(l)} h_u^{(l-1)}, W^{(l)} h_v^{(l-1)}) \quad (4)$$

The attention coefficients e_{vu} give exact information about the first-order neighbors of v (including v). Then a soft-max normalization is applied to e_{vu} to convert the value to the probability of the importance between u and v .

$$\alpha_{vu} = \text{softmax}_u(e_{vu}) = \frac{\exp(e_{vu})}{\sum_{k \in N(v)} \exp(e_{vk})} \quad (5)$$

Finally, the final representation vector is the output vector after stacked k-hop layers $Z = H^L$ (Eq. 3).

Furthermore, multi-head attention (Vaswani *et al.*, 2017) could also apply to stabilize the learning process of self-attention. To put it simply, multi-head attention computes K independent attention mechanisms (Eq. 3) and aggregates *AGG* all the features by concatenation or summation methods, as the following formula:

$$h_v^{(l+1)} = \text{AGG}_{k=1}^K \left(\sigma \left(\sum_{u \in N(v)} \alpha_{vu} W^{(l+1)} h_u^{(l)} \right) \right). \quad (6)$$

2.3 Graph Isomorphism Network

However, the above techniques have a drawback that relates to the isomorphism property of the graph. For example, suppose two

Table 1. Summary of the datasets

	Proteins	Compounds	Interactions
Kiba	229	2 111	118 254
Davis (K_d)	442	68	30 056

graphs have a distinct structure like a rectangle and a triangle. The disadvantage is shown clearly that the aggregation information of a node is indistinguishable because there are only two connections to that node. Though, they should be embedded in the different vectors in space. The earlier method to tackle this issue is Weisfeiler-Lehman (WL) hashing (Shervashidze *et al.*, 2011). WL test is effective and computationally efficient to distinguish two topologically identical graphs. Recently, a noticeably more powerful algorithm is Graph Isomorphism Network (GIN) (Xu *et al.*, 2019). The advantage of GIN is low-dimensional node embedding and the parameters of the update function which can be learned for the downstream tasks. In order to maximize the discrimination among non-isomorphism graphs, GIN utilizes a multi-layer perceptron (MLP) to learn the difference and update the node features.

$$h_v^{(l+1)} = \text{MLP}^{(l+1)} \left((1 + \epsilon^{(l+1)}) h_v^{(l)} + \sum_{u \in N(v)} h_u^{(l)} \right). \quad (7)$$

where ϵ can be a learnable parameter or fixed scalar. GIN can model injective multi-set functions. Until now, GIN is the most expressive GNN model.

3 Materials and Methods

3.1 Data Description

This work reused the two popular datasets that have been leveraged by lots of previous working papers, specifically the Davis dataset (Mindy I Davis *et al.*, 2011) and the Kiba dataset (Tang *et al.*, 2014). These two datasets are also known as the benchmark dataset for binding affinity prediction and evaluation. For the main purpose of taking advantage of graph representation, SMILES and Protein Sequence will be used to build up the relevant graphs and used as the input for the training process.

The Davis dataset includes selectivity assays for the kinase protein family and their inhibitors, as well as their affinities observed between them which are measured by the dissociation constant (Kd) values. It consists of 442 protein interactions and 68 ligand interactions. The Kiba dataset, on the other hand, was created using a method known as Kiba, which included kinase inhibitor bioactivities from several sources such as Ki, Kd, and IC50. By employing the statistical information included in Kiba scores, the consistency between Ki, Kd, and IC50 was optimized. Originally, the Kiba dataset has 467 targets and 52 498 medicines. The information of datasets that we employed in our study is summarized in Table 1.

Besides, instead of using the original dissociation constant (Kd) values in the Davis dataset, we use the log-transformed version as in the study of He *et al.*, 2017a

$$pK_d = \log_{10} \left(\frac{k_d}{1e9} \right) \quad (8)$$

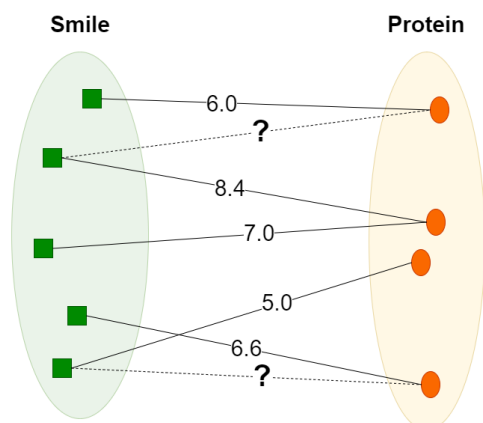


Fig. 1. Figure of Drug-Target Bipolar Graph. Drug and protein target interaction chart. The label on the edge is the binding force of the drug and the protein target.

