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# DRUG-TARGET INTERACTION/AFFINITY PREDICTION: DEEP LEARNING MODELS AND ADVANCES REVIEW

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**Ali Vefghi**

Department of Mathematics and Computer Science  
Amirkabir University of Technology  
Tehran, Iran  
alivefghi@aut.ac.ir

**Zahed Rahmati\***

Department of Mathematics and Computer Science  
Amirkabir University of Technology  
Tehran, Iran  
zrahmati@aut.ac.ir

**Mohammad Akbari**

Department of Mathematics and Computer Science  
Amirkabir University of Technology  
Tehran, Iran  
akbari.mo@aut.ac.ir

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## ABSTRACT

Drug discovery remains a slow and expensive process that involves many steps, from detecting the target structure to obtaining approval from the Food and Drug Administration (FDA), and is often riddled with safety concerns. Accurate prediction of how drugs interact with their targets and the development of new drugs by using better methods and technologies have immense potential to speed up this process, ultimately leading to faster delivery of life-saving medications. Traditional methods used for drug-target interaction prediction show limitations, particularly in capturing complex relationships between drugs and their targets. As an outcome, deep learning models have been presented to overcome the challenges of interaction prediction through their precise and efficient end results. By outlining promising research avenues and models, each with a different solution but similar to the problem, this paper aims to give researchers a better idea of methods for even more accurate and efficient prediction of drug-target interaction, ultimately accelerating the development of more effective drugs. A total of 180 prediction methods for drug-target interactions were analyzed throughout the period spanning 2016 to 2025 using different frameworks based on machine learning, mainly deep learning and graph neural networks. Additionally, this paper discusses the novelty, architecture, and input representation of these models.

**Keywords** drug-target interaction prediction · drug-target affinity prediction · Drug discovery

## 1 Introduction

Developing drugs is a slow and complex process which involves multiple stages of research, development, and testing<sup>2</sup>. These stages of development aims to ensure the safety, efficacy, and quality of pharmaceutical products before public access and patient use [1]. The diagram presented in Figure 1 shows this process and its phases. The initial step of drug development is usually drug discovery, where potential drug candidates are identified through different stages like identifying a specific target that binds to a chemical compound, determining the lead compound of the binding chemical and lead optimization to enhance the efficiency as well as the specificity [2, 3]. A discovery leading to approved medicine takes about 12 to 15 years and requires total investment of 1.8 billion US dollars, and many potential

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\*Corresponding author

<sup>2</sup>bioagilytix.com

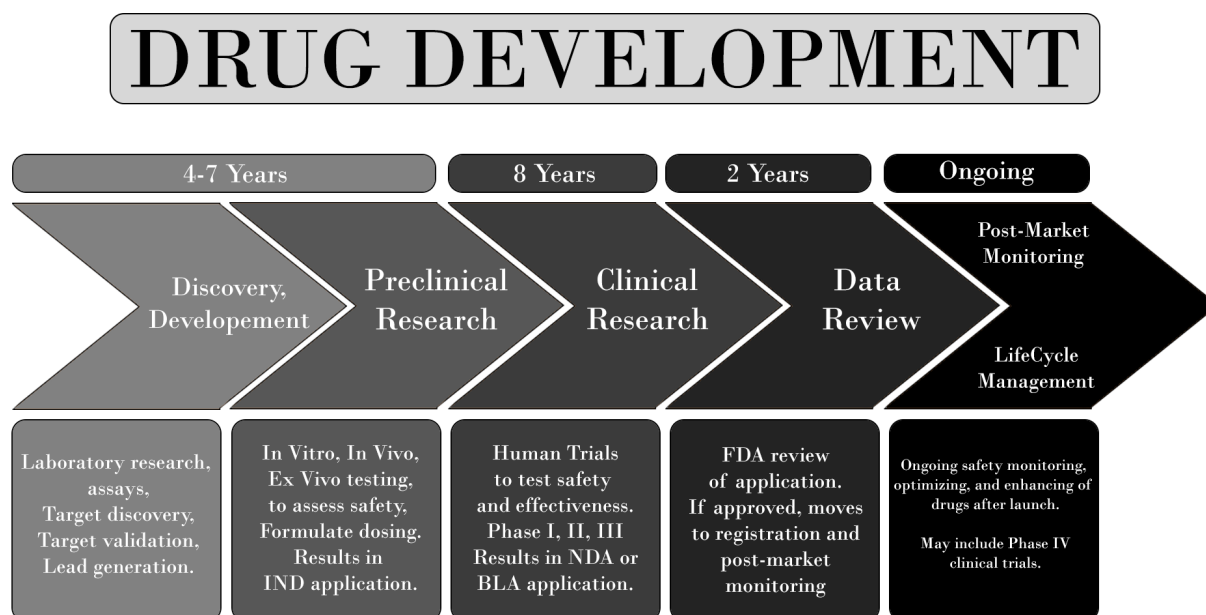


Figure 1: Overview of drug development process

drugs never make it to market due to safety concerns, lack of efficacy, or other factors [4, 5, 6]. On average, a million molecules undergo screening but the final product ends up being just one drug that reaches late-phase clinical trials and becomes available for patients. Once promising candidates are identified, pre-clinical testing assesses safety, efficacy, and pharmacokinetics in animal models. Clinical trials become the next step once the drug demonstrates potential for approval by testing it on human volunteers. These trials are typically divided into three phases: Phase I evaluates safety and tolerability, Phase II assesses efficacy and determines the optimal dosage, and Phase III confirms effectiveness and safety in a larger patient population. The drug manufacturer sends the New Drug Application (NDA) to the FDA for review after concluding successful clinical trials. The FDA evaluates the NDA, including data from pre-clinical and clinical studies, to determine whether the drug meets safety and efficacy standards. If approved, the drug can be marketed and prescribed to patients [7].

Drug-target specificity is a crucial factor in drug design which refers to the ability of a drug to be selectively bind to its intended target, while minimizing interactions with other targets. Multiple research suggests that certain drugs interact with more than one target sites, known as poly-pharmacology [8] and also some diseases have shown that they need multiple factors to be manipulated simultaneously in order to be treated effectively, which has led to the development of drug repositioning.

Drug re-purposing or repositioning [9, 10, 11, 12] is a promising technique that helps significantly speed up the drug development process, reduce time-to-market, and lower financial costs by finding novel uses outside the scope of the original medical indication for existing drugs after FDA approval or abandoned drugs before FDA approval. The main point is that the already known drugs or approved drugs mostly have identified side effects and safety of their usage is known, therefore it can accelerates the study of these drugs. Understanding how marketed drugs interact with novel targets and predicting these interactions with high precision can guide researchers in selecting the best potential candidates and optimizing their use for specific applications. [13]

The pharmacological principle also suggests that a medicine which has therapeutic effects on one target can have side effects on multiple other targets at the same time. Studying these phenomenon lead to a method called Drug side effect profiling [14, 15] which is a critical research area according to [16].

Drug-target interaction, affinity prediction (DTI/DTA), identifying binding sites and interaction types are crucial tasks in drug discovery, facilitating the identification of new therapeutic agents, optimizing existing ones, and assessing the interaction potential of various molecules for disease treatment [17]. Desired therapeutics, target specificity, long

residence, and drug resistance delay can be obtained from the intensity of binding between a drug and its target protein, therefore, its prediction is considered a very important task in drug discovery [18].

Classic experimental methods are time-consuming and expensive, making computational approaches increasingly valuable. Machine learning algorithms and AI techniques have emerged as promising tools for DTI prediction, leveraging large-scale datasets and complex computational models to accurately predict interactions between components and their targets <sup>3</sup>.

Many other studies have been conducted to review or survey the literature on DTI/DTA prediction. Some of these studies are focused on specific methods like graph neural networks (GNNs) [19, 20], while others are focused on broader scopes like machine learning and computational methods [21, 22, 23]. Zhang et al. [24] proposed a combo of models for DTI prediction and compared various models on different datasets. Sachdev et al. [25] reviewed the feature-based methods for DTI prediction. Jung et al. [26] reviewed the literature on network-based DTI prediction methods. Some other studies are focused on component-protein interactions (CPI) [27] or protein-ligand interaction (PLI) [28, 29, 30, 31]. Closest study to our work are the studies by Zeng et al. [32] and Abbasi et al. [33] (focused on the architectures) which are comprehensive reviews of the literature on deep learning models for prediction of drug target affinity. Our paper expands on their work by providing a more comprehensive review of the literature on DTI/DTA prediction, focusing on the input representations and more deep learning models used throughout the history of DTI/DTA prediction research.

This paper offers a clear perspective and categorization of nearly over 180 methods presented from 2016 to 2025 on the DTA/DTI problem and serves as a preliminary overview guide for researchers who want to have a general idea of what the models and solutions to DTA/DTI are. Models are categorized into different categories based on their input representations including sequence-based, structure-based, sequence-structure-based, complex-based, and utility-based models. Supplementary data which includes Metrics, datasets, baselines, and other information of all models are available here.<sup>4</sup>

The structure of paper is as follows:

- Section 1 provides an introduction to the drug discovery process and the importance of DTI/DTA prediction.
- Section 2 provides an overview of input representations and the definition of drugs, proteins, and the problem used in the literature.
- Section 3 presents the models used in the literature in different categories.
- Section 4 discusses the datasets and evaluation metrics which are most used in the literature.
- Section 5 discusses the challenges and future directions in the field and concludes the paper.

## 2 Input Representations

This section provides an overview of various input representations used in the literature from two aspects of the problem which are proteins and drugs. The proper representation is a crucial part in analyzing and extracting the right features from proteins and drugs for learning the best pattern that the selected features can offer. Existing methods may use different representations for drugs and proteins or both can be represented in the same way. For example, One side can use sequence representation while the other side use graph representation, and then train a model on both representations.

As Figure. 2 shows, inputs of DTI/DTA models can be string of sequences, graphs, vectors of information (e.g. physico-chemical properties) or any other form of data. The most common input representations for drugs are Simplified Molecular Input Line Entry System (SMILES), fingerprints, and molecular graphs, while for proteins, the most common representations are primary sequences, fingerprints, and protein graphs. To feed these inputs into the interaction learning models, encoding modules exist in most of models to convert the input data into a form that the model can understand.

There are lots of programs and software that can be used to manipulate and visualize drugs or proteins, e.g. PyMOL [34] is a commonly used software.

### 2.1 Drugs as ligands / compounds

Drugs are often micro-molecules that interact with cellular constituents by causing a change in constituent function that results in an overall physiological response intended for therapeutic reasons. Drugs can activate a particular cell function in the body (Agonist), block a function (Antagonist), or even do the opposite of a function (Inverse agonist). Drug action describes the influence of a drug molecule on our cells in which it binds with at least one of the target's binding sites.

<sup>3</sup>biostrand.ai

<sup>4</sup>github.com/agmlcenter/Bioinformatics

# Input representations

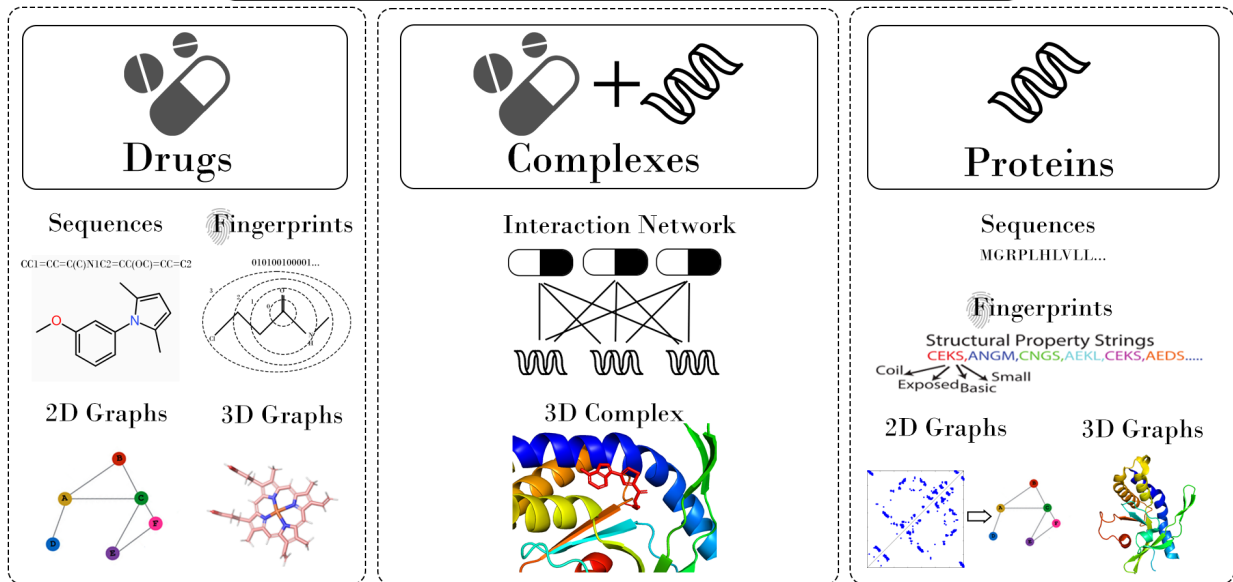


Figure 2: Overview of various input representations

Individual drug classes bind to specific targets and individual targets recognize only specific classes of drugs, while no drug acts with complete specificity. Drugs are also referred as ligands which is just an expression for the small drug molecules attaching to proteins. In general, Molecules that bind to a target are called ligands, **therefore, all drugs are ligands, but not all ligands are drugs**. Examples of other types of ligands other than drugs are endogenous ligands (like hormones, neurotransmitters, and other signaling molecules), toxins, and environmental pollutants (like heavy metals).

## 2.1.1 Drug sequences

Simplified Molecular Input Line Entry System (**SMILES**) [35] is a commonly used representation for drugs which can be obtained and processed via the RDKit [36] library. SMILES is a common notation system for drugs that uses a canonicalization algorithm to generate unique ASCII string notations for each drug in respect to the three-dimensional structure of drugs. In other words, SMILES of a drug consists of a series of characters representing atoms and bonds. With its compact nature and simple data handling system, SMILES provides standardized and unique molecular descriptions. The canonicalization algorithms first convert the SMILES to an internal representation of the molecular structure and then produces a unique SMILES string with another algorithm from that structure. One way of acquiring SMILES is through PubChem compound database based on the drug PubChem CIDs(or ChEMBL IDs) [37].

SELF-referencing Embedded Strings (**SELFIES**) [38] are another notation system which are introduced so that all of the tokens or words of the SELFIES correspond to chemically valid molecules, while SMILES respective characters do not always correspond to chemically valid molecules.

SMILES Arbitrary Target Specification (**SMARTS**) [39] is a powerful extension of the SMILES notation system, enabling the definition of molecular patterns beyond the representation of individual molecules. While SMILES provides a linear representation of a complete chemical structure, SMARTS allows for the specification of sub-structural motifs, functional groups, and other chemical features within a molecule.

**Embedding of SMILES strings can be obtained with pre-training Word2Vec** [40], use a pre-trained model like Mol2Vec [41], or simply encode SMILES with One-hot encoding. Mol2Vec is an unsupervised learning method that generates vector representations of molecular substructures, drawing inspiration from word embedding in natural language processing. By training on a large corpus of molecules, it learns to encode chemical information, capturing relationships between substructures within a continuous vector space.

### 2.1.2 Structural keys: Fingerprints

Molecular fingerprints are conventional methods for encoding chemical compounds. They represent molecules as unique identifiers based on the presence or absence of specific molecular features within a defined radius around each atom. These features can include Motifs (specific substructures), functional groups, and other chemical properties. One common approach is to represent these features as a binary vector, where each bit corresponds to a specific feature. If a molecule possesses a particular feature, the corresponding bit is considered one; otherwise, it is zero. Fingerprint methods can also incorporate more complex representations, such as feature counts or continuous values. Some commonly used fingerprints are Extended-Connectivity Fingerprints (ECFPs)/Functional-Class Fingerprints (FCFPs)/Morgan fingerprint [42], ErG fingerprint [43], Daylight fingerprint [44], MACCS Keys [45], and The PubChem fingerprint [46] which can be acquired via RD-Kit.

Morgan fingerprints are a class of circular fingerprints that encode the local chemical environment surrounding each atom within a molecule. These fingerprints are generated by iteratively expanding a circular neighborhood around each atom, considering neighboring atoms and their bond types. At each iteration, the atom's environment is hashed into an integer, representing a unique fingerprint. This process captures the structural complexity of the molecule within a fixed-size bit vector, enabling efficient comparison and analysis.

ECFPs are a specific type of Morgan fingerprint that has become a widely used standard in chemo-informatics. ECFPs are generated by extending the circular neighborhood around each atom to a specified radius, typically two or three bonds. This approach captures more extensive structural information compared to simpler fingerprints, including longer-range interactions and more complex sub-structural motifs.

Another fingerprint that can be used for compounds is algebraic graph-based fingerprints (AG-FPs), which generate low-dimensional molecular representations with element-specific weighted colored algebraic graphs while preserving essential physical/chemical information and physical insight [47].

PaDEL-Descriptor [48] is a software using Java language to calculate the chemical small molecules descriptors. It includes 134-dimensional 3D descriptors, 1444-dimensional 1D, 2D descriptors, and 10 various fingerprints.

### 2.1.3 Two-dimensional molecular topology graphs

In this kind of representation, a 2D molecular graph is used which captures both the chemical and topological information (molecular formula, atomic type, bond type, and spatial arrangement). Atoms and chemical bonds are represented as nodes and edges of the graph in this form. To generate the node feature vectors in the drug graph physical-chemical properties of atoms or SMILES can be used. Graphs can be fed into the models in the form of adjacency matrices, node features, and edge features.

Some studies use R-radius sub-graphs as input representation of drugs [49]. R-radius sub-graphs are graphs where the graph's vertices are the aggregation of all neighboring vertices and edges information within a radius  $r$ .

Chemistry software tools such as DGL-lifeSci [50] (or DGLGraph [51]), Open Babel [52], and RDKit can be employed to convert SMILES to molecular graphs (using structure diagram generation (SDG) algorithms [53]) and extract useful features including, chemical bonds, hydrogen presence, electron properties, whether the atom is aromatic, and so on.

### 2.1.4 Three-dimensional spatial structures

In 3D structural format, atoms serve as vertices and bonds act as edges in a 3D graph. Like drug 2D graphs, node features can be calculated from SMILES or other properties.

Researchers aim for representing drug molecules to be as accurate as possible while capturing their structural information. In these methods, the mesh representation splits 3D space into regular mesh units that function as volume elements. With the point cloud <sup>5</sup> representation method the three-dimensional molecular structure gets converted into a collection of discrete points where each point shows the position of atom elements. Voxel representation divides three-dimensional space into a series of small cube units, which are called voxels and maps atoms in molecules to the nearest voxel.

Also, there are new ways to represent molecules in three-dimensional space like in [54] which is a novel representation of drug 3D structures and enhancement of the TSR-based method for probing drug and target interactions.

<sup>5</sup>A point cloud is a set of data points in a three-dimensional coordinate system defined by X, Y, Z coordinates.

## 2.2 Proteins as targets

Drug-targets are mostly proteins macro-molecules like receptors (controlling signaling in the body), enzymes (catalyzing chemical reactions), carrier molecules (transporters like hemoglobin), and Ion channels. In this paper, we consider targets as proteins, which are the most common drug targets. Proteins exist as linked amino acids arranged in particular orders like a chain. The molecular unit called amino acid functions as the basic structural component that builds proteins. Twenty main types of amino acids are found in the proteins of living things, and the properties of a protein are determined by its particular amino acid sequence.

Proteins have four levels of structure: primary, secondary, tertiary, and quaternary. The simplest level of protein structure, known as primary structure, is simply the sequence of amino acids in a poly-peptide chain. The sequence of a protein is determined by the DNA of the gene that encodes the protein. The next level of protein structure, secondary structure, refers to local folded structures that form within a poly-peptide due to interactions between atoms of the backbone. The most common types of secondary structures are the alpha helix and the Beta pleated sheet. The overall three-dimensional structure of a poly-peptide is called its tertiary structure. The tertiary structure is primarily due to interactions between the R groups of the amino acids that make up the protein. Lastly, protein sub-units come together and they give the protein its quaternary structure.

Proteins are a lot more complicated to represent comparing to drugs due to various reasons. Some reasons are the lengthy sequence of proteins, different foldings, different conformations <sup>6</sup>, and vastness of combinations for proteins which are composed of different amino acids. Another reason is the unknown protein structures which nowadays is to some extent handled via structure prediction models like Alpha-fold [55].

A protein pocket is a concave surface region on a protein where small molecules, such as drugs, can bind. These pockets are essential for the protein's biological function. They often serve as active sites for enzymatic reactions or as binding sites for small molecules, including substrates, co-factors, and inhibitors. Some pocket detection models are [56, 57, 58, 59, 60, 61] which are using 3D structure or other structures of proteins. The binding sites generally possess large and flat areas with high hydrophobicity. [62]. Additionally, large conformational changes in the binding region, such as the transition between open and closed states of the binding pocket, and the local secondary structure changes induced by the ligand, are associated with the ligand binding affinity [63]. Some studies have used probe points named "anchors" describing protein pockets for better prediction of DTI [64].

### 2.2.1 Protein sequences

The most common approach of representing proteins involves the Protein sequences representation in which each protein is represented using the ordered text string of its different unique characters for each amino acid in the linear poly-peptide chain. No further information is accessible through this representation other than the names of amino acids in text form and their order in the protein chain sequence, therefore there is a need for text feature extraction including natural language processing techniques in these representations [30]. These methods take the amino acid sequence as input and try to capture sequence and structural patterns by learning the relative positions between amino acids in 1D representation to produce the best sequence embedding [65].

Common pre-processing for Protein sequences, involves converting amino acid sequences into N-gram segments (biological words) [66, 67] or integers [68] sequences inspired by methods in NLP [69]. Protein sequences are commonly encoded as one-hot or labels or other novel methods [70]. One example of sequences is proposed by [71] which is called FASTA sequences (sequences of amino acids represented with specific characters).

For capturing informative features from the protein sequences different algorithms prior to the main model can be used. For example, the Smith-Waterman algorithm compares these amino acid sequences to identify regions of similarity, which can indicate functional or evolutionary relationships between proteins. Alignment-free algorithms like Lempel Ziv Markov chain algorithm (LZMA) <sup>7</sup> can also be used.

There are other traditional methods to process and extract features from the Protein sequences of proteins such as position-specific score matrix (PSSM) [72], and Hidden Markov Matrix (HMM) [73]. A PSSM is a matrix that represents the probability of amino acid occurrences at each position in protein sequences. [74] It's derived from a multiple sequence alignment (MSA) of homologous proteins. HMMs are statistical models that can be used to model biological sequences, including proteins. They are particularly effective for identifying protein classes, families and domains, which are often defined by specific patterns in the Protein sequences. Other popular protein sequence descriptors include Auto-correlation, CTD (Composition, Transition and Distribution) descriptor, Quasi-sequence order, and Protein Sequence Composition (PSC) [75].

<sup>6</sup>the spatial arrangement of its constituent atoms, which determine the overall shape of the macro-molecule.

<sup>7</sup><http://www.7zip.org/7z.html>

Some models leverage pre-trained Word2Vec [40, 76, 77, 78, 79, 80, 81, 82] or pre-trained protein language models [83, 84] to make the embeddings more expressive. Pre-trained Protein sequences protein models are trained on massive datasets of protein sequences, therefore, it is capable of predicting protein structures with high accuracy, even for challenging protein families [85]. ESM-2 [86], ProtBERT (BERT-based pre-trained model on protein sequences using a masked language modeling objective.) [87], Prot2Vec [88], TAPE (Tasks Assessing Protein Embeddings) [89], and UniRep [90] are examples of these pre-trained Protein sequences protein models.

One of the access points for Protein sequences is UniProt protein database based on gene names/RefSeq accession numbers (or UniProt IDs) [91].

### 2.2.2 Protein fingerprints

A protein fingerprint is a unique pattern that characterizes a specific protein or a group of related proteins. This fingerprint can be derived from various properties of the protein, including its amino acid sequence, its 3D structure, or its biochemical properties. PROSITE and Pfam are two datasets that contain protein fingerprints. PROSITE contains protein domains, families, and functional sites represented as patterns and profiles [92]. Pfam contains a large collection of protein families, represented as multiple sequence alignments and hidden Markov models (HMMs) [93]. Also, Structural property sequences (SPS) (Secondary Structure, Solvent Accessibility, Hydrophobicity/Hydrophilicity, Charge, Flexibility/Rigidity) can be generated via SSPro [94] from protein sequences.

Secondary Structure Elements (SSEs) are the localized, regular arrangements of the poly-peptide backbone within a protein. The most common SSEs are alpha helices and beta sheets, which are stabilized by hydrogen bonds between the backbone atoms. SSEs and Physicochemical characteristics of Amino Acids (e.g. non-polar, polar, acidic, basic) can be used as protein fingerprints.

### 2.2.3 Protein feature Graphs

These methods represents proteins in graphical form and visual information, where nodes represent amino acids, atoms, or residues, and edges represent their real or custom made relationships.

One common graph that is used instead of the whole 3D graph of proteins is the contact map graph. The whole protein structure produces complex graph topology together with prolonged training duration because proteins contain numerous atomic elements. Instead, a contact map (a form of adjacency matrix), which reflects the high-dimensional structure of a protein, can be used to reveal the interactions between protein residues (as they are less in number, only a few hundred) [95, 96]. Generally, two C $\alpha$  atoms of residues in Euclidean space are in contact if the distance between them is less than a certain threshold. The structural features of Protein can directly be extracted from contact maps through CNN models or contact maps can be transformed into network topology to utilize GNNs. These interactions between residues make the contact map, which can be acquired using Pcons4 [97] (uses a U-net architecture, which operates on the 72 features calculated from each position in the MSA) or evolutionary scale modeling (ESM) models [98]. ESM models can save alignment time by predicting contact maps without requiring protein sequence alignment. After predicting the contact map a threshold is used to create the edges in graph.

Another graph that can be used is 2D pocket graphs which are constructed based on distances of amino acids in pocket regions of proteins. These graphs are subsets of the whole protein graph and only contain the pocket area of the protein.

### 2.2.4 Protein 3D structure

Three dimensional graph of proteins can be used to represent proteins in a more detailed way. Each node of the graph can be amino acids or atoms and edges can be the bonds between them, but this representation is not common due to the complexity of the structure and the vast number of atoms in proteins.

Protein 3D structure prediction is the process of predicting the three-dimensional structure of a protein from its amino acid sequence which is a challenging problem in drug discovery. Traditionally, for acquiring the 3D structure of proteins, researchers use X-Ray Crystallography, Nuclear Magnetic Resonance (NMR), or 3D Electron Microscopy [99, 100, 101]. However, these methods are too slow and costly. Other computational approaches tried to solve this problem like homology modeling techniques (comparative modeling, protein threading and segmenting and etc.). Crystallography makes better resolution than NMR but some proteins cannot be crystallized; therefore, NMR is needed which can present different conformations of proteins. The state-of-the-art computational method, Alpha-fold model, uses deep learning approaches to predict the 3D structure of proteins by utilizing attention heads and Multiple sequence alignment (MSA) on evolutionary similar Protein sequences [55]. Protein structure prediction with pre-trained models provides key information for CPI and DTA prediction, however, selecting a fast and accurate method to improve the efficiency is very important.

Another graph that is used recently is pocket graph representation of proteins. In this representation, the protein is represented as a graph just in the pocket area and not the whole graph, therefore, the construction of graphs can be more manageable.

### 2.3 Drug-target complexes

In these form of representations drugs and targets are not treated individually, instead, they are considered as complexes and structures from crystallized forms. Approaches based on this representation are limited to known protein ligand complex structures. As these structures are often unavailable, they often need to be first predicted by docking individual structures of proteins and compounds together.

Features like each atom’s element type, hybridization, bonding information, structural properties (hydrophobicity, aromaticity, hydrogen bonding), partial charge, molecule type (protein or ligand), and van der Waals radius can be extracted and used from the 3D structure of the complexes. Open-Babel cheminformatic tool [52] can be used to extract these features from the 3D structure of the complexes.

#### 2.3.1 Interaction network graph representation

The construction of interaction network graphs relies on three-dimensional drug-target complex structures. Researchers generate the graph by choosing particular atoms between the drug molecules and target proteins. Typically, they choose the carbon alpha atoms of the amino acids in the target protein, as well as all atoms from the drug molecule. An edge is connected between the corresponding nodes in the graph if the distance between two atoms is less than a predefined threshold. Any atoms or amino acids that are not involved in any interactions are removed. This graph can then be used as input for models to predict the binding affinity or other properties of the drug-target interaction.

#### 2.3.2 3D structural spatial grid representation

While interaction network graphs offer valuable insights, they may overlook certain interactions by focusing on a subset of atoms. To capture the complete spatial arrangement of all atoms, 3D spatial grid representations are employed. These representations, coupled with 3D Convolutional Neural Networks (3D-CNNs), can effectively extract key structural features important for drug-target binding.

### 2.4 Formulating the drug-target Problem

Given a set of drug molecules and a set of potential target proteins, predict whether a drug molecule will bind to a target protein and, if so, with what affinity. For a regression task, if we have  $D = \{d_1, d_2, \dots, d_n\}$  for drug molecules and  $T = \{t_1, t_2, \dots, t_n\}$  for target proteins, for each  $i \in n$  and  $j \in m$ , the aim is to predict  $A(d_i, t_j)$ , which represents the binding affinity of drug  $d_i$  to target protein  $t_j$ . A higher value indicates a stronger binding affinity. This regression task is called drug-target affinity prediction. The problem can also be formulated as a binary classification task, where the objective is to predict whether a drug molecule will bind to a target protein  $A(d_i, t_j) > threshold$  or not  $A(d_i, t_j) \leq threshold$ . This task is called Drug-Target Pair prediction or Drug-Target Interaction prediction. In Figure 3 binding affinity is a continuous number and binary interaction is a binary number which can be zero or one.

Binding affinities may be subject to biological constraints, such as steric hindrance or electrostatic interactions. It is more informative but also more challenging to predict the strength of the binding between a drug and its target. If the strength is not strong enough, such a drug-target pair may not be useful.

Protein-ligand interaction prediction is a related problem that focuses on predicting the interaction between a protein and a ligand, which is a small molecule that binds to a protein. Component-protein interaction (CPI) is another related problem that focuses on predicting the interaction between a component and a protein, where the component can be a drug, a ligand, or a small molecule. These tasks can be formulated as binary classification or regression tasks, similar to the drug-target interaction problem.

#### 2.4.1 Experimental settings

As shown in Figure 3, there are four different experimental settings [102] for drug-target interaction. Warm setting is the same as the traditional setting where the training and test sets are randomly split. Cold setting is the most challenging setting where the test set contains drug-target pairs that are not present in the training set. Methods tried to test their frameworks in cold settings to evaluate the robustness and generalizability of their models.



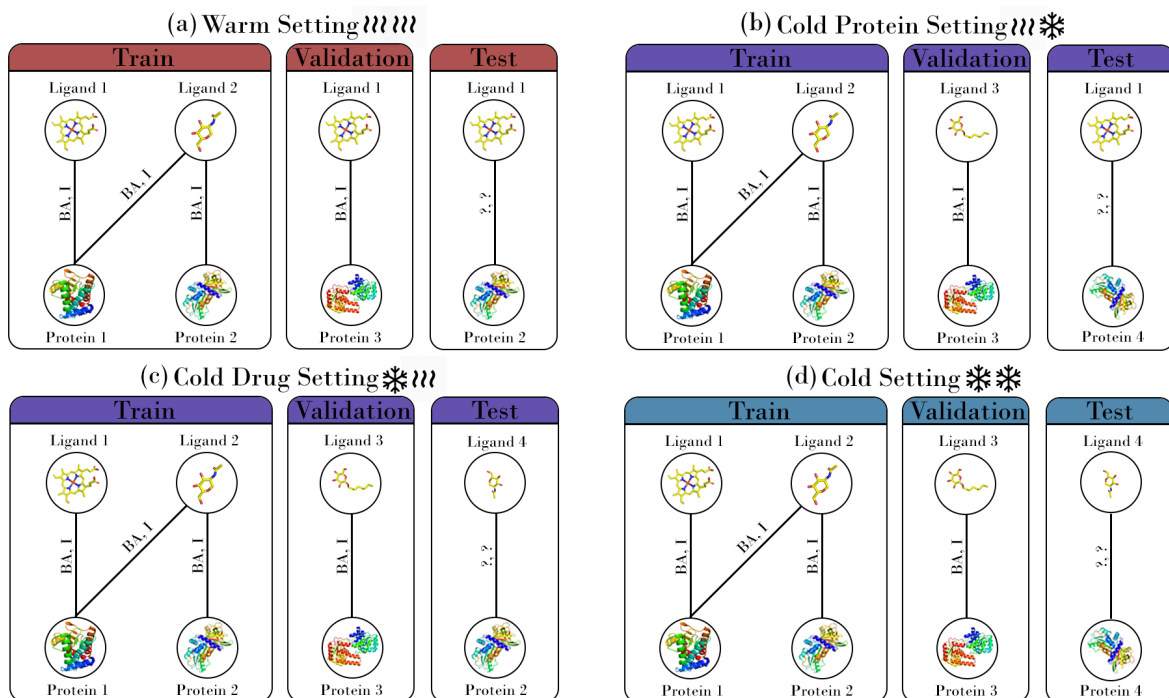


Figure 3: Overview of drug-target interaction problem in different settings. BA: binding affinity, I: binary interaction. (a) Warm setting, (b), Cold protein setting (c), Cold drug setting, (d) Cold drug-protein setting.

Using label reversal dataset [103] is another technique to show how models generalize in unseen situations. A ligand in the training set appears only in one class of interaction, whereas, in the test set, the same ligand appears only in the opposite class of interaction.

- Warm setting (Random split): Both drug and protein of pairs in test and validation sets can also be seen in the training samples. Any protein or ligand may be repeated; however, interactions are not duplicated across the two splits.
- Cold target setting (Orphan-target split): Test protein targets are not observed in the training set.
- Cold drug setting (Orphan-drug split): Test drug compounds are not observed in the training set.
- Cold setting: Both test drugs and protein targets are not observed during the training phase.

### 2.4.2 Negative samples from DTA to DTI

The designation of the negative (not-binding) samples is an important step that affects the model’s performance (recognizing the best and real negative samples is challenging)[104]. In the literature of drug discovery positive samples (pairs that exhibit interactions or have high affinity) are also referred to as active components and the negative samples (pairs that do not exhibit interactions or have low affinity) are sometimes referred to as decoys. Several DTI studies use four major datasets (Enzymes (E), Ion-Channels (IC), G-protein-coupled receptors (GPCR), and nuclear receptors (NR) which drug-target interactions are acquired from KEGG BRITE, BRENDA, SuperTarget, and DrugBank) in which DT pairs with no known binding information are treated as negative samples [105]. Some DTI studies that rely on databases with binding affinity information have been providing more realistic datasets created with a specific binding affinity threshold [106]. Formulating the drug-target prediction task as a binding affinity prediction problem enables the creation of more realistic datasets, where the binding affinity values are directly used and the challenge of selecting the best threshold is avoided.

## 3 Methods

In this section, an overview of the models used in the literature for DTI/DTA prediction is provided. First, some traditional methods and categorizations are discussed, then the machine learning and deep learning models are presented.

### 3.1 A brief history of traditional approaches

The field of drug-target interaction has developed significantly throughout time. Early research into drug-target interactions often relied on classical methods such as Chemical-biological experiments including wet lab experiments<sup>8</sup>. These methods contains laboratory experiments *in – vivo*<sup>9</sup> and *in – vitro*<sup>10</sup>. Most of these experiments are well known to be accurate but time consuming and costly, therefore Computational methods, in-silico and dry lab experiments are more desirable, as they can reduce the search space and lessen the required time and cost. [107] As more compounds are being synthesized and new diseases are being introduced, the need for more accurate, powerful and efficient methods to handle large amounts of datasets and component properties rises. The stage of drug development and the type of data are the main factors in determining in-silico methods that can be used. For example, Quantitative Structure Activity Relationships (QSAR) studies are conducted to determine the drug properties of the lead compound, by analyzing the relationship between the chemical structure and the biological activity. [108]

### 3.2 Computational methods

Computational methods can be based on machine learning approaches and non-machine learning methods or hybrids of them. Furthermore, The computational methods based on machine learning can be classified into traditional machine learning methods and deep learning methods. Traditional machine learning methods use linear regression, random forest, nearest neighbor, and support vector machine to predict [109, 110]. These methods cannot learn the high-level features automatically, however, deep learning models can overcome this limitation [111].

Scoring models estimate the likelihood of a drug-target interaction. Models like AGL-Score (Algebraic Graph Learning Score) [112], X-Score (based on empirical force field calculations) [113], ChemScore, ChemPLP [114, 115], AutoDock Vina, and AutoDock (calculates score by docking simulation) [116] are classic scoring models. Newer scoring methods are RF-Score (Random Forest Score) [117], kNN-Score, OnionNet, K-DEEP, Pafnucy. Some of these models require significant computational resources and are limited.

Because of the simplicity of calculation and their close relationship with physics-based interactions, empirical scoring functions are still used. The empirical scoring functions have been implemented to various docking programs: DOCK [118, 119], AutoDock [120], AutoDock Vina [121], Glide [122], GOLD [123], FlexX [124], and Surflex-DOCK [125].

Knowledge-based scoring functions basic assumption is highly frequent atomic pairs (distances) contribute more to a binding affinity than the less frequent ones. The advantage of knowledge-based scoring functions is the computing cost since they only require distance calculation. Examples of knowledge-based scoring functions are DrugScore [126], IT-Score [127], SMOG [128], DFIRE [129], and PMF [130].

### 3.3 Similarity/Distance-based methods

These methods assume that similar ligands bind to similar proteins, and vice versa and show similar properties and biological activities. [131] In these methods, different similarity measures can be used, including, chemical/expression/ligand/annotation/side effect-based for drugs [132] and Smith-Waterman alignment algorithm for proteins [102]. One example of these approaches is QSAR uses machine learning methods to compare a candidate ligand with the set of all known ligands to infer its binding capability. [133] These methods have some shortcomings, for instance conformation complexity, or in ligand-based methods, not using protein information and just relying on the similarity between ligands, therefore limiting the search space to ligand space only. Also, they need a large amount of ligands to form a good information space to use for the interaction prediction whereas there are not sufficient ligands for each particular protein.

### 3.4 Structural methods

Structure-based methods use the structural information of proteins or drugs, such as 3D coordinates or secondary structures or sequences, as input to represent protein and drug molecules.

Some of these approaches use the 3D structure of proteins and ligands (which may not be available for all of them) and an interaction scoring function like molecular docking simulation to calculate the binding energy [121, 134]. These 3D structures can be obtained from experimental methods like X-ray crystallography or NMR spectroscopy, or predicted using computational methods. [99, 135] Structural methods can be divided into three categories by the type of scoring function: the classic scoring function methods [136], machine learning scoring function methods [137, 138]

<sup>8</sup>A wet lab is one where drugs, chemicals, and other types of biological matter can be analyzed and tested by using various liquids.

<sup>9</sup>Research done on a living organism

<sup>10</sup>Research done in a laboratory dish or test tube

and deep learning scoring function methods [139, 79]. The main part of these methods is to accurately model the three-dimensional structure of proteins and compounds. The limitations of traditional structural approaches are the vastness of search space (therefore time consuming on large scale), unknown protein 3D structures, and unfeasibility of applying methods like docking simulation on some cases. [140, 141] Moreover, there are other non-machine learning methods available for computing affinity, such as FEP (Free-Energy Perturbation) [142] and MM/GBSA (or MM/PBSA) [143]. These traditional methods are very slow and require significant amount of computation resources. Drug compounds can directly dock to determine binding affinity when proteins have well-established structure information. However, numerous proteins lack such structural details, and even with extensive time dedicated to homology modeling, obtaining comprehensive structural information remains uncertain [144].

### 3.5 Feature-based methods

In these approaches, Feature vectors of drug-target pairs are obtained from their properties or by learning from raw data, and then fed into various classifiers or regressors [25]. Since both ligand-based and target-based aspects are considered in feature-based methods, they can be assigned to the so called "Chemo-genomic" approaches.

Chemo-genomics approaches use the information of proteins and drugs altogether and unify the chemical space of drugs (molecular weight, logP, hydrogen bond donors/acceptors, functional groups, etc) and genomic space of proteins (protein sequences, structures, functions, pathway information, etc) to make interaction predictions. chemo-genomics deals with the systematic analysis of chemical-biological interactions and can use extensive biological data that is readily available in public datasets. These data often represent high-level biological relationships and associations as features. [107, 105] The chemo-genomics methods can further be classified into feature-based and similarity-based methods [145]. The feature-based methods represent the drug-target pair with a vector of descriptors. The various properties of drugs, as well as the proteins, are encoded as corresponding features. The inputs of these methods are different feature vectors that may be produced by combining the properties of drug and targets and then they are fed into various machine learning models. On the other hand, a variety of similarity-based methods have also been developed to calculate the similarity between the drug compounds and target proteins. Various kernel functions have been defined that make use of similarity matrices which are computed using different techniques and measures.

### 3.6 Machine learning and deep learning methods

In most classic machine learning approaches, the hand-crafted features are used [146]. In recent years, however, it is shown that integrating feature learning capabilities into machine learning-based models improves prediction performance [147, 148, 149, 150]. Some traditional machine learning method for drug-target interaction prediction are similarity-based (Bipartite local models (BLM) [151], K-nearest neighbor (KNN) [152], Kronecker Regularized Least Squares (KronRLS) [102], COSINE [153], KRONRLS-MKL [154], BLM-NII [155]), feature-vector-based (Support Vector machine (SVM) [156], Adaptive Boosting Support Vector machine (Adaboost-SVM) [157]), and semi-supervised (Restricted Boltzmann machines (RBMs) [158], Gaussian Interaction Profiles (GIP/RLS-Kron) [159], and Laplacian Regularized Least Squares (LapRLS) [160]). Most of these methods cannot automatically extract high-level hidden features from drugs and proteins [161].