3.2 Model Architectures

In this section, we describe in detail the end-to-end architecture of the SG-DTA model. The goal of our work is to learn by exploring the relationship between drug and target to improve the performance of the task. We will demonstrate the benefits of our work in section 5.1.

The general setting of the SG-DTA model to predict the binding affinity between the target protein P and drug compound D depicts the entire SG-DTA architecture as the function mapping f in Figure 2. Let y be the affinity score showing how the strength of the binding force, function f maps the input vector P and D to y with parameter θ , which formulates as the equation below:

$$y = f_{\theta}(D, P) \quad (9)$$

In section 2, we introduced the overview of various well-known Graph Neural Network algorithms. We also discussed the pros and cons of distinct methods. In the two sections 3.2.1 and 3.2.2, we briefly present the mechanism to represent drug and protein features into the vector space relied on in section 2. And the last section, we explain details of the SG-DTA architecture model and also give the flexible setting for it.

3.2.1 Representation of Drug

The drug input of our model is in the Simplified Input Line Entry System format (SMILES) (Weininger, 1988) as a standard format of 1D drug’s structure in much recent research (Öztürk et al., 2018, 2019; Nguyen et al., 2020a; Zhao et al., 2019). We encode the molecular structure of the drug into vector representation of the drug via the **RDKit** tool. To make it more concrete, the drug SMILES D is a sequence of atoms, atoms degrees, and ligands between each atom (e.g. CC(C)SC1=NN=C(C=C1)NN). The SMILES string is converted into a molecular graph by **RDKit**. In a single molecular graph, vertices are the atoms of a compound while edges are the bond connecting between atoms. The node feature after encoding comprises of five properties: atom elements, the degree of the atom in the molecule, which is the number of directly-bonded neighbors (atoms), the total number of H bonds to the atom, the number of implicit H bound to the atom and whether the atom is aromatic. The adjacency list of edges is the undirected graph describing the bonds between two atoms. After pre-processing, a drug compound data can be referred to as $\mathcal{G}_D = (\mathcal{V}_D, \mathcal{A}_D, \mathcal{X}_D)$, where $\mathcal{V}_D \in \mathbb{R}^{nd}$ is a set of N nodes of the graph, nd is the size of D and $\mathcal{A}_D \in \mathbb{R}^{nd \times nd}$ denotes the bond adjacency list. Belong to the nodes, a feature node matrix $\mathcal{X}_D \in \mathbb{R}^{nd \times n}$ is also essential for learning representation of drug where n is the dimensions of

compound properties. Finally, we can leverage one of the methods (we denote GNN represents for graph layer) which is mentioned in section 2 or mixed between GAT (2.2) and GCN (2.1). A layer embedding can establish as following.

$$h_v^{(l+1)} = GNN(\mathcal{G}_D(\mathcal{V}_D, \mathcal{A}_D, \mathcal{X}_D)). \quad (10)$$

The graph representation can achieve by a *READOUT* function. A *READOUT* function is utilized in the last layer to aggregate all information to global features.

$$Z_d = READOUT(\{h_v^{(L)} | v \in \mathcal{G}_D\}). \quad (11)$$

READOUT can be any function such as *GlobalMaxPooling*, *GlobalMeanPooling* (Murphy et al., 2018; Ying et al., 2018).

3.2.2 Representation of Protein

On the other hand, the protein P is a sequence of amino acids. The sequence contains many ASCII characters and alphabet symbols associated with each amino acid type. We can capture the primary structure of the protein as previous approach (Öztürk et al., 2018). This approach digitizes the protein sequence by one-hot encoding. The advantage of this approach is the low time complexity when embedding residues into a vector space. Vector encoded $P \in \mathbb{R}^{np \times m}$ where np is the sequence length after cutting or padding and e is then embedded via an embedding layer as the formula.