KronRLS [102] uses kernels built from molecular descriptors of the drugs and targets within a regularized least squares regression (RLS) framework. Following standards of kernel learning methods, they first defined an objective function where the kernel function indicated the similarity of two drug-target pairs in the Hilbert space. Then, they regarded the problem of learning a prediction function as finding a minimizer of the objective function with the aim of binding affinities prediction.

SimBoost [162] uses the affinity similarities among drugs and among targets to build new features. After training gradient boosting machine based on final features of drug-target pairs, SimBoost can be applied to predict binding affinities of unknown drug-target pairs.

Predicting the potential space of binding sites and extracting the best features related to these sites is a key challenge in DTI/DTA. Many Deep learning-based methods tried to overcome the challenges with various models and mechanisms including The convolutional neural networks (CNNs) [163, 164], graph neural networks (GNNs) [165, 166, 167, 168, 169, 170], non-Euclidean-structured data in GNNs [171, 172, 173], equivariant graph neural networks (EGNNs) [174, 175], feed forward neural networks (FNNs) [176], long short term memory networks (LSTMs), recurrent neural networks (RNNs) [177], attentions (multihead attentions, self attentions, cross attentions) [178, 179, 180, 181, 182], autoencoders [183, 184, 185, 186], pre-training [187], transformers [188, 189, 190, 191], bidirectional encoder representations from transformer (BERT) [192, 193], language models [194, 195], image inputs [196, 197], Hierarchical learning and modeling [198, 199], neural factorization machine (NFM) [200, 201], constrastive learning [202], and interactive learning [203]. Some models try to be the fastest models to predict DTA [204, 205, 206], some try to overcome the

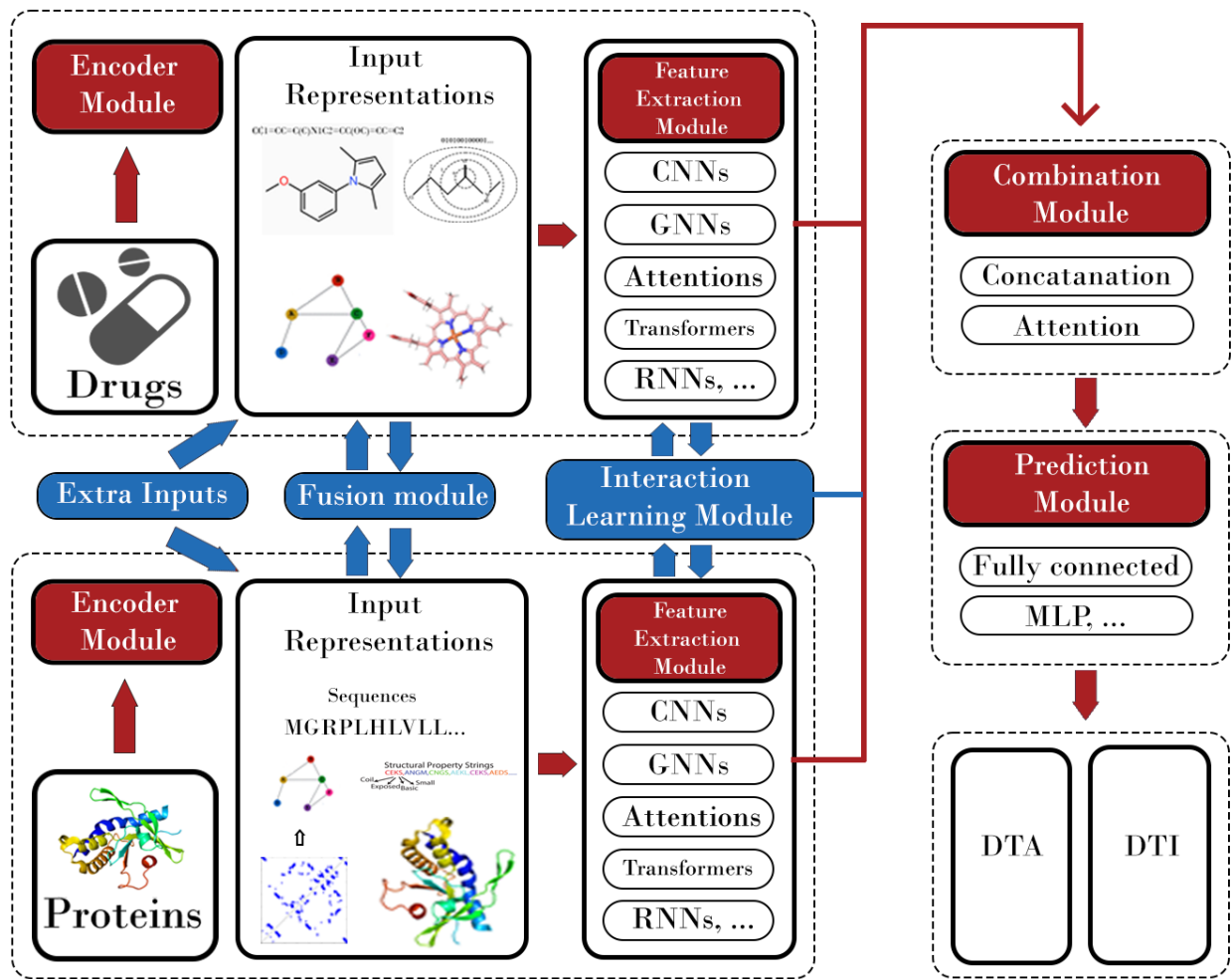
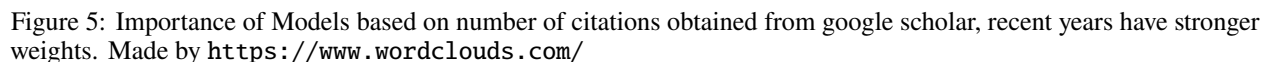


Figure 4: Overview of general frameworks used in deep learning methods. Red blocks are seen in most of the models. Blue blocks are modules that models have.

limitations of models like CNNs which only works on a particular region of information, excluding comprehensive details, and some try to learn the best interaction by using interactive learning modules.

Except some novel studies [207, 208], as Figure 4 shows, deep-learning-based methods include data pre-processing and encoder, a drug feature extraction module, a protein feature extraction module, combination module, and a prediction module in general and unlike traditional methods, these methods can extract high-level features automatically [209]. Most methods in drug-target prediction which are called Y-shaped by this review [21], extract features from both drugs and proteins, then run deep learning model on them to get an embedding for each side, and concatenate them and apply head modules like a fully connected layer (FC) to get the final prediction output. Furthermore, deep learning methods in DTI or DTA sometimes have two different kinds of model as the type of the drug input or protein input can be different. For example, GNN as a structural model can handle the feature extraction of molecular graphs of drugs while LSTM as a sequence model handles the feature extraction of string protein sequences.

Some studies [81, 210] tried to learn the interactive features of drugs and proteins alongside the two separate pipelines. Because most of the models are hybrids of other models as we are dealing with two spaces of problems (drug and protein space), therefore the categorization of the methods is better not to be based on model architecture type, instead it should be based on type of the inputs. Therefore, approaches here are divided into three main categories: sequence-based methods, structure-based methods, and sequence-structure-based methods. Sequence-based methods deal with drug and protein sequence inputs, structure-based methods get both drug and protein inputs as graphs, and sequence-structure-based methods are the models that get hybrid inputs of drug and protein graphs and sequences. It is important to note that methods employing utility networks, while fitting into these categories based on their input types,



Some mentioned models are ligand-target or compound-target interaction prediction methods, and are used for predicting the interaction between a ligand and a target protein. Drug-target interactions are a specific type of protein-ligand interactions, where the ligand is a drug molecule. Many of the fundamental principles and modeling techniques used in protein-ligand interaction studies are directly applicable to drug-target interactions. Discussing protein-ligand interaction models can provide a broader context and deeper understanding of the underlying principles involved in drug-target interactions. Most of the DTA models mentioned in the following sections can also be used for DTI task with applying a threshold on binding affinity datasets, changing the head of the framework and altering the loss of the model.

### 3.6.1 Sequence-based methods

- DeepDTA [112] employed two separate 1D-CNN modules to learn representations from the Protein sequences and SMILES strings (encoded as label encodings) and combine these two representations to feed into three fully connected layers block which was called DeepDTA. They evaluate the effectiveness of CNN blocks by replacing one pipeline with similarity matrices (with S-W and PubchemSim algorithms) and testing different combinations of it. DeepDTA compares its results to the KronRLS [102] algorithm and SimBoost [162] in which both used traditional machine learning algorithms and utilized 2D-representations of the compounds in order to obtain similarity information. In DeepDTA study, 1D representation of protein and drugs were preferred over 3D-structures of the binding complexes because there were limited to known protein ligand complex structures, with only 25 000 ligands reported in PDB in that time [113].

- WideDTA model [214] is an extension of DeepDTA in which the sequences of the drugs and proteins are first summarized as higher-order features. For example, the drugs are represented by the most common sub-structures (the Ligand Maximum Common Substructures (LMCS) [215]), while the proteins are represented by the most conserved sub-sequences (the Protein Domain profiles or Motifs (PDM) from PROSITE [216]). There are four inputs (protein sequence words, ligand sequence words, LMCS, PDM) to the 2 layered CNN models and output is followed by a concatenation and three FC layer.
- Deepaffinity [177] used a seq2seq auto-encoder model to learn protein and compound representation in an unsupervised manner. Next, the output is fed into an attention layer, and the output is given to a one-dimensional convolutional layer. The outputs of proteins convolutional layer and compounds convolutional layer are concatenated and fed into the fully connected layers.
- MT-DTI [217] propose a new MBERT drug molecule representation based on the self-attention mechanism and a MaxPool representation and CNNs module for proteins, followed by multi-layered interaction dense layers to predict affinity scores.
- Co-VAE (co-regulaized variational autoencoder) [218] used two variational autoencoders for generating drug SMILES and protein sequences, respectively, and a co-regularization part for generating the binding affinities. This model tries to maximize the lower bound of the joint likelihood of drug, target and their affinity.
- GANsDTA [219] comprises two GANs for feature extraction and a regression network for prediction. Each GAN model gets drugs or proteins sequences and learn them with a discriminator module and a generator module which produces fake noisy data.
- DeepCDA [220] uses two modules which are a combination of convolutional neural networks and long short-term memory networks, to analyze the structure of both the compound and the protein. CNN captures local patterns while LSTM learns the global patterns and far dependent sections. A key innovation is the use of a two-sided attention mechanism, which allows the model to be more interpretable and also focus on the most important parts of the compound and protein structures. Additionally, the model incorporates an adversarial discriminative domain adaptation method (ADDA) to improve its performance on new, unseen datasets and do the inference in cold setting. The effectiveness of this new method is demonstrated through experiments on three widely used datasets: KIBA, Davis, and BindingDB.
- DeepDTAF [221] integrates global and local features of proteins including protein sequence, protein-binding pockets, and secondary structural properties and SMILES of drugs. These features are then fed into embedding layers, dilated convolutions, and convolution layers for DTA prediction. DeepDTAF utilizes the pockets obtained from the protein compound complex, which suggests that the pockets used in the DeepDTAF are the ones where the interaction occurs, therefore it cannot generalize to unseen drug-target complexes.
- ML-DTI [222] formulated the DTA problem from a global perspective by adding mutual learning layers between the two pipelines. The mutual learning layers consist of multi-head attention and position-aware attention.
- MATT-DTI [223] uses a relative self attention for drug sequences and a Multi Head Attention to combine the results. CNNs are used for FASTA sequences of proteins.
- SimCNN-DTA [224] calculates the Smith-Waterman and Tanimoto similarity of proteins and drugs, respectively and uses 2D CNN for their outer product to predict DTA.
- FingerDTA [225] utilizes CNNs to extract local patterns from drug and protein one-hot vectors and use generated fingerprints as a guide to predict DTA.
- MultiscaleDTA [226] uses multiscale CNNs and pooling with self attention for both drugs and protein sequences. The extraction of different scale of features allow the model to learn the features in multiple levels.
- CSatDTA [227] enhances the DTA prediction with CNNs by using a convolution model with self-attention mechanisms on molecular drug and target sequences. Furthermore, a web server was used to implement the CSatDTA model. <sup>11</sup>
- AttentionDTA [228] utilizes a label encoder, embedding layer and a 1D-CNN block to extract features from both drugs and proteins separately. A bilateral multi-head attention and a multi layer perceptron layer is used for the head of the framework to predict the affinity.
- MRBDTA [229] consists of three main parts including, embedding and positional encoding, Trans block, and the head. This models utilizes transformers and skip connections for drug and protein sequences to predict DTA and offer some interpretability as it uses attention weights.

<sup>11</sup><http://nsc.lbio.jbnu.ac.kr/tools/CSatDTA/>

- DTITR [230] proposes an end-to-end transformer-based architecture with cross attention transformer encoders for predicting DTA.
- ELECTRA-DTA [231] incorporates an unsupervised learning mechanism to pre-train two ELECTRA-based contextual embedding models and uses it alongside a squeeze-and-excitation (SE) convolutional neural network block stacked over three fully connected layers.
- FusionDTA [232] encodes drug molecules as SMILES strings, and proteins as word embeddings. The LSTM layers are designed to construct the basic blocks of the encoder layer. The intermediate carriers of drug molecules and proteins are imported into the fusion layer to obtain an output carrier representation of binding affinity. Furthermore, FusionDTA leverages knowledge distillation to combine the predictions from multiple models.
- AffinityVAE [233] (Affinity variational autoencoder) uses interaction feature mapping and a variational autoencoder, which consists of A multi-objective model that combines the affinity prediction and ligand generation based on data augmentation to validate the prediction performance. The design of the adaptive autoencoder of target chemical properties and interaction feature maps allows them to generate new ligands similar to known ligands and add them to the original training set. The protein sequences are first encoded on a pre-trained protein language model to fully capture their local and global structural information of the protein. For the ligand SMILES sequence, the first branch represents SMILES as an atom graph to extract the high-order structure information of the ligand, while the second branch feeds the ligand into a one-dimensional sequence feature extraction module in order to extract its atomic-level information. Furthermore, the extracted protein and ligand features are fed into the mutual attention module to capture the influence of different parts of the protein or ligand on the interaction. Based on the binding of proteins and ligands at the residue and atomic levels, innovative protein-ligand feature interaction module (ARCM) captures local features and constructs feature maps to identify the most important interaction features. A final prediction module employs the captured features to determine the affinity of the pairs of features.
- ArkDTA [234] incorporates non-covalent interactions (NCIs) knowledge with multi-head attention modules to obtain better results. This model use FASTA sequence of proteins with ESM and SMILES of drugs with Morgan fingerprint as inputs and two novel modules which are called Pooling by Multi-head Attention (PMA) and Multi-head Attention Block (MAB) as model to predict DTA.
- CAPLA [235] employs the cross attention mechanism to capture the mutual effect of protein binding pockets and ligands. Dilated convolution and 1D convolution is used for ligands/proteins and protein pockets, respectively.
- BiComp-DTA [236] argues that similarity-based information, such as Smith-Waterman scores have shown poor prediction performances, or depends on employing multiple information types. Therefore, this model employs Lempel-Ziv-Markov chain algorithm (LZMA) alongside with Smith-Waterman to construct the unified measure for the DTA prediction task. The novelty of this study is the BiComp encoding module which is the Hadamard product [237] of the normalized Smith-Waterman (SW) and normalized compression distance (NCD) [238] similarity matrices.
- MT-DTA [239] utilizes mutual learning / Information interaction learning with self-attention between the drug and protein learning pipelines for DTA prediction. A label encoding layer, an embedding layer, a CNN block and a Transformer block is used for both pipelines.
- PCNN-DTA [240] employs two feature pyramid network (FPN) with skip-connections and multi-head self-attentions (MHSA) as heads for drug and protein pipelines. FPN fuses the features obtained in each layer of a multilayer convolution network to have more low-level feature information.
- DGDτα [241] uses a dynamic graph attention network for drugs and a bidirectional long short-term memory (Bi-LSTM) network with CNN for proteins to predict DTA.
- FastDTI [205] is a fast framework that uses pre-trained models like Grover [242], ProtBERT, and ChemBERTa to construct multimodal inputs and concatenates them via dense layers to predict DTA.
- TransVAE-DTA [243] consists of a VAE module, a transformer module, and an adaptive attention pooling (AAP) module. AAP block for feature fusion significantly improves the prediction performance.
- ImageDTA [244] treats word vector-encoded SMILES sequences as images and applies multiple single-layer multi-scale 2D-CNNs horizontally. CNN is used for protein sequences and BiLSTM is utilized as a final model to predict the task.
- TEFDTA [245] applies a transformer encoder on fingerprint representation (MACCS) of drugs and CNN on protein sequences (FASTA with label encoding) for bonded and non-bonded drug-target affinities.



- DCGAN-DTA [246] inspires from generative adversarial networks (GAN) and applies a deep convolutional GAN (DCGAN) on drug and protein sequences. This model uses CNN as discriminator and generator and tries to distinguish between real or fake (adding noise) SMILES and real or fake protein sequences.
- PLAPT [247] utilizes two pre-trained models (ProtBERT and ChemBERTa) and a branching neural network for DTA prediction.
- DEAttentionDTA [248] is based on dynamic word embeddings and a self-attention mechanism. SMILES, protein, and pocket sequences are fed into a dynamic word-embedding layer based on a 1D convolutional neural network.
- MREDTA [249] utilizes BERT and Transformer encoders in BERT-Trans block and Multi-Trans block to capture the relations between sequences in drugs and proteins separately and concatenates them for DTA prediction.
- MDF-DTA [250] uses 1D, 2D, and 3D representations obtained from different pretrained models for both drugs (Mol2Vec, GIN, E3NN) and targets (ProVec, BERT, ESM-Fold).
- MFDR [251] used Auto-Encoders as building blocks of deep network for reconstructing drug and protein features to low-dimensional new representations, followed by a support vector machine module.
- DeepDTI [252] models DTI using Deep Belief Network (DBN), which is a stack of Restricted Boltzmann Machines (RBMs) [253, 254]. It uses the concatenation of ECFP2, ECFP4, ECFP6 as the drug feature and uses protein surface classification for protein features.
- DeepConv-DTI [139] performs convolution on various lengths of amino acids subsequences to capture local residue patterns of generalized protein classes. For drugs it uses Morgan/Circular fingerprints and a fully connected layer to extract drug features.
- Hu et al. [255] used a 2D-CNN on drug-target augmented matrices of drug-target pairs to predict DTI. Drugs were obtained from PaDEL descriptor program and targets were from different physicochemical properties of amino acids in Protein sequences.
- DrugVQA [256] utilizes DynCNN and Sequential attention for 2D distance map of proteins and BiLSTM with Multi head attention for Smiles of drugs. This study is the first to utilize protein 2D distance map for predicting drug-protein interaction.
- MolTrans [257] utilized knowledge inspired sub-structural pattern mining algorithm (FCS) and interaction modeling module and an augmented transformer encoder to better extract and capture the semantic relations among sub-structures extracted from massive unlabeled biomedical data.
- EnsembleDLM [258] utilizes different fingerprints and combination of 1Dconv and linears and integrate multiple models by taking the arithmetic mean on the predicted binding affinity scores of different models.
- CA-DTI [180] uses two Transformer encoders as feature extractors and the Cross Attention as a task executor, key regions of interest for novel drug candidates were found.
- BridgeDPI [259] constructed a learnable drug-protein association network, which has drug nodes, protein nodes and new nodes which are called "bridge nodes". A 3-layer graph-conv layer and 2 FFN layers are applied to predict DPI.
- HyperAttentionDTI [260] models complex non-covalent inter-molecular interactions among atoms and amino acids using an attention module and assign an attention vector to each atom or amino acid.
- MPS2IT-DTI [261] encodes protein and drug sequences to images by reshaping the normalized k-mer count vectors and pass them through 2D CNNs, separately.
- AMMVF-DTI [77] employs two modules named ITM (interaction transformers) and NTN (neural tensor networks) for node level embeddings and graph level embeddings of drugs and proteins, respectively. ITM consists of two parallel interacting transformer encoders. This module serves to extract node-level interaction features between drugs and targets. NTN is employed to explore potential K major associations between drugs and targets as interactive eigenvector outputs. To get the graph level embeddings of proteins and drugs, BERT and an attention layer is used for node level embedding of drugs which is acquired with word2vec model and GAT and an attention layer is utilized for node level embeddings of drugs. Outputs of NTN and ITM is concatenated and fed into a MLP for the classification task.
- MCL-DTI [262] utilize both molecular image and chemical features of drugs. The image of the drug mainly has the structural information and spatial features of the drug, while the chemical information includes its functions and properties. The framework consists of feature decoder and encoder block with Multi-head self attention (MSA) and Multi-head cross attention (MCA) modules.



- FOTF-CPI [210] uses encoders to extract features of fragmented proteins and drugs, learns each one with fully connected layers, and also learns the interaction between these features with local affinity attention. This study experiments with different methods such as character-based slicing (CS), BRICS [263], Byte Pair Encoding (BPE) [264], FCS [257], and FSOT (their method) and comes to a conclusion that FSOT is the better slicing strategy for fragmenting.
- DeFuseDTI [265] includes base encoder and detail encoder to extract locally aggregated features and detailed features of each target residue and drug atom. The detail encoder (utilizing Invertible Neural Networks for targets and graph transformers for drugs) can capture the features of each atom and residue. Protein output and output of GCN feed with molecular drugs are fed into the Multi-view Fusion Attention learning module (MFA).
- PHCDTI [266] handles combinatorial effects (i.e., high-order crossover between drugs and proteins) when multiple non-covalent interactions coexist by a multi-channel parallel high-order prediction model. A tri-channel parallel model structure is used, allowing each channel to independently learn the interaction patterns (designed from low-order to high-order, incorporating linear, inner-product, and pair-interaction feature crossover methods). The stacking of residual connections enables the model to effectively model high-order crossover. Multi-head attention mechanisms and squeeze-excitation networks (SENET) is used for inner product and pair-interaction, respectively.
- CWI-DTI [267] employ an innovative auto-encoder framework which is called Stacked De-noising Sparse Auto-encoders (SDSAE) to fuse multiple drug/target topological similarity matrices. This model compares its results in different datasets from Chinese and Western medicine.

### 3.6.2 Structural-based methods

Since the 1D sequence is not a natural representation for molecules, some important structural information of drugs could be lost, degrading model prediction performance. Structural features can be acquired from 3D or 2D structures of drugs and proteins to predict the interaction between them. Modeling the 3D structure of proteins is a challenging task, and the 3D structure of proteins is not always available. For unknown or rare protein structures and functions, models prediction effectiveness may be limited. Table 2 shows the summary of structural-based models and corresponding inputs are shown in the table in Appendix C.

1. DGraphDTA [95] constructs target graphs (contact maps) from the corresponding protein sequences via the protein structure prediction methods and applies GNNs to mine structural information hidden in drug molecular graphs and target molecular graphs.
2. GEFA (Graph Early Fusion Affinity) [268] transfers a drug molecule graph to a protein graph for learning via an attention mechanism which is called fusion. This fusion enables the model to learn the interaction between drugs and proteins in a novel approach. This model uses GCNs for molecular graph of drugs and contact map graphs of proteins. After the fusion, GEFA concatenates the outputs and uses a FC layer for DTA prediction.
3. GSAML-DTA [269] used the molecular graph representation for drug Smiles and protein graphs created from contact maps to feed the separately into a GAT-GCN learning module. The output features were concatenated and optimized via mutual information and fed into a FC head for affinity prediction.
4. HGRL-DTA [270] utilized a hierarchical graph representation learning model for predicting DTA. Drug-target binding affinity data was represented as an affinity graph, with drugs and targets as vertices within the graph. Also, drugs and targets were represented as molecular graphs, respectively. GNN was used to learn global-level affinity relationship within the affinity graph and another GNN was also used to separately capture the local chemical structural features of drugs and proteins. Through a message propagation mechanism, the learned hierarchical graph information was integrated, and the structural features of drugs and targets were refined using GCN. Finally, features were combined and a FC network was used to predict DTA.
5. WGNN-DTA [271] constructs weighted protein and molecular graphs through sequence and SMILES that can effectively reflect their structures. To utilize the detail contact information of protein, graph neural networks (GAT, GCN) are used to extract features and predict the binding affinity/interaction. Unlike DGraphDTA which required extensive database scanning, particularly during the sequence alignment step, WGNN-DTA uses Contact map of proteins which are carefully built by the ESM model.
6. Ma et al. [272] used the graph structure of drugs and proteins (graph from contact maps acquired from Pcons4 with PSSM features) and tested different graph models (S2GC, GCN, GAT, GraphConv, SAGE) for DTA prediction.

Table 1: Summary of sequence-based models

Model	Task	Architecture	Drug/Ligand models	Protein/Target models	Extra models
FastDTI	DTA	Comb-FC	Dense	Dense	Dense
DeepDTA	DTA	Comb-FC	CNN	CNN	N/A
WideDTA	DTA	Comb-FC	CNN	CNN	CNN
MATT-DTI	DTA	MHA-FNN	SA, FNN and CNN	CNN	MHA
TC-DTA	DTA	Comb-FC	CNN	Encoder blocks	N/A
BiComp-DTA	DTA/DTI	Comb-FC	CNN	3 FCs	N/A
DeepDTAF	PLA	Comb-FC	Dilated conv	Dilated conv	3 Convs
CAPLA	PLA	Comb-FC	1D-Dilated Conv	1D-Dilated Conv	CA
DeepAffinity	CPA	Comb-FC	RNN-Attention-CNN	RNN-Attention-CNN	N/A
ImageDTA	DTA	Comb-FC	Multiscale 2D-CNNs	1D-CNN	BiLSTM, Skip concatenations
FingerDTA	DTA	Comb-FC	Dense Convolutional Block CNN, FC	Dense Convolutional Block CNN, FC	N/A
DCGAN-DTA	DTA	Comb-FC	DCGAN+CNN	DCGAN+CNN	BLOSUM encoding for protein
SimCNN-DTA	DTA/DTI	1pipe-FC	2D-CNN	2D-CNN	N/A
MT-DTI	DTA/DTI	Comb-Multilayered FFN-FC	Transformer	CNN	Dense network
ML-DTI	DTA	Comb-FC	3Convs+maxpool	3Convs+maxpool	Mutual learning blocks
MT-DTA	DTA	Comb-FC	CNN + Transformer	CNN + Transformer	Mutual learning with SA
MDF-DTA	DTA	Comb-FC	Mol2Vec, GIN, E2NN	ProVec, BERT, ESM-Fold	N/A
MultiscaleDTA	DTA/DTI	Comb-FC	Multi-scale CNNs+SA	Multi-scale CNNs+SA	N/A
AttentionDTA	DTA	Comb-BAH-FC	Encoder-CNN	Encoder-CNN	N/A
ArkDTA	DTA	Comb-FC	MHA+Pooling, Pooling by MHA	MHA+Pooling, Pooling by MHA	N/A
CSatDTA	DTA	Comb-FC	SA augmented Conv block	SA augmented Conv block	N/A
MRBDTA	DTA	Comb-Attention-FC	Modified Transformer	Modified Transformer	N/A
DTITR	DTA	Comb-FC	(CA) Transformer-encoder	(CA) Transformer-encoder	N/A
DGDTA	DTA	Comb-FC	GATv2, GATv2+GCN	BiLSTM+CNN	Dense layers
TransVAE-DTA	DTA	Comb-FC	Drug encoder	Target encoder	Adaptive attention pooling
DEAttentionDTA	DTA	Comb-FC	Dynamic word embedding+MHA	Dynamic word embedding+MHA	SA
GANsDTA	DTA/DTI	Comb-Convolutional regressor	GAN	GAN	convolutional regressor
TEFDTA	DTA	Comb-FC	Transformer encoder	CNN	N/A
PLAPT	PLA	Comb-Linear, FC	ChemBERTa	ProtBert	N/A
MREDTA	DTA	Comb-Linear	BERT, Transformer encoder	Transformer encoders	N/A
DeepCDA	CPA/CPI	Comb-BAH	CNN-LSTM	CNN-LSTM	N/A
FusionDTA	DTA	Comb-Attention-MLP	BiLSTM	BiLSTM	DNN
Co-VAE	DTA	Comb-FC	VAE	VAE	Co-regularization part
AffinityVAE	PLA	Mutual learning, Comb-Resnet	GRUMultiEncode	Pretrained Model, GRU	VAE
ELECTRA-DTA	DTA	Comb-FC	Pretrained ELECTRA + SE	Pretrained ELECTRA + SE	N/A
PCNN-DTA	DTA	Comb-FC	Feature pyramid network	Feature pyramid network	2 MHA, RegressionNet
BridgeDPI	DPI	Comb-FFN	Conv+POOL, FFN	Conv+POOL, FFN	3Graph-Conv
PHCDTI	DTI	Comb-FC	1D-CNN	1D-CNN	MHA, Pair-interaction layer
DeepConv-DTI	DTI	Comb-FC	FC	CNN	N/A
EnsembleDLM	DTI	Comb-FC	Linear and Conv1D	Linear and Conv1D	N/A
Hu et al.	DTI	Representation Comb-1 pipe	2D-CNN	2D-CNN	N/A
MCL-DTI	DTI	Comb-FC	CNN backbone+MSA, MSA+MCA	MSA+MCA	N/A
CWI-DTI	DTI	Comb-FC	SDSAE	SDSAE	CNN
HypAttentionDTI	DPI	Comb-FC	CNN	CNN	Attention+Pooling
MPS2IT-DTI	DTI/DTA	Comb-FC	Conv 2D layers	Conv 2D layers	Dense layers
MFDR	DTI	1pipe-FC	Stacked auto-encoder, SVM	Stacked auto-encoder, SVM	N/A
DeepDTI	DTI	1pipe-FC	Deep Belief Network	Deep Belief Network	N/A
MolTrans	DTI	Interaction module-Decoder	Transformer	Transformer	FCS mining module
AMMVF-DTI	DTI	Comb-MLP	BERT-Attention	GAT-Attention	NTN, ITM
DeFuseDTI	DTI	Comb-MLP	GCN	CNN residual connection blocks	Multiview attention learning
DrugVQA	DPI	Comb-FC	BiLSTM, MHA	DynCNN, Sequential attention	N/A
FOTF-CPI	CPI	Comb-FC	Transformer encoder	Transformer encoder	Local affinity attention
CA-DTI	DTI/DTA	Comb-FC	Transformer encoder	Transformer encoder	CA

- MSGNN-DTA [273] employed a multi-scale graph construction approach. Two graphs (atomic level and motif level graph) were constructed for drugs and one graph (weighted graph from target sequence contact map using ESM-1b [274]) for proteins. After learning each one with GNNs, attention was employed to fuse the multi-scale structural features and generate a join feature representation. For the prediction of DTA, a FC head was used.
- PLANET [275] takes the graph represented 3D structure of the binding pockets on the target proteins as input of Equivariant Graph Convolutional Layer (EGCL) and the 2D chemical structure of the ligand molecules as input of a multi-head attention mechanism and updates the features using a protein ligand communication module (cross-attention). This model is trained through a multi objective process with three tasks, including deriving the protein-ligand binding affinity, protein-ligand contact map, and intra-ligand distance matrix.
- HiSIF-DTA [276] is a hierarchical semantic information fusion framework for DTA prediction. In this framework, a hierarchical protein graph is constructed that includes not only contact maps as low-order structural semantics but also protein-protein interaction (PPI) networks as high-order functional semantics.
- CGraphDTA [277] transforms the protein structure into graph with node features calculated by PSSM, HMM, and DSSP [278] and drug SMILES to molecular graphs with node features calculated by pre-training features from Mol2Vec. Neural network layer (NNL), Convolutional neural network with kernel x (CNNX), and Variant GNN (VGNN) is used to predict DTA.

Table 2: Summary of structural-based models.

Model	Task	Architecture	Drug/Ligand models	Protein/Target models	Extra models
DGraphDTA	DTA	Comb-FC	GNN(GCN,GAT)	GNN(GCN,GAT)	N/A
WGNN-DTA	DTA/DTI	Comb-FC	GNN(GCN,GAT)	WGNN(GCN,GAT)	N/A
HGRL-DTA	DTA	Comb-MLP readout-FC	GCN	GCN	GCN
Ma et al.	DTA	Comb-FC	GNNs (GCN, GAT, GraphConv, SAGE, SGC)	GNNs (GCN, GAT, GraphConv, SAGE, SGC)	N/A
GSAML-DTA	DTA	Comb-FC	GAT-GCN	GAT-GCN	N/A
MSGNN-DTA	DTA	Comb-Attention-FC	GCN-GAT	GCN-GAT	GCN-GAT
GEFA	DTA	EF-Comb-Linear	GCN with residual blocks, Linear, Max pooling	GCN with residual blocks, Linear	N/A
de Fusion					
S2DTA	DTA	Comb-FC	GNN (GCN)	GNN (GCN)	1D-CNN
STAMP-DPI/X-DPI	DPA/DPI	Comb-FC	GCN, Mol2Vec	GCN, TAPE	Transformer decoder (BERT)
HGTDP-DTA	DTA	Comb-FC	GCN	GCN	Transformer+Multi view fusion
NG-DTA	DTA	Comb-FC	GNN	GNN+Conformer +Attention weighted sum	N/A
GraphScoreDTA	PLA	Comb-Dense	Bi-transport+GNN-GRU	Bi-transport+GNN-GRU	Distance dependant GNN+SCs
CGraphDTA	DTA	Comb-FC	NN, CNN with kernel X, Variant GNN	NN, CNN with kernel X, Variant GNN	Mol2vec, PSSM, HMM
GNPDTA	DTA	Comb-FC	Pre-trained GIN+2D-CNN	Pre-trained GIN+2D-CNN	N/A
AttentionSiteDTI	DTI/DTA	Comb-MLP	Topology Adaptive Graph CNN	Topology Adaptive Graph CNN	SA
AttentionMGT-DTA	DTA	Comb-attention-FC	Graph Transformer	Graph Transformer, cross CA	ESM-2
GTAMP-DTA	DTA	Comb-attention-FC	Graph Transformer	Graph Transformer	ESM-2, Mol2Vec CA, Conformation and Interaction Modules
PLANET	PLA	Comb-FC	Graph encoder(JT-VAE)	EGCL	
EMPDTA	DTA	Comb-DNN	RGCN, MolFormer	Cloud Points Sampling +Quasi-Geodesic Convolution +MLP	ESM-2, GearNet
CASTER-DTA	DTA	Comb-FC	Geometric Vector Perceptron	Geometric Vector Perceptron	CA
Graph-CNN	DTI	Comb(Average)-FC	GCN	GCN	N/A

11. S2DTA [279] creates a heterogeneous graph from protein graph, pocket graph (enriched with 1D CNN semantic feature extraction from both Protein sequences and pocket sequences), and molecular graph of drugs which a GNN (GCN) is applied on it. Final features are concatenated and a FC is used for DTA prediction.
  12. NG-DTA [280] takes molecular graphs of drugs and n-gram molecular sub-graphs of proteins as inputs which are then processed by graph neural networks and GNNs with a Conformer block, respectively. A Conformer block consists of a feed-forward module, a multi-head self attention module, and a convolution module.
  13. GraphscoreDTA [281] takes the combination of GNNs (GRU-GNN), bi-transport information mechanism, and physics-based distance vina terms into account. This model uses 2D graphs of proteins (from contact maps), ligand-protein sub-graphs (from interaction contact maps), and graphs of drugs to predict the DTA task.
  14. HGTDP-DTA [282] utilizes dynamic prompts (context-specific prompts for each drug-target pair) within a hybrid Graph-Transformer framework.
  15. GTAMP-DTA [283] uses two separate graph transformer on molecular graph of drugs and pocket graph of proteins. After using an attention layer, it concatenates features from pre-trained Mol2Vec and ESM-2 with its current output features and utilizes a MLP layer to predict the task.
  16. AttentionMGT-DTA [284] is a method very similar to GTAMP-DTA which uses two attention modules alongside graph transformer module on pocket graph and molecular graph of drugs.
  17. GNPDTA [285] uses two pre-training models which are utilized to extract low-level features from drug atom graphs and target residue graphs. Then, two 2D convolutional neural networks are employed to combine the extracted drug atom features and target residue features into high-level representations of drugs and targets.
  18. EMPDTA [286] integrates protein pocket prediction and DTA prediction. This framework consists of pocket online detection (POD), multi-modal representation learning for affinity prediction, and multi-task joint training. EMPDTA uses MolFormer and RGCN for drug graphs, ESM-2b and GearNet for pocket graphs, and POD module (Cloud Points Sampling, Quasi-Geodesic Convolution, and MLP) for protein structures from Alpha-fold structures.
  19. CASTER-DTA [175] makes use of an SE(3)-equivariant graph neural network to learn more robust protein representations alongside a standard graph neural network. This model uses Geometric Vector Perceptron (GVP) with GNN (Graph Isomorphism Network with Edge Enhancement) for drugs and GVP-GNN for proteins. Finally, a cross attention module fuses two pipelines together for DTA prediction.
- Graph-CNN [287] uses protein pocket graphs and molecular graphs for drugs and two GCN layers and a FC as a head to predict DTI.

- STAMP-DPI/X-DPI [288, 96] constructed a structure-aware graph neural network method from the protein sequence by combining predicted contact maps and graph neural networks. This method utilizes Mol2Vec for drugs to obtain drug drug associations, and a pre-trained BERT to learn embedded representations from a large set of unlabeled protein sequences provided by TAPE. A transformer decoder head is applied on the output embeddings from drug and protein pipelines.
- AttentionSiteDTI [289] utilizes attention in molecular graphs of drugs and binding pocket graphs of proteins to find the important nodes and edges and predict DTI/DTA more accurately.

### 3.6.3 Sequence-Structural-based methods

These methods use the structural features and sequences of drugs and Proteins and try to capture the local and global patterns of the proteins and drugs. The structural features allow the model to learn the relations in 2D/3D structure of the proteins and drugs, while the sequence features provide the model with the amino acid and atom level information. Table 3 shows the summary of hybrid-based models and corresponding inputs are shown in the table in Appendix C.

- Interpretable drug-target Prediction Using Deep Neural Representation [290] uses LSTMs for protein sequences, and modified CNNs for Drug 2D molecular graph, and a FC for head.
- PADME [291] introduces two model architectures named PADME-ECFP and PADME-GraphConv which are trained with each drug-target pairs. PADME-ECFP uses ECFP and PSC with MLP and PADME-GraphConv uses embeddings from Molecular Graph Convolution (MGC) and PSC with MLP to predict DTA.
- Wang et al. [69] propose a DTA model based on dipeptide frequency of word frequency encoding and a hybrid graph convolutional network. Word frequency characteristics of natural language are used to improve the frequency characteristics of peptides to express target proteins. The obtained protein features and drug graph structure are used as the input of convolution neural network and the input of graph convolution neural network, respectively.
- DeepGS [80] utilizes Smi2vec with BiGRU, and molecular graphs with GAT for drugs, and Prot2Vec with CNN for proteins. All of these outputs are concatenated together and were fed into a FC layer for prediction. The contextual information contained in protein and drug sequences are considered using Prot2Vec and Smi2Vec.
- DeepRelations / DeepAffinity+ [292] use protein sequences and compound graphs in DeepRelations model with three novel module called Rel-CPI to integrate different relations in drug-protein interaction prediction learning. These relations, including predicted solvent exposure, intermediate predicted k-mer binding residues, intermediate predicted binding residues, and predicted protein contact map, were used as inputs to different Rel-CPI modules.
- DeepH-DTA [293] propose using a heterogeneous graph attention (HGAT) for topological information of compound molecules, bidirectional ConvLSTM layers for modeling spatio-sequential information in SMILES, and a squeezed-excited dense convolutional network (SE) for protein sequences.
- GanDTI [294] employs a residual graph neural network for the compound molecular fingerprint data and forms a vector that could project product-based attention on the protein sequence to determine the binding importance on the sequence. Then the two parts of the data are concatenated and a MLP is used for prediction. The results are reported for both DTI and DTA tasks.
- DeepFusionDTA [295] utilizes sequence (SMILES and Protein sequences) and structure information (protein secondary structure, molecular fingerprint) of protein and drugs to generate fusion feature map of candidate protein and drug pair through StruM (Dilated-CNN) and SeqM (fusion of Dilated-CNN and BiLSTM) modules. Then it applies bagging-based ensemble learning strategy for regression prediction with Light Gradient-Boosting Machines. Similar framework to DeepFusionDTA is DFDTA-MultiAtt [296] which uses a dilated-CNN block and Bi-LSTM with a multi-attention module.
- GraphDTA [68] leveraged the structural features of drugs meaning molecular graphs and one-hot encoding of protein sequences. A 3-layer GNN (GCN, GAT, GIN, GAT-GCN) for the extraction of structural features for drugs, a 3-layer 1D-CNN for Protein sequences and FC as head was used to predict DTA.
- SAG-DTA [297] introduces global or hierarchical pooling with GCN to aggregate node representations weightedly for molecular drugs. 1D-CNNs are used for proteins and two FC layers for the final output.
- EmbedDTI [298] leverages GloVe for pre-training amino acid feature embeddings, which are then fed into a 1D-TextCNN. Both an atom graph and a substructure graph is constructed to capture structural information at different levels for drugs, used by GCN. Finally, the outputs are concatenated and FC layers are applied to predict DTA and labels.

Table 3: Summary of structural-sequence-based models.