$$X_P = Embedding(P). \quad (12)$$

The output of the embedding operation is $X_P \in \mathbb{R}^{np \times e}$ and expresses information through some LSTM or Conv1D layers. By doing so, however, the output representation just simply covers the primary structure but not the tertiary structure. In addition, the similarity between elements is not concretely defined and this choice of representation fails to leverage the contextual dependencies between residues (Nguyen et al., 2020b). To overcome this limitation, DGraphDTA (Jiang et al., 2020) constructs the tertiary structure gives critical information in terms of drug-target interaction. By constructing 2D structure of protein via a contact map, we could gain more information about protein in the real world. The protein sequence is converted into a protein graph by **Pconsc4** (Michel et al., 2019). The output of **Pconsc4** is the probability of whether the residue pair contacts. The adjacency matrix $\mathcal{A}_P \in \mathbb{R}^{nd \times nd}$ is created by the output of **Pconsc4** with a threshold. Also, the node feature consists of those properties: residue symbol, position-specific scoring matrix (PSSM), residue weight, hydrophobicity of residue, whether the residue is aliphatic, aromatic, polar neutral, acidic charged or basic charged and the dissociation constant for the $-COOH$ group, $-NH_3$ group and any other group in the molecule. Subsequently, a protein can be presented as $\mathcal{G}_P = (\mathcal{V}_P, \mathcal{A}_P, \mathcal{X}_P)$, where $\mathcal{V}_P \in \mathbb{R}^{np}$ is a set of amino acids of a protein sequence, \mathcal{A}_P is the residues adjacency matrix and a feature node $\mathcal{X}_P \in \mathbb{R}^{nd \times m}$ can enhance the learning capability where m is the dimension of protein features. Eventually, protein representation can be expressed as below

$$h_v^{(l+1)} = GNN(\mathcal{G}_P(\mathcal{V}_P, \mathcal{A}_P, \mathcal{X}_P)). \quad (13)$$

$$Z_p = READOUT(\{h_v^{(L)} | v \in \mathcal{G}_P\}). \quad (14)$$

3.2.3 Stacked Graph DTA

The affinity score shows the strength of the binding interaction between a single biomolecule (e.g. protein) to its ligand binding partner (e.g. drug). Binding affinity is influenced by non-covalent intermolecular interactions such as hydrogen bonding, electrostatic interactions, hydrophobic and Van der Waals forces between the two molecules or by the presence of other