Model	Task	Architecture	Drug/Ligand models	Protein/Target models	Extra models
ViDTA	DTA	Comb-FC	Graph transformer	1D-CNN	Attention
PADME	DTA	Comb-FC	GCN+MLP/MLP	MLP	N/A
Wang et al.	DTA	Comb-FC	GNN(GCN,GAT,GIN,GAT-GCN)	CNN with TF-IDF	N/A
GraphDTA	DTA	Comb-FC	GCN,GAT,GIN,GAT-GCN	CNN	N/A
LSTM-SAGDTA	DTA	Comb-FC	GCN+GAT+SAG-pool	LSTM+1D-CNN	N/A
T-GraphDTA	DTA	Comb-FC	GAT-GCN	Pretraining module	N/A
SAG-DTA	DTA/DTI	Comb-two FC	GCN+SAGpool (hierarchical and global)	1D-CNN	N/A
DeepGLSTM	DTA	Comb-FC	multiblock GCN	BiLSTM	GCN, Global pooling
DeepNC	DTA	Comb-FC	GEN, HGC-GCN	1D Convs	N/A
Xia et al.	DTA	Comb-FC	GCN	2D-CNN with word2Vec	N/A
GPCNDDTA	DTA	Comb-FC	Residual CensNET	Residual EW-GCN	SA, CA
MGraphDTA	DTA/DTI	Comb-MLP	Deep multi-scale GNN	Multi-scale CNN	N/A
GanDTI	DTA/DTI	Comb-MLP	Residual GNN	Attention on other pipelines	N/A
Tian et al.	DTA	Comb-FC	GNN	LSTM	BiGRU
SSR-DTA	DTA	Comb-FC	MLP, Multilayer GNN with GAT	Multilayer GNN with BIGNN	SSA-Fusion block
PocketDTA	DTA	Comb-FC	FCN, GraphMVP-Decoder	FCN, GVP-GNN layers	MHBAN
ColdDTA	DTA	Comb-Attention head-FC	GNN	CNN	N/A
KC-DTA	DTA	Comb-FC	GNN	2D-CNN, 3D-CNN	FC
AGraphDTA	DTA	Comb-FC	GNN	GNN, CNN	N/A
PGraphDTA	DTA	Comb-FC	GAT	PLMs (DistilProtBert, ProtBert, Seq2Vec)	N/A
EmbedDTI	DTA/DTI	Comb-FC	Graph attention layer and GCN+Pooling	1D-TextCNN	GloVe for proteins
DeepRelations	CPA/CPI	Inter-attention in Rel-CPI-FC	GCN, Attention	RNN, Attention	N/A
PSG-BAR	PLA	Comb-Linear	RGATs+Pool	RGATs+Attention weighted pooling	Interaction attention module
GEFormerDTA	DTA	Comb-FC	Attention, Maxpool	GCN, res blocks, graph pooling	Linear
GraphCL-DTA	DTA	Comb-FC	GCN	1D-CNN	Graph constrastive learning
DeepFusionDTA	DTA	Comb-FC-LightGBMs	StruM(Dilated-CNN), SeqM(Fusion of Dilated-CNN and BiLSTM)	N/A	
BACPI	CPI/CPA	Comb-BiAttention-FC	GAT	CNN	Bidirectional Attention
SSGraphCPI	CPA	Comb-FC	RNN encoding, Attention 1D-CNN	RNN encoding, Attention 1D-CNN	GCNN+Attention
DEELIG	PLA	Comb-FC/1pipe-FC	FC	3D-CNN	N/A
DLSSAffinity	DTA	Comb-FC	CNNs	CNNs	FCNNs
GDGRU-DTA	DTA	Comb-FC	Gated graph+TransformerConv	GRU/BiGRU	N/A
DeepGS	DTA	Comb-FC	GAT, BiGRU with Smi2Vec	CNN with Prot2Vec	N/A
DeepH-DTA	DTA/DTI	Comb-FC	Bi-Directional ConvLSTM	Dense+SE block	HeteroGAT
PLA-MoRe	PLA	Comb-FC	GIN	Transformer encoder	Auto encoder
DeepTGIN	PLA	Comb-FC	GIN	Transformer	Transformer
NHGNN-DTA	DTA	Comb-FC	BiLSTM, Multilayer GIN	BiLSTM, Multilayer GIN	MHSA
HBDTA	DTA	Comb-FC	MHGAT+GCNs/ MHGAT+GenConv	multi-layer BiLSTM	Attention
GK BertDTA	DTA	Comb-MLP	GIN, KB-BERT	DenseSENet	yes
MFR-DTA	DTA/DTI	Comb-Attention-FC	BioMLP Block	BioCNN Block	Elem feature fusion block
3DProtDTA	DTA	Comb-FC	GNNs+Dense network	GNNs+Dense network	Dense layers
SubMDTA	DTA	Comb-FC	pretraining GIN encoder	BiLSTMs	N/A
DataDTA	DTA	Comb-Attention-MLP	Linear, Residual dilated gated CNN	Linear, Residual dilated gated CNN	Dual-interaction module
UCMPNN-DTA	DTA	Comb-FC	Undirected-CMPNN	MLM and CPCprot	Attention
IMAE	DTA/DTI	Comb-FC	MSAM	ISCEM	N/A
TDGraphDTA	DTA	Comb-FC	Diffusion-based graph optimization+graph conv	Convs+skip maxpools	Multi scale interaction block
DrugBAN	DTI	Comb-FC	GCN	CNN	Bilinear interaction attention module+pooling, CDAN
Lin et al.	DTI	EarlyComb-FC	GCN	GCN	N/A
GraphCPI	CPI	Comb-FC	GNN (GCN/GAT/GIN)	Prot2Vec + CNN	N/A
TransformerCPI	CPI	Comb-Transformer Decoder-FC	GCN	(Conv1D) with gated linear units	N/A
FDTIIT	DTI	Comb-FC	GCN	multilayer CNN	Mutual attention fusion network, Interaction information tradeoff
Kim et al.	DPI	Comb-FC	GraphNet	Transformer+CNN	N/A
DeepMGT-DTI	DTI	Comb-FC	MCGCN+Transformer	CNN+FC	N/A
IIFDTI	DTI	Comb-FC	GAT	CNN	Bidirectional encoder decoder
MINDG	DTI	Comb-FC	MPNN+CNN	MPNN+CNN	HOAGCN
DTIAM	DTI/DTA/MoA	Comb-FC	Transformer, MaskedLM+DescriptorPred+FunctionalPred	Transformer, MaskedLM+ContactPred	N/A
DeepCPI, GNN-CPI	CPI	Comb-Attention-Softmax	GNN	CNN	Attention
CPGL	CPI	Comb-FC-Attention	GAT	BiLSTM	Two-sided attention
MHSADTI	DTI	Comb-FC	GAT	GAT	MHSA
CPIformer	CPI	Comb-Conv-FC	SA	Prob SA	N/A
CaoDTI	DTI	Comb-FC	GraphSAGE	Transformer	Co-attention module
DrugformerDTI	DTI	Comb-FC	Drug encoder	Protein encoder	Transformer decoder
CSDTI	DTI	Comb-FC	Drug molecule aggregator	Encoder (Conv1D)	CA

- DEELIG [299] used different features for pocket protein structure and ligands. This model employed atomic (one pipeline) and composite (two pipelines) models with protein-ligand and ligand features.
- SSGraphCPI [300] is composed of RNNs with an attentional mechanism and GCNNs on SPS, SMILES and molecular graph data.
- PLA-MoRe [301] applies an autoencoder model on bio-active property of drugs, GIN on molecular graph of drugs and transformer encoder on protein sequences.
- MGraphDTA [302] also, used the graph of drugs and target sequences in form of an embedded vector. However, it enhanced the global structural features extraction by employing a deeper multi-scale GNN (MGNN) (GCN with 27 layers), inspired by dense connections. Simultaneously, multi-scale CNN (MCNN) was applied to extract multi-scale features from target sequences. The resulting fused features were concatenated to form a combined representation of drug-target pair. Finally, the combined representation was fed into MLP to predict DTA/DTI. Drug-Online is an online platform for drug-target interaction that uses MGraphDTA and other models. [303]
- Tian et al. [304] improved GraphDTA model and changed the model’s channel to a triple-channel. They interpreted the protein sequences as time series and used LSTM, used GNNs for drug molecular graphs and BiGRU for local chemical background of drugs.
- DeepNC (Deep Neural Computation) [305] utilized Generalized Aggregation Networks (GENConv), Graph Convolutional Networks (GCNConv), and Hypergraph Convolution-Hypergraph Attention (HypergraphConv). This framework learns the features of drugs and targets by the layers of GNN and 1D convolution network, respectively. Then, representations of the drugs and targets are fed into fully-connected layers to predict the binding affinity values. This study also proposes Allergy dataset to test their model further.
- DeepGLSTM [306] uses a parallel GCN module composed of three GCNs with different layers for molecular graphs. Alongside the drug module, it adopts a bi-LSTM for protein sequences.
- GDGRU-DTA [307] utilizes GRU/BiGRU for proteins and GNNs for compounds. The GRU model processes the same task more quickly than LSTM because it has a different and more simple internal structure.
- BACPI [78] uses a bidirectional attention module on the outputs of GAT for molecular graphs for drugs and CNN for amino acid sequences of proteins in 3 character words.
- Xia et al. [82] proposes a DTA model based on graph neural networks and word2vec. In this model, the word embedding method is used to convert proteins sequence into sentences containing words to capture the local chemical information. SMILES is used to convert drug molecules into graphs. After feature fusion, DTA is predicted by graph convolutional networks.
- PSG-BAR (Protein Structure Graph-Binding Affinity Regression) [308] utilizes 3D structural information of proteins, ESM of Protein sequences, and 2D graph of ligands. Framework consists of residual graph attention layers (RGAT), pooling for drugs, attention weighted pooling for graphs of protein contact maps, and an interaction attention module learning the interaction between two pipelines. Output of RGAT for drugs, RGAT for protein graphs, and ESM for protein sequences are concatenated and are used for linear layers to predict PLA.
- DLSSAffinity [309] uses the pocket-ligand structural pairs as the local information to predict short-range direct interactions and uses the full-length protein sequence and ligand SMILES as the global information to predict long-range indirect interactions.
- GeneralizedDTA [310] introduces pre-training tasks for drugs and proteins and a multi-task learning model with dual adaptation mechanism (MAML-based updating strategy [311]) for addressing the forgetting problem of pre-training parameters.
- T-GraphDTA [187] developed a novel protein pre-training method (PTR) for protein representation learning, then proposed a DTA prediction framework based on PTR and hybrid graph neural network (GAT-GCN).
- AGraphDTA [166] employs GNNs to extract graph features of drugs and proteins. Then it employs CNN to extract amino acid sequence features. Also, a fusing block is employed to generate the fusion feature that represent the complex information of proteins.
- ColdDTA [312] enhanced the model’s generalization performance by data augmentation and attention-based feature fusion techniques. It used structural knowledge of drugs and target sequence information. Firstly, a new drug-target pair was generated by removing a sub-graph from the original graph of drug. Next, the structural features of drug and the sequence features of target were extracted using GNN and CNN, respectively. These extracted features were then fused via an attention-based fusion block and the fused features were fed into MLP to predict DTA.

- DataDTA [313] uses four different inputs, including Protein sequences and drug SMILES strings, as well as binding pocket descriptors (acquired from a pre-trained scorer) and AG-FPs. Then, it is concatenated after an embedding module with CNN sub-modules and the fusion strategy with a highway block and a multihead attention block (dual-interaction module) was designed to integrate and capture multi-scale interaction information. Finally, a MLP is used for the DTA prediction.
- MFR-DTA [314] uses amino acid embedding and word embedding for protein feature representation, and uses functional-connectivity fingerprints (FCFPs) and graph neural network (GNN) features for drugs. The proposed BioMLP module assists the model in extracting individual features of sequence elements and an Elem feature fusion block to refine the extracted features. A Mix-Decoder block was designed to extract drug-target interaction information and predicts their binding regions.
- UCMPNN-DTA [315] uses an undirected cross graph message passing neural network (CMPNN) for molecular embedding and combines CPCProt and MLM models for protein embedding. This model also uses an attention to find the important parts of proteins. MLP head was used to predict the final result and framework is evaluated with MSE and CI.
- KC-DTA [316] utilizes sequence information learning and converts protein sequences to 2D and 3D matrices using k-mer analysis and Cartesian product calculation. This model applies GNN for drug molecular graphs and 2D and 3D CNNs for the calculated matrices.
- SubMDTA [66] pre-trains a GIN encoder using constrastive learning method for drug feature extraction. This model also uses 3 Bidirectional LSTMs for 2,3, and 4 gram protein sequences.
- PGraphDTA [84] utilizes GAT and CNN for molecular graphs of drugs and proteins, respectively. It also uses several protein language models for protein sequences and adds contact maps as an extra input to improve its results.
- TDGraphDTA [317] employs diffusion-based optimization for drug molecular graphs and uses Convs for protein sequences. This model utilizes a multi head (two) cross-attention module which uses a drug query matrix, a protein key matrix and a protein value matrix for one cross attention and the other cross attention uses the rest of the matrices.
- GPCNDTA [318] utilizes GNN module, the linear projection and self attention layer to extract features from graphs of drugs (from SMILES) and proteins (from protein data bank and Alpha-fold structure predictions) and sequences of drugs (pharmacophore, SMILES) and proteins (FASTA). This model used residual CensNet and the residual EW-GCN to correspondingly extract features of drug and protein graphs and devised intramolecular and intermolecular cross-attention to respectively fuse and interact features of drugs and proteins.
- 3DProtDTA [319] uses structures obtained from Alpha-fold model for proteins, sequences (Morgan fingerprints) and structures of drugs with GNNs.
- NHGNN-DTA [320] feed the text embeddings into an adaptive feature generator including a tokenizer, BiLSTM and LayerNorm layers and the output is fed into the multi-head self-attention layer. This model combines the graphs of proteins and drugs with a central node and integrates adaptive node features, which are then fed into a multilayer GIN. The sequence-based and graph-based prediction results are integrated to obtain the final DTA prediction.
- GraphCL-DTA [321] employs a graph constrastive learning framework for drugs which allows the model to preserve the semantic information of drugs without data augmentation methods i.e. dropout-based augmentation strategies. GCN and 1DCNN is used for drug graphs and protein sequences, respectively.
- IMAEN [322] employs a molecular augmentation mechanism in its Molecular Structure Enhancement Module (MSAM) to enhance drug molecular structures by fully aggregating molecular node neighborhood information. It then uses multi-scale GCN and CNN in its interpretable stack convolutional encoding module (ISCEN) for drug and protein processing, respectively.
- ViDTA [323] adds virtual nodes to drug molecular graphs and applies a graph-transformer-based encoder. This model uses 1D-CNNs for protein sequences and fuses the features using an attention-based linear feature fusion block.
- DeepTGIN [324] uses graph isomorphism network (GIN) encoder and transformer encoder on molecular graphs and protein/pocket residue sequences, respectively.
- PocketDTA [325] enhances the generalization performance by using pre-trained models like ESM-2 and GraphMVP. This framework utilizes both sequences and structural information alongside pocket information for precise DTA prediction. GVP-GNN layers are used for pocket inputs and a multi-head bilinear attention network is used for generating and learning the interaction matrix.

- GEFoRmerDTA [326] proposes a framework that considers bond encoding, degree centrality encoding, spatial encoding of drug molecule graphs, and the structural information of proteins such as secondary structure and accessible surface area. This method uses a graph early fusion module that fuses drugs and protein graphs and applies GCN to obtain graph-based representation of proteins. Information in this framework is passed between protein and drug pipelines to learn the interaction better.
- LSTM-SAGDTA [327] utilizes LSTM and CNN for protein sequences from seqvec (ELMo) model and two encoders consisting GCN, GAT, and SAG-Pool in different order for molecular graphs of drugs.
- HBDTA [328] employs multi-head graph attention networks (Multi-head GAT), generalized aggregation networks (GENConv), and graph convolutional networks (GCNConv) for drugs. This model utilizes a multi-layer bi-directional long short-term memory (MBLSTM) with residual blocks to extract protein features.
- GK BertDTA [329] utilized GIN for molecular graphs of drugs, DenseSENet for proteins, and knowledge-based BERT semantic model on SMILES of drugs to obtain rich pre-trained semantic embeddings.
- SSR-DTA [330] uses BIGNN and a multi-layer graph network capable of adapting to diverse structural sizes, which enables the capture of molecular motifs across different scales, ranging from atomic to macro-cyclic motifs.
- DeepCPI/GNN-CPI [79] used a GCN to learn compound features and used CNN to learn protein sequence features. They used an attention mechanism to compute the attention coefficients, which considers the affinity, and the protein’s feature vector is obtained using the weighted sum of protein sub-sequence’s features along with attention coefficients.
- GraphCPI [76] employed 3-gram encoding with pretrained Word2Vec (Prot3Vec) to process protein sequences, followed by a CNN to handle the protein embeddings. Drug molecular graphs are fed into a GCN to extract their features, and the outputs are combined and a FC layer is used. This work claims that they were first to combine the local chemical context and topological structure to learn the interaction between compound protein pairs.
- TransformerCPI [331] used word2vec for protein sequences and transformer encoder (1Dconv) and GCN for molecular representation of drugs. This model aims to learn the interaction with transformer decoder module.
- Kim et al. [83] used transfer learning in encoding protein sequences with a pre-trained model, which trains general sequence representations in an unsupervised manner. GraphNet model is used for molecular graphs of drugs and 1D CNNs is utilized for proteins. They used a Bayesian neural network to make a robust model by estimating the data uncertainty.
- MHSADTI [332] employs GAT model for drugs and proteins with multi-head self-attention mechanism.
- CaoDTI [333] incorporates the Co-attention mechanism to learn the interaction between drugs and targets. This method uses graphSAGE for R-radius sub-graphs from SMILES of drugs and a transformer for protein sequences.
- IIFDTI [81] considers interactive features of local substructures of drug-target pairs with bidirectional encoder decoder and independent features for both targets and drugs with CNN and GAT, respectively.
- Lin et al. [334] constructed a drug-target interaction graph based on fusing drug and target similarity graphs using similarity network fusion (SNF) method. Graph isomorphic network (GIN) and TextCNN were used for drugs and proteins, respectively and GCN is used for the constructed DTI graph.
- CPGL [103] uses GAT and Bidirectional LSTM for drug substructures and 3-grams of Protein sequences, respectively. CPGL also utilizes a two-sided attention mechanism to capture the interaction between drugs and proteins and utilizes a FC to predict DTI based on concatenated features of proteins and compounds. This model experiments on label reversal datasets to ensure its robustness and generalization.
- CPInformer [335] extracts heterogeneous compound features, including structural graph features and functional class fingerprints, to reduce prediction errors caused by similar structural compounds. Then, they combine local and global features using dense connections and apply ProbSparse self-attention to protein features, under the guidance of compound features, to eliminate information redundancy.
- DeepMGT-DTI [336] utilizes a transformer network incorporating multilayer graph information for drug graphs and a CNN for protein embeddings.
- CSDTI [337] utilizes a molecular aggregator to learn the structural representation of drug graphs and uses a protein encoder for protein representations acquired from Prot2Vec model. This model fuses these representations using a cross attention block, receiving protein features as key and values and drug features as queries.



- DrugormerDTI [189] uses Graph Transformer on the input molecule graph and protein embeddings from Residual2vec.
- DTIAM [338] proposes a unified framework that uses transformer encoder and pre-training for drug molecular substructures and protein sequences and predicts DTI, DTA, and mechanism of action/activation/inhibition (MoA).
- DrugBAN [339] employs GCN and CNN blocks to encode molecular graph and protein sequences, respectively. Then they use a bilinear attention network module to learn local interactions between the representations of drugs and proteins and generate an interaction map. This model also tries to generalize to out of domain datasets and integrates a Conditional Adversarial Domain Adaptation (CDAN) module to its framework to better predict DTA.
- FDTIIT [340] uses flexible mutual attention to extract interaction information about drugs and targets, and then limit the dependence between them with an interactive information trade-off module to avoid redundant information. This model uses GCN and multiplayer CNN for drugs and proteins, respectively.
- MINDG [341] utilizes a mixed deep network (MPNN and CNN) to extract sequence features of drugs and proteins, a higher-order graph attention convolutional network (HOAGCN) is proposed to better extract and capture structural features, and a multi-view adaptive integrated decision module (concatenation).

### 3.6.4 Complex-based models

Deep learning methods have been introduced to predict DTIs by direct use of 3D protein-compound complexes [342, 343, 109]. Studies like PLIG [344], PaxNet [345], GLI [346], GIGN [347], IGN [348], PotentialNet [349], SchNet[350], FGNN [351] are examples of these methods. In some studies, input features were based on 3D matrix defined around pocket-ligand complexes instead of the whole complex. These methods generated a large number of input variables, and had the problem of limited number of training set. To overcome this problem, some studies used voxelization, which limits a regular cube range to reduce the number of input variables. Most of the complex-based models rely heavily on the time-consuming docking process, but they provide more interpretability than complex-free models. The protein structure prediction models like AlphaFold [352, 353] and RoseTTA [354] can provide better and more accurate templates for target proteins, resulting in better DTI/DTA prediction. Table 4 summarizes the complex-based models.

- AtomNet is a deep CNN for modeling bioactivity and chemical interactions [355].
- Atomic convolutional neural network (ACNN) [356] was developed for binding affinity by generating new pooling and convolutional layers specific to atoms.
- 3D-CNN [357] used 3D CNN with molecular representation of 3D voxels assigned to various physicochemical property channels.
- Cang and Wei [358] represented 3D structures in novel 1D topology invariants in multiple channels for CNN.
- TopologyNet [358] uses protein ligand complex 3D structures and the element-specific persistent homology (ESPH) method and CNNs to generate representations of these structures for prediction.
- Pafnucy [117] utilizes a 3D convolution neural network to produce a feature map of protein ligand 3D structures, followed by dense layers for predicting affinity values. Also, a voxel representation of protein and ligand complexes is used, which allows the visualization of protein and ligand structures and interactions. Using a regularization technique, their designed network focused on capturing the general properties of interactions between proteins and ligands.
- DeepAtom [359] designed a light-weight model based on 3D-CNN which includes Atom information integration block, 3D shuffle groups (3D PW/DwConvs), 3D pointwise Conv, and FCs to minimize two losses for PLA prediction.
- GNN-DTI [360] employed a GNN which directly incorporates the 3D structure of a protein-ligand complex. They also applied a distance-aware graph attention algorithm with gate augmentation for DTI prediction.
- OnionNet-1 [361, 362] used features of all inter molecular contacts in circles which are called onions to predict DTA using a CNN network. Also, in OnionNet-2, the protein-ligand interactions are characterized by the number of contacts between protein residues and ligand atoms in multiple distance shells.
- DeepBindRG [363] applied a 2D CNN and ResNet on protein-ligand complexes in the 2D format of interface spatial information.
- AK-score [364] utilizes ensemble of several residual networks with multiple channels of 3D convolutional neural network layers to improve the DTA prediction tasks (scoring, ranking, and docking).

- Jones et al. [365] fused spatial graph convolutional neural network (SG-CNN) for distance of pairs and 2D molecular graphs of drug-targets and 3D-CNN for complexes in two levels (mid and late).
- SIGN [366] attempts to model the 3D structural complex and protein-ligand spatial interactions with representing complexes as a complex interaction graph and feeding it into polar-inspired graph attention layer (PGAL) and pairwise interactive pooling layer (PiPool). PGAL can propagate the node’s and edge’s embeddings alternately with learning the spatial distance and angle information. PiPool performs on the edges’ representations to obtain the atomic type-based interaction matrix of the complexes which tries to approximate the overall interactions.
- GAT-Score [367] designed a dynamic feature mechanism to enable the model to deal with bond features for graph of drug-target complexes. Also, a virtual super node is introduced to aggregate node-level features into graph-level features, so that the model can be used in the graph-level regression problems.
- OctSurf [368] uses a novel space partitioning structure which has a flexible search hierarchy [369]. This paper shows the higher performance of this new representation against dense voxel representation in DTA prediction via 3D-CNN, ResNet, and VGG models.
- BAPA [370] employs 1D conv layers and attention layer for 1D vector of intermolecular descriptors of protein-ligand complexes. Descriptors were generated focused on contacted protein and ligand atom pairs using nine heavy atoms commonly observed in protein-ligand complexes,.
- APMNet [371] integrate the ARMA graph convolution (based on an auto-regressive moving average filter) [372] method and the graph convolution layer in the MPNN module [373].
- Sfenn [374] employed 3D-CNN to generate a score function for DTA prediction. Drug-target complexes were transformed into a 3D grid representation. This grid served as input to 3D-CNN, which learned high-level structural features. Finally, multiple density layers were applied to the extracted features for DTA prediction.
- IMCP-SF [375] uses profiles of intermolecular contacts (IMCP, IMCPiDB, IMC, IMCiDB, ECIF, APIF, SPLIF, PLEC FP) of proteins and ligands with random forest to score the interaction.
- KIDA [376] builds a complex-free model inspired by knowledge distillation framework and implements a method for modeling protein atomic features by fusing atomic chemical and spatial position features. This model needs ball query graph and pocket 2D graph of proteins, drug 2D graphs and bipartite graph of complexes to use EGNN, MPNN, student block and teacher block to predict the drug-target affinity.
- SS-GNN [377] constructs a single undirected graph based on a distance threshold for protein-ligand interactions and applies GNNs and MLP layers. The novelty of this framework causes the scale of the graph data to be greatly reduced.
- InterGraph [378] modeled protein-ligand complexes as 3D topological multi-graphs (generated interaction spheres around each ligand atom, specifically to enclose proximity-based contacts) and fed them to a four-layer graph convolutional neuronal network.
- MBP [379] proposes a pre-training framework for structure-based PLA prediction which constructs a pre-training dataset called ChEMBL-Dock with more than 300k experimentally measured affinity labels and about 2.8M docked 3D structures. By introducing multi-task pre-training to treat the prediction of different affinity labels as different tasks and classifying relative rankings between samples from the same bio-assay.

Table 4: Summary of complex-based models.

Model	Task	Architecture	Representation	Model
Kdeep	PLA	1pipe-FC	Complex	3D-CNN+Subsampling
DeepBindRG	PLA	1pipe	Complex (interface spatial info in 2D format)	2D-CNN model and ResNet
GNN-DTI	DTI	1pipe-FC	Complex	Embedding and distance-aware graph attention mechanism
Onionnet	PLA	1pipe-FC	3D-Complex	CNN
DeepAtom	PLA	1pipe	Voxelized complex	3D PWConvs and 3D DWConvs
AK-Score	PLA	1pipe-Dense	Complex	Ensemble-based residual network 3D convolutional
OctSurf	PLA	1pipe-FC	Protein pocket ligand complex	3D-CNN/ResNet/VGG
Jones et al.	PLA	Comb-FC	Complex	3D-CNN, SG-CNN
APMNet	PLA	1pipe-Linear	Complex	Linear, ARMA graph conv, MPNN
SIGN	PLA	1pipe-MLP	Complex interaction graph	PGAL, PiPool
GAT-Score	PLA	1 pipe	Graph of complex	GAT
BAPA	PLA	1pipe-FC	Complex using intermolecular descriptors	1D Conv layer, attention layer
IMCP-SF	PLA	Comb-FC	Profiles of intermolecular contacts	RF
Sfenn	PLA	1pipe	3D	3DCNN
KIDA	DTA	Comb-FC	Drug 2D graph, protein pocket as 2D chemical graphs, ball query graph	MPNN, EGNN+student and teacher blocks
SS-GNN	DTA	1Pipe-MLP	Complex	MLP, GNN(GIN)+global graph add pool
MBP	PLA	1pipe	Graph	encoder+interacting module+readout
InterGraph	PLA	1pipe	Graph using pairwise atomic distances in complexes	GCN

Table 5: Summary of utility-based models.

Model	Task	Architecture	Representation	Model
DTINet	DTI/DRep	lpipe	Heterogenous graphs DSS, DDI, PSS, PPI, DDA, DiDA, side effect, DPI, PDiA	RWR+Diffusion component analysis (DCA)
NeoDTI	DTI	lpipe	DPP graph BiPartite Graph+G17	neighborhood information aggregation
GCN-DTI	DTI	Comb-DNN	DSide, DDI, DDi and similarities, PPI, PDi and similarities	GCN+DNN
SBGDTI	DTI	lpipe-MLP	Heterogenous graph	Weisfeiler-Lehman algorithm, MLP
DTI-CNN	DTI	Comb-Autoencoder-CNN-FC	DDi, DDI, PPI, PDi, DPI, other relations	Jaccard similarity, RWR, denoising autoencoder, CNN
EEG-DTI	DTI	Comb-FC	SMILES, Protein sequences, DTBA Matrix and weighted graph	GCN
KGE-NFM	DTI	Comb-MLP	Metapaths in heterographs	DistMult, NFM, Bi-Interaction layer
Affinity2Vec	DTA/DTI	Comb-FC	Metapath-based graphs	ML regressor+ Min-Max normalization
SGCL-DTI	DTI	Comb-FC	Molecular graphs, PPI, PSeqS	GCN
MHGNN	DTI	Comb	Heterogenous graphs	GAT, GCN
MSF-DTA	DTA/DTI	Comb-FC	Tanimoto coefficient, DDi, Smith-Waterman score, PPI, similarity of disease DAGs, DsideA, DDiA, DPA, PDiA	GCN+Maxpool+FC, VGG+FC
MHTAN-DTI	DTI	Comb-FC	SMILES, Protein sequences, DDI and PPI	Transformer, Attention
EDC-DTI	DTI	Comb-FC		GAT with memory units+MLP+2DConv
TripletMultiDTI	DTI DTI,	Comb-Triplet loss-FC		CNN, Node2Vec
DeepTraSynergy	toxic effect, and drug synergy	Comb-MLP-3 output heads	SMILES, PPI, DTI	transformer, Node2Vec, Synergy module, MHSA
TTGCN	DPI	Comb-FC	Neighbour graph based on metapaths from hetero networks	ResGCN, GAT+Attention, inductive matrix completion
CCL-DTI	DTI	Comb-FC	SMILES, protein sequences, PPI, DDI	CNN, Node2Vec
GSL-DTI	DTI	Comb-MLP	MetaPath subgraph	Attention, filter gate, GCN
MSH-DTI	DTI	Comb-FC	Molecular graph from SMILES, Target sequences, PPI, DDI, DDS, PDI	InfoGraph/CPCProt+GCN+Attention
DrugMAN	DTI	Comb-FC	DDi, DSide, Transcriptome-based drug similarity, Structure-based drug similarity, Gene-disease, Gene-pathway, Gene-chromosomal location, Transcriptome-based gene sim, PPI, Gene-coexpress, Protein sequence sim	GAT, MHSA+FC+skips

### 3.6.5 Utility networks and heterogeneous graph-based models

Network-based methods make their prediction based on various biological networks such as drug-drug interaction graph (DDI), protein-protein interaction graph (PPI), or drug-disease graphs (DDi) [380, 381]. Most of traditional approaches cannot learn the complex relations between ligands and proteins as they are learning just from utility networks in a non-detailed way, however, different methods do not have this limitation, recently. These methods may use or combine the utility networks [382, 383, 384, 385, 386, 387] or make a new heterogeneous graph from ligands and proteins [140, 388, 389, 390, 391]. Methods can be similarity-based (DTINet [392], deepDTNET [393], MEDTI [394], NEDTP [395], MultiDTI [396], HAS-DTI [397]), knowledge graph-based (DistMult [398], KGE-NFM [201]), GNN-based (NeoDTI [399], IMCHGAN [400], DTI-MGNN [401], SGCL-DTI [402], MAGNN [403], MHGNN [404], MLGANN [405], MVGCN [406]). Some methods apply hierarchical learning (MHADTI [407]) or use metapaths (AMGDTI [408], DTI-HAN [409]) or hybrids of them (MHTAN-DTI [390]). Table 5 summarizes the utility based models.

- DTINet [392] learns low-dimensional representations of drugs and targets by Random Walk with Restart (RWR) and diffusion component analysis (DCA). Then, DTINet finds the optimal projection from the drug space to the target space and predicts new drug-target interactions based on the geometric proximity of the mapping vector in the unified space.
- NeoDTI [399] in close relation of DTINet [392] integrates various information from different heterogeneous networks including drug structure similarities, drug side effect associations, drug-protein interactions, drug drug interactions, drug disease associations, protein sequence similarities, protein drug interactions, protein disease associations, protein protein interactions, disease protein associations, disease drug associations, side effect drug associations. This model learns topology-preserving representations of drugs and targets to predict DTIs by adopting a neighborhood information aggregation operation.
- DTI-CNN [410] utilizes seven graphs including, drug side-effect graph, drug-drug interaction graph, drug-disease association graph and drug-disease similarity graph, protein-protein graph, protein-disease association graph, and protein-disease similarity graph. This model applies two jacquard similarity, two Random walk with restart (RWR), and a de-niosing auto-encoder for features extraction and a CNN module for drug-target interaction prediction.
- SBGDTI [411] constructed a semi-bipartite graph by known DTIs and drug-drug and protein-protein similarity. They used Weisfeiler-Lehman algorithm in graph labeling process and employed deep neural network to learn the complex pattern of interacting pairs from embedded graphs.

- GCN-DTI [412] constructs DPP networks and assigns equal weights to directly and indirectly related DPP pairs. GCN is used to learn the topological structure and obtain features and DNN is utilized for prediction.
- EEG-DTI [413] constructs a heterogeneous network with multiple entities (i.e. drug, protein, disease, side-effect) and multiple types of edges. They propose a HGCN-based method to learn the drug and target feature representation based on a heterogeneous network. Finally, they concatenate the two outputs and predict the DTI task.
- Affinity2Vec [414] constructed a weighted heterogeneous graph that integrates data from several sources including similarities and predict binding affinity using several computational techniques from feature representation learning, graph mining, and machine learning.
- SGCL-DTI [402] learns representations of drugs and proteins in heterogeneous networks through meta-paths using attention. The topology and semantic structure of the DPP network are then constructed, and a novel contrastive optimization module is used to generate a collaborative contrastive loss of the two views, and guide the model optimization in a supervised manner.
- MHGNN [404] simulates complex biological entity inter-relationships and uses them for DTI prediction by way of capturing the contextual relationships of the meta-paths. The meta-paths of the MHGNN are heterogeneous graphs, and thus can learn complex biological relationships well. GAT is used for graphs and GCN is utilized for the DTP correlation graph at the end.
- KG-DTI [415] propose a novel knowledge graph-based deep learning method for DTIs predictions. Specifically, a knowledge graph of 29,607 positive drug-target pairs is constructed by DistMult embedding method. A Conv-Conv module is proposed to extract features of drug-target pairs, which is followed by a FC layer for DTIs prediction.
- TripletMultiDTI [416] uses DDI and PPI networks and feed them into node2vec modules, then combines it with the output of CNN blocks for drug and proteins with a triplet loss function.
- DeepTraSynergy [417] is a model for drug combinations which proposes a new architecture that effectively combines drug-target interaction, PPI, and cell target interaction to incorporate drug synergy prediction using transformers. Their approach is a multitask approach that predicts three outputs including the drug-target interaction, its toxic effect, and drug combination synergy. Drug combination synergy is the main task and the two other ones are the auxiliary tasks that help the approach to learn a better model.
- MSF-DTA [418] gathers additional information for the proteins from its biologically related neighboring proteins in protein-protein interaction and sequence similarity networks to get prior knowledge. The representation was learned using a graph pre-training framework, VGAE, which could not only gather node features but also learn topological connections, therefore contributing to a richer protein representation.
- EDC-DTI [419] employs ontology-based feature construction (Tanimoto coefficient, Smith-Waterman score, similarity of disease DAGs) and graph topology-based feature construction (DDI, PPI, drug-side-effect, drug-disease, drug-protein and protein-disease associations) and learns them via graph attention network with memory units, MLP and 2DConv.
- DrugMAN [420] used utility networks such as Drug-Disease, Drug side effect, transcriptome-based drug similarity, structure-based drug similarity, gene-disease, gene-pathway, gene-chromosomal location, transcriptome-based gene similarity, protein-protein, gene-coexpress, protein sequence similarity networks. This model applies GAT on all of them and concatenates the drug output with protein output and feed it to 5 blocks of multi-head self attention and FC.
- GSL-DTI [421] constructs a heterogeneous network by integrating data from various sources, employs a GCN to learn representations of proteins and drugs by utilizing meta-paths that encode relationships between various types of nodes, constructs the network of Drug-Protein Pairs (DPPs) using a filter gate on the affinity scores of DPPs, and learns low-dimensional representations for each node in this network using another GCN.
- MSH-DTI [422] uses self-supervised learning methods (CPCProt and InfoGraph) and heterogeneous aggregation from DDI, PPI, and DDS networks with GCN and attention layers.
- TTGCN [423] utilizes ResGCN and GAT and attention on drug and target neighbor graphs obtained from meta-paths from diverse heterogeneous networks. Novelty of this framework is that it uses an inductive matrix completion technique to forecast DTIs while preserving the network's node connectivity and topological structure.
- KGE-NFM [201] learns a low-dimensional representation for various entities in the KG, and then integrates the multi-modal information via neural factorization machine (NFM).

- MHTAN-DTI [390] is a meta-path-based hierarchical transformer and attention network which applies meta-path instance-level transformer, single-semantic attention and multi-semantic attention to generate low-dimensional vector representations of drugs and proteins. Meta-path instance-level transformer employs internal aggregation on the meta-path instances, and models global context information to capture long-range dependencies. Single-semantic attention learns the semantics of a certain meta-path type, introduces the central node weight and assigns different weights to different meta-path instances to obtain the semantic specific node embedding. Multi-semantic attention captures the importance of different meta-path types and performs weighted fusion to obtain the final node embedding.
- CCL-DTI [424] used multi-modal knowledge (DDI, PPI, sequences) as input and proposed an attention-based fusion technique. They also investigated how utilizing constrastive loss functions (max-margin contrastive loss function, triplet loss function, Multi-class N-pair Loss Objective, and NT-Xent loss function) could help the prediction.

### 3.6.6 Matrix factorization-based models

The approach for these models often involves decomposing the drug-target interaction matrix into two lower dimensional matrices using matrix factorization method. NRLMF [425] focuses on modeling the drug-target interaction probability by logistic matrix factorization, where the properties of drugs and targets are represented by drug-specific and target-specific latent vectors, respectively. This model proposes regularization to incorporate neighborhood information for the local structure of the drug-target interaction data. NRLMF $\beta$  [426] is NRLMF with beta distribution rescaling which addresses the issue of limited sample information leading to inaccurate predictions. KBMF2K [427] employs Bayesian matrix factorization on kernel matrices obtained from drug and target information. SPLCMF [428] uses collaborative matrix factorization techniques and utilizes a self-paced learning strategy based on weighted low-rank approximation to progressively select training samples and control the feature learning process.

### 3.6.7 Interpretability

While research into DTI and DTA prediction is fairly mature, generalizability and interpretability are not always addressed in the existing works in this field. By leveraging explainable AI techniques, researchers can develop more accurate, reliable, and interpretable AI models for DTA and DTI prediction. Also, it is necessary in some cases for researchers in drug discovery to understand the reasoning of the models and important parts of proteins and drugs which are responsible for the prediction results. It is difficult to understand how deep learning black box models reach their prediction results and the contribution of each input feature to the results due to the large number of hidden layers and parameters. Currently, the main methods of interpretation are general methods for neural networks that cannot be easily adapted to biology.

In order to ensure the model could focus on the important parts of the proteins, the attention mechanism is usually used, some intuitive explanations can be provided by attention mechanisms. Some methods that use attention modules can check the weights and find the binding cites that are predicted through their model. The attention mechanism is not always able to provide a clear explanation of the model’s decision-making process.

Gradient-weighted Affinity/Class Activation Mapping (Grad-AAM/Grad-CAM) is utilized in some research like MGraphDTA [302] to identify hot-spots for binding affinity prediction task. This technique detects the sum of the magnitude of gradients that activated the nodes of the last layer and highlights the important parts of a molecule that contribute to the predicted drug-target affinity. The model’s gradients are calculated with respect to the input molecule’s features, the gradients are used to weight the activation maps of the model’s layers, and the weighted activation maps are visualized as heat-maps. However, the binding of proteins and ligands is based on the potential contact of amino acids and atoms. Therefore, this mechanism for providing interpretability through attention alone has a low accuracy.

MONN (Li et al., 2020) is a multi-objective model for the prediction of non-covalent interactions and binding affinity between proteins and ligands and provides some interpretability for the final affinity prediction results. AttentionSiteDTI [289] which utilizes a graph-based attention mechanism to identify the protein binding sites that contribute most to the drug-target interaction. ICAN (Interpretable Cross-Attention Network) [429] which employs a cross-attention mechanism to capture the complex interactions between drug molecules and target proteins and analyzes the interpretability via attentions. BindingSiteAugmentedDTA [430] reduces the search space of potential binding sites of the protein and can provide a deeper understanding of its underlying prediction mechanism by mapping attention weights back to protein binding sites. The limitations of affinity prediction in terms of interpretability are tackled in AffinityVAE [233] by proposing the concept of a protein-ligand interaction feature map.

SHAP (SHapley Additive exPlanations) [422] and LIME (Local Interpretable Model-Agnostic Explanations) can also be used to explain and optimize the existing methods. Ru et al. [431] utilized SHAP values and the incremental feature selection approach to obtain the high-quality features.

## 4 Datasets and Evaluation Metrics

### 4.1 Datasets and databases

There are currently lots of various datasets available for the tasks of DTI or DTA. The most used resources are Davis [432], KIBA [433], PDBbind [434], BindingDB [435], Metz [436], Human [437], and C.elegans [79]. Other used datasets are ToxCast [438], DUD-E [439], DTC (drug-target Commons) [440], Allergy [305], and GPCR [331]. In learnings with utility networks HPRD [441], SIDER [442], and CTD [443] are used. Human and C. elegans datasets are specifically used in DTI task while other datasets are usually used in DTA Tasks. Datasets used for DTA tasks are all convertible to datasets for DTI task by selecting an appropriate threshold on affinity score. Usually, In two-pipeline methods datasets are combined and gathered from multiple resources as there are more than one area to consider (proteins and drugs). Figure 6 shows the portion of dataset occurrence in examined models.

Some datasets can have missing information or there may be a need for more information on drugs or proteins, therefore supplementary databasess are commonly used in the literature. Some of these databases are UniProt [444], UniRef [445], PDB [446], STITCH [447], and ZINC [448].