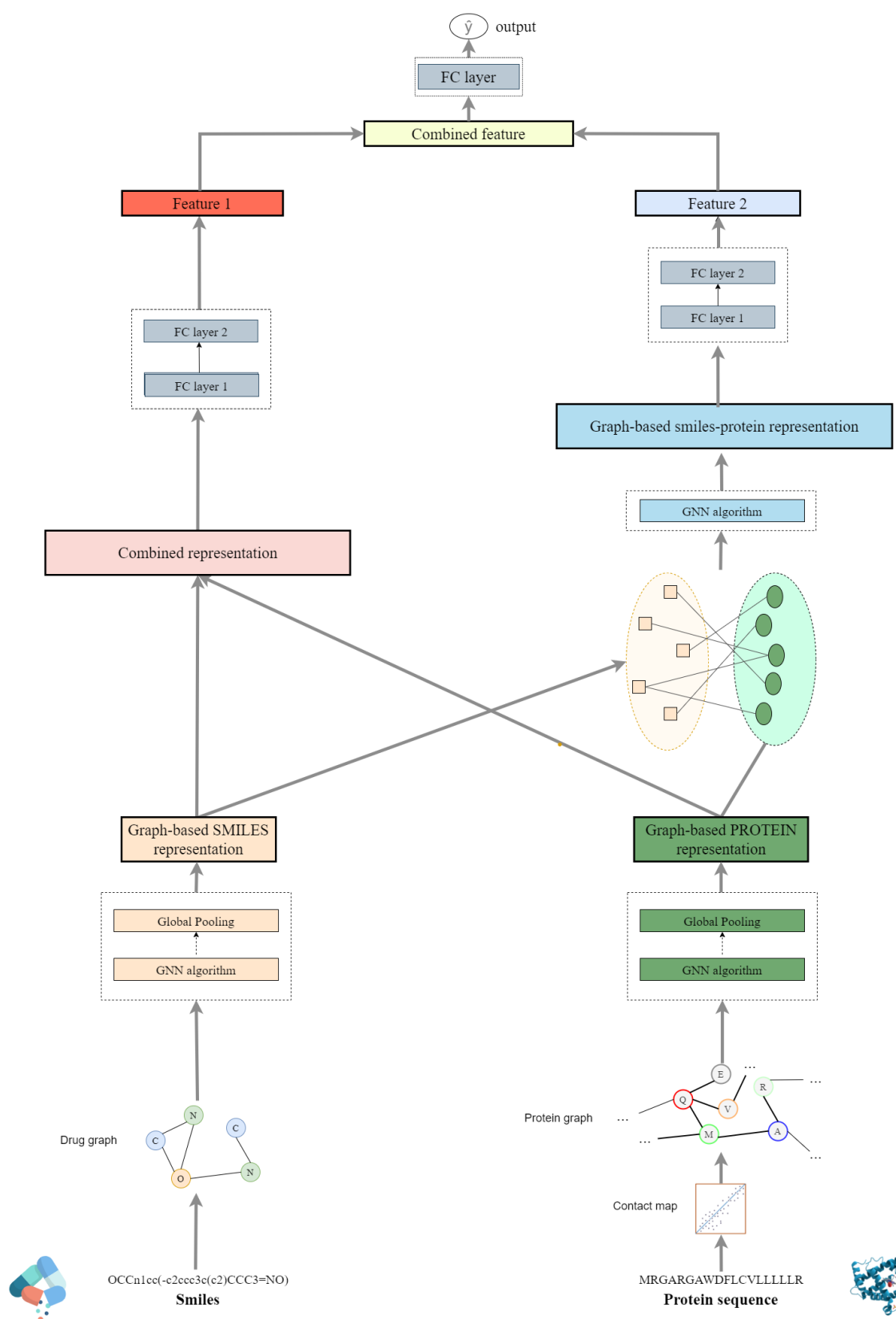


Fig. 2. Illustration of the Stack Graph DTA (SG-DTA) for drug and protein binding affinity prediction. SG-DTA takes as input a graph representation of the drug molecule and protein target. We first use a deep learning algorithm to learn a graph representation to refine the drug feature and protein-target feature. The two representation vectors are concatenated and passed through several fully connected layers to estimate the value of the first feature. The second feature is obtained by using graph representation algorithms to learn the features of drug and protein-targeted interaction graphs. Finally, the two features are paired and over some layers are fully connected to estimate the drug-target output affinity value.

molecules. Hence, we make the assumption that (i) many drugs affect the same a single biomolecule might have the relevant information and vice versa. We (ii) leverage both information from a distinct factor and information which aggregates from (i) as local features and global features, respectively, to make a powerful model. In addition, modern deep learning architectures are often designed according to (iii) the end-to-end approach. From then on, the learning information from the distribution of labels can be back-propagated through all parts of the model.

Figure 2 summarizes the entire architecture. Specifically, SG-DTA constructs a bipartite graph between drug and protein representation in sections 3.2.1 and 3.2.2. A bipartite graph (Figure 1) illustrates the relationship between drugs and targets. We denote $\mathcal{G}_{bp} = (\mathcal{V}_{bp}, \mathcal{A}_{bp}, \mathcal{X}_{bp})$ as referred for drug-target bipartite graph, where $\mathcal{V}_{bp} \in \mathbb{R}^{(v)}$ is a set of drug and target nodes of the graph, $\mathcal{A} \in \mathbb{R}^{v \times v}$ indicates the interaction between drug and target where $v = nd + np$ and feature vectors \mathcal{X}_{bp} is the output of graph-based representation of drug Z_d and protein Z_p . The embedding vector Z_{bp} satisfies (i) which is expressed as follow

$$Z_{gf} = h_v^{(t+1)} = GNN(\mathcal{G}(\mathcal{V}_{bp}, \mathcal{A}_{bp}, \mathcal{X}_{bp})). \quad (15)$$

On the other hand, we combine Z_d and Z_p by concatenating method to represent as local features Z_{lf} between each drug-target pairwise.

$$Z_{lf} = [Z_d, Z_p] \quad (16)$$

The output of SG-DTA attaining (ii) can be expressed as below where ρ is a fully connected non shared parameter layer with non-linear activation function

$$\hat{y} = \rho([\rho(Z_{lf}), \rho(Z_{gf})]) \quad (17)$$

During the training phase, the dataset is chunked into each batch. It turns out that we do not have enough information to compute feature vectors \mathcal{X}_{bp} in a direct way because each batch consists of a full set of the id of neither drug nor protein. It leads to the limitation that the implicit way to define \mathcal{X}_{bp} and the intractable derivative term $\frac{\partial y}{\partial x_{bp}}$. To exceed this limitation, \mathcal{X}_{bp} is initialized as Uniform distribution, $\mathcal{X}_{bp} \sim \mathcal{U}(a, b)$. Hence, we can gain (iii) directly without out of memory error when we try to compute $\frac{\partial y}{\partial x_{bp}}$ by all datasets.