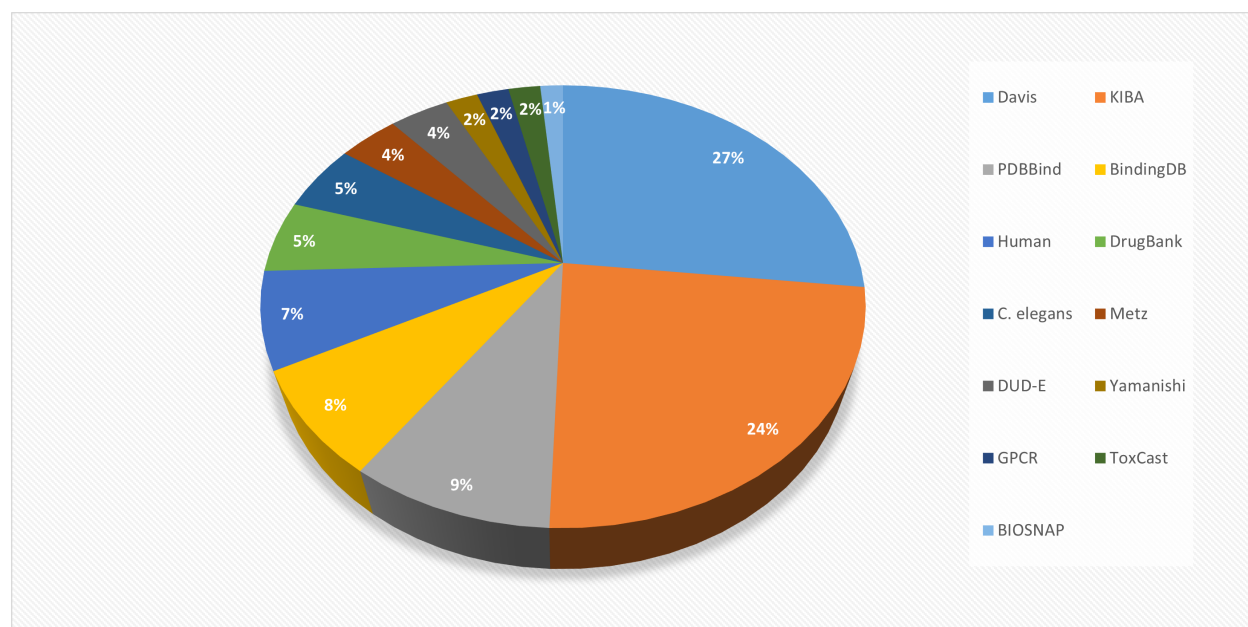


Figure 6: Portion of dataset occurrence in examined models.

- The Davis dataset contains selectivity assays of the kinase protein family and the relevant inhibitors with their respective dissociation constant ( $K_d$ ) values. It comprises all interactions of 442 proteins and 68 ligands, which is 30056 interactions. All drug-target pairs that cannot be experimentally measured for bio-activity are assigned a  $pK_d$  of 5 (bio-activity value of 10  $\mu$ M). Filtered Davis dataset is generated by omitting pairs with  $pK_d$  of 5, as there are lots of these interactions which their  $pK_d$  is 5.
- The KIBA database originated from an approach called KIBA, in which kinase inhibitor bio-activities from different sources such as  $k_i$ ,  $k_d$ , and  $IC_{50}$  were combined (KIBA score ranges from 0.0 to 17.2). KIBA scores were constructed to optimize the consistency between  $k_i$ ,  $k_d$ , and  $IC_{50}$  by utilizing the statistical information they contained. The KIBA dataset originally comprised 467 targets and 52498 drugs. Filtered KIBA contains only drugs and targets with at least 10 interactions yielding a total of 229 unique proteins and 2111 unique drugs.
- PDBbind involves a collection of experimentally measured binding affinity data ( $k_i$ ,  $k_d$ , and  $IC_{50}$ ) for biomolecules complexed from the Protein Data Bank (PDB), which also have multiple versions (PDBbind2008-

Table 6: Statistics of some Drug-Target affinity/Interaction Datasets/databases. Values can vary as they get updated overtime.

Dataset Name	Drugs/Components	Proteins/Targets	Total Samples/interactions
Davis [432]	68	442	30,056
Filtered Davis [176]	68	379	9,125
KIBA [433]	52,498	467	246,088
Filtered KIBA [162]	2111	229	118,254
Metz [436]	1,423	170	35,259
ToxCast [438]	9,076	1,192	530,000
Human [437]	2,726	2001	6728
C. elegans [79]	1767	1,876	7786
GPCR [331]	5,359	356	15,343
PDBbind2020	41,847	1,469	194,443
BindingDB	1,160,301	9,021	2,701,247
BindingDB (IC50_labeled)	265,627	2,793	376,751
BindingDB (Kd_labeled)	5,895	812	12,589
BindingDB (Ki_labeled)	93,437	1,619	144,525
BindingDB (EC50_labeled)	31,970	513	37,896

2021) with default version and refined version. This dataset consist of drug SMILES, target sequences, 3D structure of targets, target pocket information. Refined versions exclude several cases including, ligands, ternary complexes, steric hindrance complexes with resolution higher than 2.5 Å(Angstrom), instances of covalent bonding, and complexes missing  $k_i$  or  $k_d$ , or  $k_d$  lower than 1 pM (picomolar). PDBbind version 2020 provides binding affinity data for a total of 23,496 biomolecular complexes in PDB, including protein-ligand (19,443), protein-protein (2,852), protein-nucleic acid (1,052), and nucleic acid-ligand complexes (149). PDBbind2020 general set consist of 14127 samples and 5316 samples in its refined set. Moreover,some CASF [449, 450] core datasets are derived from PDBbind refined sets.

- The BindingDB is a public and web-accessible dataset with drug-target pairs for  $k_i$ ,  $k_d$ ,  $IC_{50}$ , and  $EC_{50}$  labels which can provide drug SMILES and target sequences.
- The Metz dataset provides the  $pK_i$  as a measure of binding affinity. It consist of 1,423 drugs and 170 targets with 35,259 pairs.
- ToxCast contains toxicology data obtained from in vitro high-throughput screening of drugs (i.e., chemicals). Several companies have done ToxCast curation with 61 different measurements of binding affinity scores.
- C. elegans, a simple nematode worm, has emerged as a powerful model organism for drug discovery and repurposing research. Its genetic simplicity, rapid life cycle, and conserved biological pathways with humans make it an ideal system for studying the effects of drugs on various biological processes. C. elegans drug datasets, which often include information on drug concentration, exposure time, and phenotypic outcomes, provide valuable insights into drug efficacy, toxicity, and potential mechanisms of action. C. elegans can be acquired from ChEMBL and DrugBank and is provided with highly confident negative samples.
- Human drug dataset provide comprehensive information on the efficacy, safety, and pharmacokinetics of various drugs, derived from clinical trials, observational studies, and electronic health records. By analyzing this dataset, researchers can identify potential drug-targets, optimize drug dosing, and predict adverse drug reactions. Human dataset, like C. elegans dataset, is also provided with highly confident negative samples.
- UniProt is a comprehensive database of over 220 million protein sequences and functional information. It has the ability to add new protein entries and update publicly available annotation information.
- The ZINC database is a free massive collection of commercially available compounds, often used in drug discovery and virtual screening. It provides both 2D and 3D representations of molecules, making it a valuable resource for researchers working with molecular data. It contains over 230 million purchasable compounds in ready-to-dock, 3D formats.
- UniRef is a database of protein sequences that are clustered based on sequence similarity. It provides three levels of clustering: UniRef100, UniRef90, and UniRef50. These clusters help to reduce redundancy in protein sequence data and improve search efficiency. For example, UniRef50 is built by clustering UniRef90 seed sequences that have at least 50 percent sequence identity to.
- The Protein Data Bank (PDB) is a global repository of experimentally determined 3D structures of biological macromolecules, such as proteins and nucleic acids. PDB entries contain detailed information about the molecule’s structure, including atomic coordinates, bond lengths, and angles. This data allows researchers to visualize and analyze the molecule’s shape, interactions, and potential binding sites.
- STITCH (Search Tool for Interactions of Chemicals) includes information on interactions between 43,000 compounds and 9,643,763 proteins from 2,031 species. Each interaction in STITCH database is assigned a

score value. STITCH also provides information on compounds that are similar to the drug of target, along with their similarity scores.

- The ChEMBL database contains compound bio-activity data against drug-targets. Bio-activity is reported in  $k_i$ ,  $k_d$ ,  $IC_{50}$ , and  $EC_{50}$ . ChEMBL version 2 (ChEMBL02) included 2.4 million bio-assay measurements covering 622,824 compounds, including 24,000 natural products. ChEMBL08 was launched with over 2.97 million bio-assay measurements covering 636,269 compounds. ChEMBL10 saw the addition of the PubChem confirmatory assays, in order to integrate data that is comparable to the type and class of data contained within ChEMBL.
- PubChem is a public chemical information database maintained by the National Center for Biotechnology Information (NCBI). It provides a vast repository of chemical substances, including small molecules, proteins, and bio-assays. Researchers can use PubChem to search for compounds by name, structure, or properties. It also offers information on the biological activities of compounds, including their interactions with proteins and their effects on cells.
- DrugBank is a comprehensive, freely accessible online database which combines detailed drug (chemical, pharmacological, and pharmaceutical) data with comprehensive drug-target (sequence, structure, and pathway) information. It provides information on Drugs, targets, drug interactions and drug side effects.
- The Therapeutic Target Database (TTD) provides information on known and explored therapeutic protein and nucleic acid targets, the targeted diseases, pathway information, and the corresponding drugs directed at each of these targets.
- DUD-E benchmark consists of 102 targets, a set of active compounds known to bind these targets, and a lot of decoys for each active one. The DUD-E is a huge dataset consisting of over one million compounds and every target has a different number of active compounds to bind it.
- BioSNAP [257, 451] is a collection of diverse biomedical networks, including protein-protein interaction networks, single-cell similarity networks, and drug-drug interaction networks. The BioSNAP dataset is created from the DrugBank database by [257] and [451], consisting of 4,510 drugs and 2,181 proteins. It is a balanced dataset with validated positive interactions and an equal number of negative samples randomly obtained from unseen pairs. The MINER DTI dataset from the BIOSNAP collection [451] includes 13,741 DTI pairs.
- DTC/TDC serves as a valuable repository for researchers investigating DTIs. This platform provides a curated collection of standardized datasets encompassing various DTI-related aspects, such as binding affinity,  $IC_{50}$  values, and  $K_i$  constants.
- GPCR dataset is constructed from GLASS database [452]. GPCR dataset contains 15343 interactions between 5359 drugs and 356 targets and has a 6.0 threshold for negative and positive sample separations.

#### 4.1.1 Binding affinity measures

Binding affinity indicates the strength of the interaction between drug-target pair. It is usually expressed in measures such as dissociation constant ( $K_d$ ), inhibition constant ( $K_i$ ) or the half maximal inhibitory concentration ( $IC_{50}$ ) [453]. Since all of these three measures are concentrations, the lower the measure number, the higher the affinity is. ( $K_d$ ) and ( $K_i$ ) values are usually represented in terms of ( $pK_d$ ) or ( $pK_i$ ), the negative logarithm of the dissociation or inhibition constants. For example Equation. 1 shows the negative logarithm of the dissociation constant.

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

- Dissociation Constant ( $K_d$ ) represents the concentration of drug at which half of the target sites are occupied. Lower  $K_d$  values indicate higher affinity, meaning the drug binds more tightly to the target. Dissociation Constant can be acquired via various experimental techniques, including Radio-ligand Binding Assays, Surface Plasmon Resonance (SPR), Fluorescence Spectroscopy, and Isothermal Titration Calorimetry (ITC).
- Inhibition constant ( $K_i$ ) [454] represents the concentration of inhibitor required to reduce the enzyme activity by half when the substrate concentration is constant. Inhibition constant is essentially an equilibrium dissociation constant for the inhibitor-target complex. Inhibition constant can be determined by Dixon Plot, Lineweaver-Burk Plot or Direct Binding Assays like ITC and SPR.
- Half maximal inhibitory concentration ( $IC_{50}$ ) is a measure of a substance’s potency in inhibiting a specific biological function. It represents the concentration of a drug or compound required to inhibit a specific biological process or component by half.  $IC_{50}$  can be influenced by factors like the experimental conditions,



the specific assay used, and the mechanism of action of the compound. IC50 can be acquired from different assays, including Enzyme Inhibition, Cell-Based, and Biochemical assays.

- Half maximal effective concentration *EC*50 and Half Maximal Active Concentration *AC*50 represent the concentration of a drug that induces a 50 percent response compared to the maximum possible effect. A lower *EC*50 value indicates a more potent drug, as it requires a lower concentration to achieve the same effect.

## 4.2 Common evaluation metrics

One major challenge in drug-target interaction research is the absence of a unified evaluation framework and benchmarks. This makes it difficult to compare and assess the performance of different models and methods, therefore, in this paper, models are not compared with each other with numbers. However, Information regarding the datasets, baselines, and evaluation metrics used in the models are provided in the supplementary data. In this section, several common evaluation metrics for both regression and classification tasks are mentioned.

### 4.2.1 Drug-target affinity prediction evaluation metrics

Common evaluation metrics for drug-target regression task are Mean Absolute Error, Mean squared error, Root mean squared error, R-squared, Pearson correlation coefficient, Spearman correlation coefficient, and Confidence interval count.

- Mean Absolute Error (MAE) Equation. 2 indicates the size of actual prediction error. It measures the absolute mean of differences between predicted and real values.  $n$  is the number of samples,  $y_i$  is the vector of actual value,  $\hat{y}_i$  is the prediction vector.

$$MAE = \frac{1}{n} \sum_{i=1}^n |\hat{y}_i - y_i| \quad (2)$$

- MAPE (Mean Absolute Percentage Error) is Equation. 3 and sMAPE (Symmetric Mean Absolute Percentage Error) is Equation. 4. These formulas are designed for situations where both  $\hat{y}_i$  and  $y_i$  are non-negative. sMAPE is generally preferred over MAPE because it avoids issues when  $y_i$  is close to or equal to zero.

$$MAPE = \frac{100}{n} \sum_{i=1}^n \left| \frac{y_i - \hat{y}_i}{y_i} \right| \quad (3)$$

$$sMAPE = \frac{100}{n} \sum_{i=1}^n \frac{2 |y_i - \hat{y}_i|}{|y_i| + |\hat{y}_i|} \quad (4)$$

- Mean squared error (MSE) Equation. 5 is defined as the average squared difference between the predicted and actual binding affinity scores.

$$MSE = \frac{1}{n} \sum_{i=1}^n (\hat{y}_i - y_i)^2 \quad (5)$$

- Root mean squared error (RMSE) Equation. 6 is defined as the root of MSE. In this equation and equations before, the smaller the value is, the better the prediction because the final score shows the error rate of the model.

$$RMSE = \sqrt{\frac{1}{n} \sum_{i=1}^n (\hat{y}_i - y_i)^2} \quad (6)$$

- Standard deviation (SD) of the regression Equation 7 can also be used. Terms  $a$  and  $b$  are the slope of interception of the linear regression line of predicted and measured  $y$  datapoints.

$$SD = \sqrt{\frac{1}{n-1} \sum_{i=1}^n ((a * \hat{y}_i + b) - y_i)^2} \quad (7)$$

- R-squared ( $R^2$ ) Eq. 8 / Squared correlation coefficient (Regression towards the Mean Index) ( $r_m^2$  index) [455] Equation. 10 are measures used to show how well the prediction value fits the actual value (the degree of match). The more closer the score is to 1, the better the model is.

$\bar{y}$  is the average value of all actual values  $y_i$ .  $r_2$  is the squares of the correlation coefficients with intercept and  $r_0^2$  is the squares of the correlation coefficients without intercept.

$$R^2 = 1 - \frac{\sum_{i=1}^n (y_i - \hat{y}_i)^2}{\sum_{i=1}^n (y_i - \bar{y})^2} \quad (8)$$

$$R = \frac{(\hat{y}_i - \bar{\hat{y}})(y_i - \bar{y})}{SD_{\hat{y}_i} \cdot SD_{y_i}} \quad (9)$$

$$r_m^2 = r^2 \times \left(1 - \sqrt{r_2 - r_0^2}\right) \quad (10)$$

- Pearson correlation coefficient (*PCC*) Equation. 11 is used to measure the mutual relationship (linear correlation) between two variables X and Y. PCC score ranges from -1 to +1, showing the strength of correlation.  $cov(X, Y)$  represents the covariance of two variables,  $\sigma_X$  is the standard deviation of X, and  $\sigma_Y$  is the standard deviation of Y. If the score is positive, the variables are positively correlated, if the score is negative, the variables are negatively correlated, and if the score is zero, the variables are not correlated.

$$\rho_{XY} = \frac{cov(X, Y)}{\sigma_X \sigma_Y} \quad (11)$$

- Spearman correlation coefficient (*SCC*) Equation. 12 is another correlation metric which is a nonparametric measure of the dependence of two variables.  $d_i$  is the difference between prediction value and actual value of each group. Like pearson correlation the closer score is to -1 or +1, the stronger the correlation is.

$$\rho = 1 - \frac{6 \sum d_i^2}{n(n^2 - 1)} \quad (12)$$

- Confidence interval count (*CI*) Equation. 13 evaluates the ranking performance of the model in discrimination. *CI* ranges from 0 to 1, and the closer the score to 1, the better the model fit is. Where  $b_i$  is the prediction value for affinity  $\sigma_i$ ,  $b_j$  is the prediction value for affinity  $\sigma_j$ ,  $Z$  is a normalization constant. For function  $\varphi(x)$ , it is 1 if the value of  $x$  is greater than 0, 0.5 if the value of  $x$  is equal to 0, and 0 if the value of  $x$  is less than 0.

$$CI = \frac{1}{Z} \sum_{\sigma_i > \sigma_j} \varphi(b_i - b_j) \quad (13)$$

#### 4.2.2 drug-target interaction prediction evaluation metrics

Common evaluation metrics for drug-target classification task are accuracy, precision, recall, specificity, F1-score, and area under the precision recall curve.

- Accuracy 14 is the proportion of correct predictions.

$$Accuracy = (TP + TN) / (TP + TN + FP + FN) \quad (14)$$

- Precision 15 is the proportion of positive predictions that are actually positive.

$$Precision = TP / (TP + FP) \quad (15)$$

- Recall (Sensitivity) 16 is the proportion of actual positive cases that are correctly identified.

$$Recall = TP / (TP + FN) \quad (16)$$

- Specificity 17 is the proportion of actual negative cases that are correctly identified.

$$Specificity = TN / (TN + FP) \quad (17)$$

- F1-Score 18 is the harmonic mean of precision and recall.

$$F1 - Score = 2 \times (Precision \times Recall) / (Precision + Recall) \quad (18)$$

- matthews correlation coefcient (MCC) Equation 19

$$MCC = (TP * TN) - (FP * FN) / \sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)} \quad (19)$$

- Area Under the Precision-Recall Curve (AUPR/AUCPR/PRC) is a measure of the trade-off between precision and recall. It is The area under the curve plotted with precision on the y-axis and recall on the x-axis.
- Area Under the Receiver Operating Characteristic Curve (AUROC) is the area under the plot of the true positive rate (sensitivity) against the false positive rate (1-specificity) for various threshold values.

The AUPR assesses a binary model by averaging the precision across all recall values. Some datasets in DTI are imbalanced and have skewed distribution. Therefore, AUPR should be chosen as the right evaluation metric because the precision-recall curve is more appropriate than the receiver operating characteristic (ROC) curve for imbalanced data. AUPR is suitable for tasks in which there is a significant skew in the class distribution.

## 5 Conclusion and Future work

### 5.1 Conclusion

Researchers are rapidly developing and proposing new powerful frameworks for predicting the interaction between proteins and drugs. This paper aimed to provide a comprehensive review of the methods for drug-target interaction prediction to help the researchers become familiar with the current state-of-the-art methods and to provide a reference for future research. Moreover, the paper aimed to provide a comprehensive overview of the different common representations for proteins and drugs, the different settings, the datasets used in the literature, and the evaluation metrics used to assess the performance of the models. In this paper, more than 180 models in three main categories (sequence-based, structural-based, and sequence-structural-based methods) for DTI and DTA prediction tasks were reviewed. Matrix factorization methods, 3D complex-based methods, and interpretability considerations of models were also discussed. We hope that by providing this comprehensive review, we paved the way for future research in this field.

### 5.2 Future work and challenges

After being studied after so many years, the field of drug-target interaction prediction still has many challenges and opportunities for future research. A major challenge in DTI prediction lies in accurately capturing the conformational flexibility of both drugs and proteins. Proteins are dynamic entities that undergo constant conformational changes, and drugs can also exhibit multiple conformations. Current methods often rely on rigid or simplified representations of these molecules, limiting their ability to accurately predict binding affinities and understand the nuances of the interaction. Future work should focus on developing more sophisticated computational methods that can effectively sample the conformational space of both drug and protein molecules, incorporating techniques like enhanced sampling methods and machine learning approaches. Additionally, advancements in experimental techniques that can provide more detailed information about the dynamic behavior of protein-ligand complexes will be crucial for refining and validating these models.