4 Experiment

We evaluate our proposed SG-DTA method using two public benchmark datasets (Section 3.1). Our setting for hyper-parameter and well-known evaluation metrics mention in sections 4.1 and 4.2.

4.1 Parameter Setting

We select hyperparameters based on the performances of the validation set of k-fold. The training dataset is divided into a 5-fold cross-validation set. We train all models using Adam (P.Kingma and Ba, 2015) with $\beta_1 = 0.9$ and $\beta_2 = 0.999$, weight decay 0.00001 and batch size 512. We also use the Cosine Annealing Warm Restarts technique with $T_o = 10$ (Loshchilov and Hutter, 2017) to schedule the learning rate. We get learning rate $lr = 0.0005$ from the grid search over $lr \in \{0.00001, 0.0005, 0.0001, 0.005, 0.001, 0.05\}$. The values of all metrics in 4.2 are obtained after 49 and 193 steps for Davis and Kiba datasets respectively in each epoch. For dropout, we try dropping rates $d = 0.2$. The embedding size for SG-DTA is in a set $\{16, 32, 64, 128, 256, 512\}$ and models achieve the best results at size 128. We exclude L1 and Smooth L1 loss because of non-significant increasing performance. To recap, table 2 reports fully details all those hyperparameters settings.

Table 2. The hyperparameters setting for SG-DTA

Learning rate	0.0005
Learning rate decay	cosine
T_0	10
Optimizer	Adam
Adam(β_1, β_2)	(0.9, 0.999)
Weight decay	0.00001
Activation function	$GeLU$
Dropout rate	0.2
Epochs	4000
$\mathcal{U}(a, b)$	(0, 1)
Embedding size	128
Loss function	MSE

4.2 Evaluation Metrics

For filtering and ranking several models in our experiment as well as comparing easily with other studies, some popular evaluation metrics have been used. There has four metrics which include Concordance Index (CI), Mean Square Error, Pearson and Spearman Rank Correlation.

Firstly, the Concordance Index (CI) has the vital role of evaluating the predictive accuracy of a nonlinear statistical model (Gönen and Heller, 2005). The formula of CI has been given as

$$CI = \frac{1}{Z} \sum_{d_i > d_j} h(b_i - b_j)$$

Normally, there is the predicted value b_n for each ground-truth value d_n , then we need to implement pairwise checking whether the predicted value is higher than the other or not. Because the result of this subtraction can be negative, the step function $h(x)$ would be employed to hands-on the positive index for ranking. In which, $h(x)$ is defined as below

$$h(x) = \begin{cases} 1 & \text{if } x > 0 \\ 0.5 & \text{if } x = 0 \\ 0 & \text{if } x < 0 \end{cases}$$

and Z is the normalization constant.

Secondly, the MSE is calculated in order to measure the mean square error of the predicted value. Given that, \hat{y}_i is the predicted value, y_i is the true value, the formula of MSE is constructed as below:

$$MSE = \frac{1}{N} \sum_{i=1}^N (\hat{y}_i - y_i)^2$$

Lastly, two types of correlation are measured between the ground truth and predicted value to see the general pattern of the predicted process, or in another way, these two measurements show how good the model is in the out-of-sample data set. The first measurement is Pearson correlation for linear correlation:

$$Pearson = \frac{\phi(\hat{y}, y)}{\phi(\hat{y})\phi(y)}$$

in which, $\phi(\hat{y}, y)$ is the covariance between the true and predicted affinity value.

The other is Spearman for measuring the rank correlation:

$$SpearmanRank = 1 - \frac{6 \sum_{i=1}^n d_i^2}{n(n^2 - 1)}$$

where d_i is the difference between predicted and ground-truth value ordered in rank.

Table 3. Performances of various methods on Davis dataset

Method	Proteins and compounds	CI↑	MSE↓	Pearson↑	Spearman↑
KronRLS (Nascimento <i>et al.</i> , 2016)	S-W & Pubchem Sim	0.871	0.379	-	-
SimBoost (He <i>et al.</i> , 2017b)	S-W & Pubchem Sim	0.872	0.282	-	-
WideDTA (Öztürk <i>et al.</i> , 2019)	PS + PDM & LS + LMCS	0.886	0.262	0.820	-
MATT_DTI (Zeng <i>et al.</i> , 2021)	Rel_sa:CNN & CNN	0.890	0.229	-	-
DeepDTA (Öztürk <i>et al.</i> , 2018)	CNN & CNN	0.886	0.240	0.843	0.693
GraphDTA (Nguyen <i>et al.</i> , 2020a)	GIN & 1D	0.896	0.228	0.846	0.708
DGraphDTA (Jiang <i>et al.</i> , 2020)	GCN & GCN	0.896	0.212	0.859	0.707
SG-DTA (Our)	GCN & GCN & GAT	0.906	0.209	0.861	0.724

Table 4. Performances of various methods on Kiba dataset

Method	Proteins and compounds	CI↑	MSE↓	Pearson↑	Spearman↑
KronRLS (Nascimento <i>et al.</i> , 2016)	S-W & Pubchem Sim	0.782	0.411	-	-
SimBoost (He <i>et al.</i> , 2017b)	S-W & Pubchem Sim	0.836	0.222	-	-
WideDTA (Öztürk <i>et al.</i> , 2019)	PS + PDM & LS + LMCS	0.875	0.179	0.856	-
MATT_DTI (Zeng <i>et al.</i> , 2021)	Rel_sa:CNN & CNN	0.889	0.150	-	-
DeepDTA (Öztürk <i>et al.</i> , 2018)	CNN & CNN	0.889	0.144	0.888	0.882
GraphDTA (Nguyen <i>et al.</i> , 2020a)	GIN & 1D	0.889	0.139	0.892	0.884
DGraphDTA (Jiang <i>et al.</i> , 2020)	GCN & GCN	0.901	0.126	0.903	0.896
SG-DTA (Our)	GCN & GCN & GCN	0.903	0.125	0.904	0.898

5 Results and Discussion

5.1 Main Results

Tables 3 and 4 illustrate the comparison among previous studies versus our proposed models on both benchmark datasets Davis and Kiba. The column "Proteins and compounds" is the method to represent a drug or target. Difference from the others, our SG-DTA architecture puts the bipartite graph on in order to indicate the relationship between the two objects and indicates by the third part of the architecture.

All evaluation metrics are mentioned in section 4.2. We re-implemented three top methods DeepDTA (Öztürk *et al.*, 2018), GraphDTA (Nguyen *et al.*, 2020a), and DGraphDTA (Jiang *et al.*, 2020) in the similar model training system for serving the fairness comparison as well as the reproducibility of other study results based on their original sources code and papers. We consider the highest accuracy models. Due to the unavailability of some study’s sources code and paper, we have marked them as "-" on the tables.

Although our result is slightly superior to the DGraphDTA model on the Davis dataset, SG-DTA still achieves an overall strong performance. Notably, for the Davis dataset, the CI, Pearson, and Spearman scores are better when compare with the others. SG-DTA achieves the minimum error on the MSE metric at 0.206. This is also true for the Kiba dataset, while all the metrics outperform the others except the DGraphDTA model. All in all, these produced result shows that SG-DTA obtains a good predictive performance.

5.2 Ablation study

We conduct a number of previous ideas trying to demonstrate the improvement of the SG-DTA model of various previous methods. We first implement and evaluate those previous methods on two datasets Davis and Kiba. Then, we remove the combination layer of each method and replace them with the SG-DTA (section 3.2.3) to show the effectiveness of our method. Results are shown in Table 5 and Table 6.

As shown in Table 5 and Table 6, results by leveraging the SG-DTA contribute to a performance improvement in general on each dataset. It can be observed that the performance gains on SG-DTA with GCN and GAT algorithms. However, the model tends to overfit with mixed GAT-GCN and DGraphDTA (Jiang *et al.*, 2020). This is because the mixed GNN algorithms increase the complexity of the model.

5.3 Cases Study For Palbociclib and ChEMBL565612

In order to justify that SG-DTA can learn better node embedding by leveraging the relationship between drugs and targets, we extract the node embedding layer of SG-DTA of a sample drug and protein and project it into 2D space by utilizing the t-SNE method. The left Figure 3 illustrates the interaction of all proteins with drug ChEMBL565612 in the Kiba dataset and the right one is for protein P48736. As can be observed, the 2D projection of the node embedding by our method could present more coherent clusters of relationship which is marked as redpoint and it is also true for the non-interaction bluepoint node. (The figures 4 and 5 are samples for the 3D simulations of the interaction between Palbociclib with KINASE 6 (PDB ID 5L2I) and KINASE with Suramin (PDB ID 3PP7), which are one of the most pairs gaining the lowest Mean Square Error). For this reason, our model is crucial to achieving better representation learning.

6 Conclusion

In this paper, we have proposed the upgraded architecture model, which fully implementing the advances of graph representation, called SG-DTA (Stacked Graph for Drug-Target binding Affinity prediction). In which, both the protein and drug are represented under the graph method, and the binding level is exhibited using the bipartite graph (Figure 1). For the comparison purpose, we have measured the performance of our architecture using common methods such as Concordance Index,

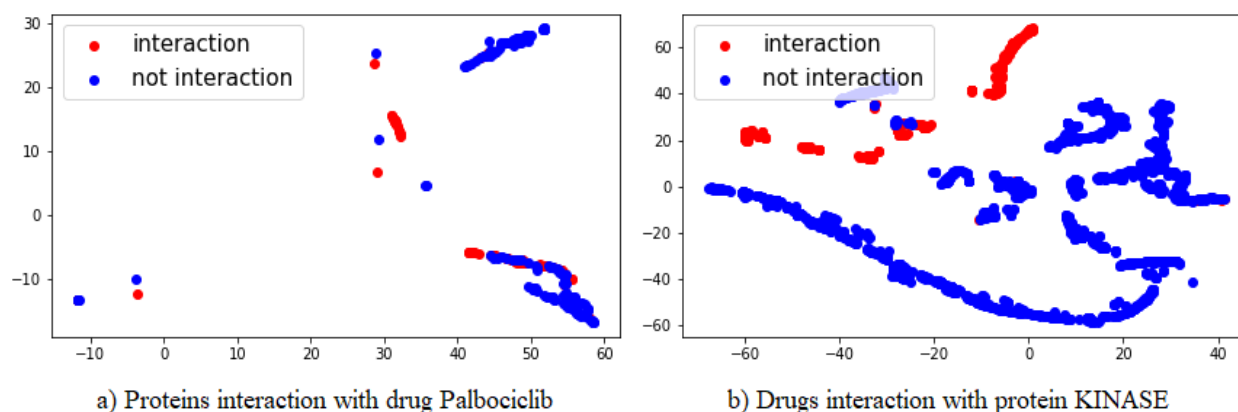


Fig. 3. 2D projection space of samples Palbociclib and KINASE interactions in Kiba dataset by t-SNE method

Table 5. The result of quantitative experiments in Davis dataset

Method	Architecture	MSE↓	Pearson↑	Spearman↑	CI↑
DeepDTA (Öztürk et al., 2018)	CNN & CNN	0.24050	0.84260	0.69339	0.88618
SG-DTA (our)	CNN & CNN & GCN	0.22983	0.84462	0.71210	0.89806
	CNN & CNN & GAT	0.22300	0.85016	0.71564	0.90063
	CNN & CNN & GAT-GCN	0.21762	0.85495	0.70868	0.89600
GraphDTA (Nguyen et al., 2020a)	GIN & CNN	0.22818	0.84649	0.70839	0.89580
SG-DTA (our)	GIN & CNN & GCN	0.22333	0.85002	0.71319	0.89863
	GIN & CNN & GAT	0.21936	0.85246	0.71903	0.90192
	GIN & CNN & GAT-GCN	0.22175	0.85052	0.71679	0.90095
DGraphDTA (Jiang et al., 2020)	GCN & GCN	0.21238	0.85850	0.70696	0.89619
SG-DTA (our)	GCN & GCN & GCN	0.21224	0.85841	0.71322	0.89931
	GCN & GCN & GAT	0.20946	0.86081	0.72415	0.90580
	GCN & GCN & GAT-GCN	0.22880	0.84789	0.69686	0.88976

Table 6. The result of quantitative experiments in Kiba dataset

Method	Architecture	MSE↓	Pearson↑	Spearman↑	CI↑
DeepDTA (Öztürk et al., 2018)	CNN & CNN	0.14362	0.88816	0.88181	0.88865
SG-DTA (our)	CNN & CNN & GCN	0.14092	0.89108	0.88741	0.89453
	CNN & CNN & GAT	0.14285	0.88890	0.88790	0.89549
	CNN & CNN & GAT-GCN	0.14717	0.88520	0.87967	0.89041
GraphDTA (Nguyen et al., 2020a)	GIN & CNN	0.13912	0.89180	0.88389	0.88929
SG-DTA (our)	GIN & CNN & GCN	0.12983	0.89974	0.89336	0.89786
	GIN & CNN & GAT	0.12714	0.90223	0.89778	0.90211
	GIN & CNN & GAT-GCN	0.15613	0.87796	0.86779	0.87959
DGraphDTA (Jiang et al., 2020)	GCN & GCN	0.12608	0.90283	0.89566	0.90089
SG-DTA (our)	GCN & GCN & GCN	0.12505	0.90375	0.89772	0.90314
	GCN & GCN & GAT	0.12636	0.90265	0.89816	0.90318
	GCN & GCN & GAT-GCN	0.12653	0.90247	0.89653	0.90209

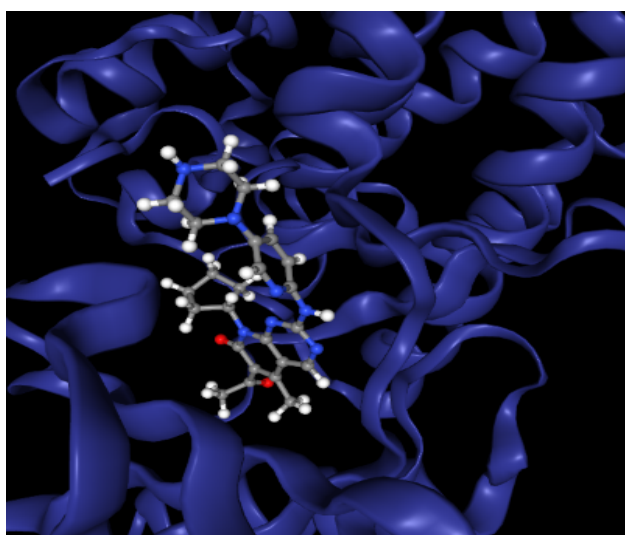


Fig. 4. 3D projection of protein CYCLIN-DEPENDENT KINASE 6 interacting with Palbociclib drug (PDB ID 5L2I)

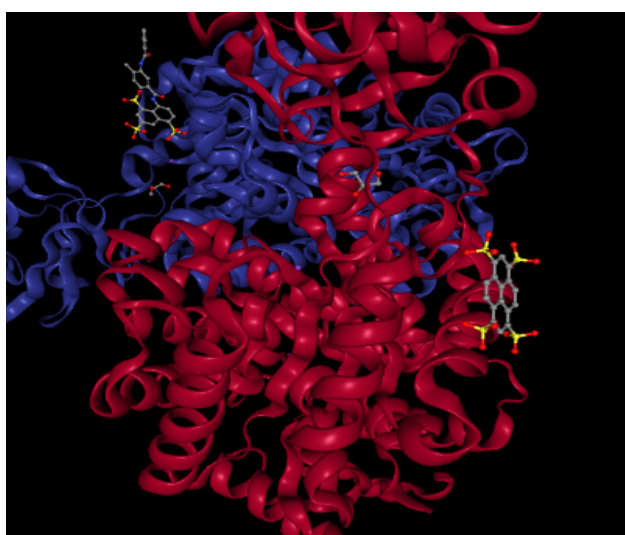


Fig. 5. 3D projection of protein KINASE interacting with Suramin drug (PDB ID 3PP7)

correlation, and the Mean Square Error. As the result, we found that the stacked block is the better feature extractor on the rendered bipartite graph, and it gives a better result on all chosen metrics. The result is also proven on both two datasets Kiba and Davis.

Our study opens the new idea of using the graph to exemplify the protein feature as well its relationship with drugs at lower cost while still reach a better result than the other. Again, the outperform of deep-learning methods, the graph representation is proven, and this paper opens the room for future research on re-implementing various deep-learning architectures from other fields to improve this crucial task for faster virtual drug screening and repurposing.

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