New interaction and binding information can be extracted from the protein-ligand complex structures. Pocket information is mostly ignored in the current DTA/DTI prediction framework because binding pocket prediction is regarded as another prediction task than drug-target prediction. This task can be integrated into the DTI/DTA prediction framework to improve the performance of the models. Also, finding the best combination of informative features for the models is still a challenge. One major challenge in drug-target interaction research is learning the mutual information between proteins and drugs. Another challenge is how to find and highlight the important atoms of the drugs and residues of the proteins.

The Alpha-fold 3 [353] model, with its remarkable accuracy in predicting protein structures within drug-target complexes, has significantly impacted the field of DTI prediction. This will lead to improvements in DTI prediction models, as they can now leverage highly accurate protein structures as input, leading to more reliable predictions of binding affinities. By integrating Alpha-fold 3 predictions with existing DTI prediction models, researchers can develop more accurate and reliable models for drug discovery and re-purposing.

Evaluations for models in DTI/DTA predictions should be standardized to allow for more accurate comparisons between different models. Many models in the literature show high performance but perform poorly in real datasets, indicating

high bias towards a specific dataset. Performance should be evaluated on data that significantly differs from the training data in terms of drug and target properties and should be in cold setting. Also, models should be assessed on their ability to predict interactions for newly discovered drugs. Lastly, interpretability of the models should be examined as they can ensure that predicted interactions are not only accurate but also biologically plausible and potentially useful for drug discovery.

## References

- [1] Natesh Singh, Philippe Vayer, Shivalika Tanwar, Jean-Luc Poyet, Katya Tsaïoun, and Bruno O. Villoutreix. Drug discovery and development: introduction to the general public and patient groups. *Frontiers in Drug Discovery*, 3, 2023. ISSN 2674-0338. doi:10.3389/fddsv.2023.1201419. URL <https://www.frontiersin.org/journals/drug-discovery/articles/10.3389/fddsv.2023.1201419>.
- [2] Antonio Lavecchia and Carmen Di Giovanni. Virtual screening strategies in drug discovery: a critical review. *Current medicinal chemistry*, 20(23):2839–2860, 2013.
- [3] Lixia Yao, James A Evans, and Andrey Rzhetsky. Novel opportunities for computational biology and sociology in drug discovery: corrected paper. *Trends in biotechnology*, 28(4):161–170, 2010.
- [4] Amol B Deore, Jayprabha R Dhumane, Rushikesh Wagh, and Rushikesh Sonawane. The stages of drug discovery and development process. *Asian Journal of Pharmaceutical Research and Development*, 7(6):62–67, 2019.
- [5] Steven M Paul, Daniel S Mytelka, Christopher T Dunwiddie, Charles C Persinger, Bernard H Munos, Stacy R Lindborg, and Aaron L Schacht. How to improve r&d productivity: the pharmaceutical industry’s grand challenge. *Nature reviews Drug discovery*, 9(3):203–214, 2010.
- [6] Hailin Chen and Zuping Zhang. A semi-supervised method for drug-target interaction prediction with consistency in networks. *PloS one*, 8(5):e62975, 2013.
- [7] JP Hughes, S Rees, SB Kalindjian, and KL Philpott. Principles of early drug discovery. *British Journal of Pharmacology*, 162(6):1239–1249, 2011. doi:<https://doi.org/10.1111/j.1476-5381.2010.01127.x>. URL <https://bpspubs.onlinelibrary.wiley.com/doi/abs/10.1111/j.1476-5381.2010.01127.x>.
- [8] Jin-Jian Lu, Wei Pan, Yuan-Jia Hu, and Yi-Tao Wang. Multi-target drugs: the trend of drug research and development. *PloS one*, 7(6):e40262, 2012.
- [9] Joel T Dudley, Tarangini Deshpande, and Atul J Butte. Exploiting drug–disease relationships for computational drug repositioning. *Briefings in bioinformatics*, 12(4):303–311, 2011.
- [10] S Joshua Swamidass. Mining small-molecule screens to repurpose drugs. *Briefings in bioinformatics*, 12(4):327–335, 2011.
- [11] Fabrice Moriaud, Stéphane B Richard, Stewart A Adcock, Laetitia Chanas-Martin, Jean-Sébastien Surgand, Marouane Ben Jelloul, and François Delfaud. Identify drug repurposing candidates by mining the protein data bank. *Briefings in bioinformatics*, 12(4):336–340, 2011.
- [12] A Arun Kumar, Samarth Bhandary, Swathi Gopal Hegde, and Jhinuk Chatterjee. Knowledge graph applications and multi-relation learning for drug repurposing: A scoping review. *Computational Biology and Chemistry*, page 108364, 2025.
- [13] Stephen M Strittmatter. Overcoming drug development bottlenecks with repurposing: old drugs learn new tricks. *Nature medicine*, 20(6):590–591, 2014.
- [14] Eugen Lounkine, Michael J Keiser, Steven Whitebread, Dmitri Mikhailov, Jacques Hamon, Jeremy L Jenkins, Paul Lavan, Eckhard Weber, Allison K Doak, Serge Côté, et al. Large-scale prediction and testing of drug activity on side-effect targets. *Nature*, 446(7139):361–367, 2012.
- [15] Edouard Pauwels, Véronique Stoven, and Yoshihiro Yamanishi. Predicting drug side-effect profiles: a chemical fragment-based approach. *BMC bioinformatics*, 12:1–13, 2011.
- [16] Kathleen M Giacomini, Ronald M Krauss, Dan M Roden, Michel Eichelbaum, Michael R Hayden, and Yusuke Nakamura. When good drugs go bad. *Nature*, 446(7139):975–977, 2007.
- [17] Andrew L Hopkins. Predicting promiscuity. *Nature*, 462(7270):167–168, 2009.
- [18] Robert A Copeland, David L Pompliano, and Thomas D Meek. Drug–target residence time and its implications for lead optimization. *Nature reviews Drug discovery*, 5(9):730–739, 2006.
- [19] Zehong Zhang, Lifan Chen, Feisheng Zhong, Dingyan Wang, Jiaxin Jiang, Sulin Zhang, Hualiang Jiang, Mingyue Zheng, and Xutong Li. Graph neural network approaches for drug-target interactions. *Current Opinion in Structural Biology*, 73:102327, 2022.

- [20] Yue Zhang, Yuqing Hu, Na Han, Aqing Yang, Xiaoyong Liu, and Hongmin Cai. A survey of drug-target interaction and affinity prediction methods via graph neural networks. *Computers in Biology and Medicine*, 163: 107136, 2023.
- [21] Wen Shi, Dandan Peng, Jinyuan Luo, Guozhu Chen, Hong Yang, Linhai Xie, Xiao-Xia Yin, and Yanchun Zhang. A review on predicting drug target interactions based on machine learning. In *International Conference on Health Information Science*, pages 283–295. Springer, 2023.
- [22] A Suruliandi, T Idhaya, and SP Raja. Drug target interaction prediction using machine learning techniques—a review. ., 2024.
- [23] Xing Chen, Chenggang Clarence Yan, Xiaotian Zhang, Xu Zhang, Feng Dai, Jian Yin, and Yongdong Zhang. Drug–target interaction prediction: databases, web servers and computational models. *Briefings in bioinformatics*, 17(4):696–712, 2016.
- [24] Xinnan Zhang, Jialin Wu, Junyi Xie, Tianlong Chen, and Kaixiong Zhou. Benchmark on drug target interaction modeling from a structure perspective. *arXiv preprint arXiv:2407.04055*, 2024.
- [25] Kanica Sachdev and Manoj Kumar Gupta. A comprehensive review of feature based methods for drug target interaction prediction. *Journal of biomedical informatics*, 93:103159, 2019.
- [26] Lee Soo Jung and Young-Rae Cho. Survey of network-based approaches of drug-target interaction prediction. In *2020 IEEE International conference on bioinformatics and biomedicine (BIBM)*, pages 1793–1796. IEEE, 2020.
- [27] Sangsoo Lim, Yijingxiu Lu, Chang Yun Cho, Inyoung Sung, Jungwoo Kim, Youngkuk Kim, Sungjoon Park, and Sun Kim. A review on compound-protein interaction prediction methods: data, format, representation and model. *Computational and Structural Biotechnology Journal*, 19:1541–1556, 2021.
- [28] Lingling Zhao, Yan Zhu, Junjie Wang, Naifeng Wen, Chunyu Wang, and Liang Cheng. A brief review of protein–ligand interaction prediction. *Computational and Structural Biotechnology Journal*, 20:2831–2838, 2022.
- [29] Gelany Aly Abdelkader and Jeong-Dong Kim. Advances in protein-ligand binding affinity prediction via deep learning: A comprehensive study of datasets, data preprocessing techniques, and model architectures. *Current drug targets*, 25(15):1041–1065, 2024.
- [30] James Michels, Ramya Bandarupalli, Amin Ahangar Akbari, Thai Le, Hong Xiao, Jing Li, and Erik FY Hom. Natural language processing methods for the study of protein-ligand interactions. *arXiv preprint arXiv:2409.13057*, 2024.
- [31] Huiwen Wang. Prediction of protein–ligand binding affinity via deep learning models. *Briefings in Bioinformatics*, 25(2):bbae081, 2024.
- [32] Xin Zeng, Shu-Juan Li, Shuang-Qing Lv, Meng-Liang Wen, and Yi Li. A comprehensive review of the recent advances on predicting drug-target affinity based on deep learning. *Frontiers in Pharmacology*, 15:1375522, 2024.
- [33] Karim Abbasi, Parvin Razzaghi, Antti Poso, Saber Ghanbari-Ara, and Ali Masoudi-Nejad. Deep learning in drug target interaction prediction: current and future perspectives. *Current Medicinal Chemistry*, 28(11):2100–2113, 2021.
- [34] Warren L DeLano et al. Pymol: An open-source molecular graphics tool. *CCP4 Newsl. Protein Crystallogr*, 40(1):82–92, 2002.
- [35] David Weininger. Smiles, a chemical language and information system. 1. introduction to methodology and encoding rules. *Journal of chemical information and computer sciences*, 28(1):31–36, 1988.
- [36] Greg Landrum. Rdkit: Open-source cheminformatics. 2006. *Google Scholar*, 2006.
- [37] Evan E Bolton, Yanli Wang, Paul A Thiessen, and Stephen H Bryant. Pubchem: integrated platform of small molecules and biological activities. In *Annual reports in computational chemistry*, volume 4, pages 217–241. Elsevier, 2008.
- [38] Mario Krenn, Florian Häse, AkshatKumar Nigam, Pascal Friederich, and Alan Aspuru-Guzik. Self-referencing embedded strings (selfies): A 100% robust molecular string representation. *Machine Learning: Science and Technology*, 1(4):045024, 2020.
- [39] Robert Schmidt, Emanuel SR Ehmki, Farina Ohm, Hans-Christian Ehrlich, Andriy Mashychev, and Matthias Rarey. Comparing molecular patterns using the example of smarts: theory and algorithms. *Journal of Chemical Information and Modeling*, 59(6):2560–2571, 2019.
- [40] Tomas Mikolov, Ilya Sutskever, Kai Chen, Greg S Corrado, and Jeff Dean. Distributed representations of words and phrases and their compositionality. *Advances in neural information processing systems*, 26, 2013.

- [41] Sabrina Jaeger, Simone Fulle, and Samo Turk. Mol2vec: unsupervised machine learning approach with chemical intuition. *Journal of chemical information and modeling*, 58(1):27–35, 2018.
- [42] David Rogers and Mathew Hahn. Extended-connectivity fingerprints. *Journal of chemical information and modeling*, 50(5):742–754, 2010.
- [43] Nikolaus Stiefl, Ian A Watson, Knut Baumann, and Andrea Zaliani. Erg: 2d pharmacophore descriptions for scaffold hopping. *Journal of chemical information and modeling*, 46(1):208–220, 2006.
- [44] Daylight Toolkit. Daylight chemical information systems. *Inc.: Aliso Viejo, CA*, 2007.
- [45] Joseph L Durant, Burton A Leland, Douglas R Henry, and James G Nourse. Reoptimization of mdl keys for use in drug discovery. *Journal of chemical information and computer sciences*, 42(6):1273–1280, 2002.
- [46] National Institutes of Health (NIH). Pubchem database, 2019. URL <https://pubchem.ncbi.nlm.nih.gov/>.
- [47] Dong Chen, Kaifu Gao, Duc Duy Nguyen, Xin Chen, Yi Jiang, Guo-Wei Wei, and Feng Pan. Algebraic graph-assisted bidirectional transformers for molecular property prediction. *Nature communications*, 12(1):3521, 2021.
- [48] Chun Wei Yap. Padel-descriptor: An open source software to calculate molecular descriptors and fingerprints. *Journal of computational chemistry*, 32(7):1466–1474, 2011.
- [49] Fabrizio Costa and Kurt De Grave. Fast neighborhood subgraph pairwise distance kernel. In *Proceedings of the 27th International Conference on International Conference on Machine Learning*, pages 255–262, 2010.
- [50] Mufei Li, Jinjing Zhou, Jiajing Hu, Wenxuan Fan, Yangkang Zhang, Yaxin Gu, and George Karypis. Dgl-lifesci: An open-source toolkit for deep learning on graphs in life science. *ACS omega*, 6(41):27233–27238, 2021.
- [51] Minjie Wang, Da Zheng, Zihao Ye, Quan Gan, Mufei Li, Xiang Song, Jinjing Zhou, Chao Ma, Lingfan Yu, Yu Gai, et al. Deep graph library: A graph-centric, highly-performant package for graph neural networks. *arXiv preprint arXiv:1909.01315*, 2019.
- [52] Noel M O’Boyle, Michael Banck, Craig A James, Chris Morley, Tim Vandermeersch, and Geoffrey R Hutchison. Open babel: An open chemical toolbox. *Journal of cheminformatics*, 3:1–14, 2011.
- [53] Harold E Helson. Structure diagram generation. *Reviews in Computational Chemistry*, 13:313–398, 1999.
- [54] Tarikul I. Milon, Yuhong Wang, Ryan L. Fontenot, Poorya Khajouie, Francois Villinger, Vijay Raghavan, and Wu Xu. Development of a novel representation of drug 3d structures and enhancement of the tsr-based method for probing drug and target interactions. *Computational Biology and Chemistry*, 112:108117, 2024. ISSN 1476-9271. doi:<https://doi.org/10.1016/j.compbiolchem.2024.108117>. URL <https://www.sciencedirect.com/science/article/pii/S1476927124001051>.
- [55] John Jumper, Richard Evans, Alexander Pritzel, Tim Green, Michael Figurnov, Olaf Ronneberger, Kathryn Tunyasuvunakool, Russ Bates, Augustin Židek, Anna Potapenko, et al. Highly accurate protein structure prediction with alphafold. *nature*, 596(7873):583–589, 2021.
- [56] Vincent Le Guilloux, Peter Schmidtke, and Pierre Tuffery. Fpocket: an open source platform for ligand pocket detection. *BMC bioinformatics*, 10:1–11, 2009.
- [57] Andrea Volkamer, Axel Griewel, Thomas Grombacher, and Matthias Rarey. Analyzing the topology of active sites: on the prediction of pockets and subpockets. *Journal of chemical information and modeling*, 50(11):2041–2052, 2010.
- [58] Hongbo Zhu and M Teresa Pisabarro. Mspocket: an orientation-independent algorithm for the detection of ligand binding pockets. *Bioinformatics*, 27(3):351–358, 2011.
- [59] Ayome Abibi, Andrew D Ferguson, Paul R Fleming, Ning Gao, Laurel I Hajec, Jun Hu, Valerie A Laganas, David C McKinney, Sarah M McLeod, D Bryan Prince, et al. The role of a novel auxiliary pocket in bacterial phenylalanyl-trna synthetase druggability. *Journal of Biological Chemistry*, 289(31):21651–21662, 2014.
- [60] David Rooklin, Cheng Wang, Joseph Katigbak, Paramjit S Arora, and Yingkai Zhang. Alphaspace: Fragment-centric topographical mapping to target protein–protein interaction interfaces. *Journal of chemical information and modeling*, 55(8):1585–1599, 2015.
- [61] Seyed Majid Saberi Fathi and Jack A Tuszynski. A simple method for finding a protein’s ligand-binding pockets. *BMC Structural Biology*, 14:1–9, 2014.
- [62] Joseph Katigbak, Haotian Li, David Rooklin, and Yingkai Zhang. Alphaspace 2.0: representing concave biomolecular surfaces using  $\beta$ -clusters. *Journal of chemical information and modeling*, 60(3):1494–1508, 2020.

- [63] Ikki Yasuda, Katsuhiro Endo, Eiji Yamamoto, Yoshinori Hirano, and Kenji Yasuoka. Differences in ligand-induced protein dynamics extracted from an unsupervised deep learning approach correlate with protein–ligand binding affinities. *Communications biology*, 5(1):481, 2022.
- [64] Shuya Li, Tingzhong Tian, Ziting Zhang, Ziheng Zou, Dan Zhao, and Jianyang Zeng. Pocketanchor: Learning structure-based pocket representations for protein-ligand interaction prediction. *Cell Systems*, 14(8):692–705, 2023.
- [65] Jun Zhang and Bin Liu. A review on the recent developments of sequence-based protein feature extraction methods. *Current Bioinformatics*, 14(3):190–199, 2019.
- [66] Shourun Pan, Leiming Xia, Lei Xu, and Zhen Li. Submdta: drug target affinity prediction based on substructure extraction and multi-scale features. *BMC bioinformatics*, 24(1):334, 2023.
- [67] Qi-Wen Dong, Xiao-long Wang, and Lei Lin. Application of latent semantic analysis to protein remote homology detection. *Bioinformatics*, 22(3):285–290, 2006.
- [68] Thin Nguyen, Hang Le, Thomas P Quinn, Tri Nguyen, Thuc Duy Le, and Svetha Venkatesh. Graphdta: predicting drug–target binding affinity with graph neural networks. *Bioinformatics*, 37(8):1140–1147, 2021.
- [69] Xianfang Wang, Yifeng Liu, Fan Lu, Hongfei Li, Peng Gao, and Dongqing Wei. Dipeptide frequency of word frequency and graph convolutional networks for dta prediction. *Frontiers in bioengineering and biotechnology*, 8:267, 2020.
- [70] Sean R Eddy. Where did the blosum62 alignment score matrix come from? *Nature biotechnology*, 22(8):1035–1036, 2004.
- [71] David J Lipman and William R Pearson. Rapid and sensitive protein similarity searches. *Science*, 227(4693):1435–1441, 1985.
- [72] Stephen F Altschul, Thomas L Madden, Alejandro A Schäffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J Lipman. Gapped blast and psi-blast: a new generation of protein database search programs. *Nucleic acids research*, 25(17):3389–3402, 1997.
- [73] Michael Remmert, Andreas Biegert, Andreas Hauser, and Johannes Söding. Hhblits: lightning-fast iterative protein sequence searching by hmm-hmm alignment. *Nature methods*, 9(2):173–175, 2012.
- [74] Zaynab Mousavian, Sahand Khakabimamaghani, Kaveh Kavousi, and Ali Masoudi-Nejad. Drug–target interaction prediction from pssm based evolutionary information. *Journal of pharmacological and toxicological methods*, 78:42–51, 2016.
- [75] Dong-Sheng Cao, Qing-Song Xu, and Yi-Zeng Liang. propy: a tool to generate various modes of chou’s pseAAC. *Bioinformatics*, 29(7):960–962, 2013.
- [76] Zhe Quan, Yan Guo, Xuan Lin, Zhi-Jie Wang, and Xiangxiang Zeng. Graphcpi: Graph neural representation learning for compound-protein interaction. In *2019 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, pages 717–722. IEEE, 2019.
- [77] Lu Wang, Yifeng Zhou, and Qu Chen. Ammvf-dti: A novel model predicting drug–target interactions based on attention mechanism and multi-view fusion. *International Journal of Molecular Sciences*, 24(18):14142, 2023.
- [78] Min Li, Zhangli Lu, Yifan Wu, and YaoHang Li. Bacpi: a bi-directional attention neural network for compound–protein interaction and binding affinity prediction. *Bioinformatics*, 38(7):1995–2002, 2022.
- [79] Masashi Tsubaki, Kentaro Tomii, and Jun Sese. Compound–protein interaction prediction with end-to-end learning of neural networks for graphs and sequences. *Bioinformatics*, 35(2):309–318, 2019.
- [80] Xuan Lin, Kaiqi Zhao, Tong Xiao, Zhe Quan, Zhi-Jie Wang, and Philip S Yu. Deepgs: Deep representation learning of graphs and sequences for drug-target binding affinity prediction. In *ECAI 2020*, pages 1301–1308. IOS Press, 2020.
- [81] Zhongjian Cheng, Qichang Zhao, Yaohang Li, and Jianxin Wang. Iifdti: predicting drug–target interactions through interactive and independent features based on attention mechanism. *Bioinformatics*, 38(17):4153–4161, 2022.
- [82] Minghao Xia, Jing Hu, Xiaolong Zhang, and Xiaoli Lin. Drug-target binding affinity prediction based on graph neural networks and word2vec. In *International Conference on Intelligent Computing*, pages 496–506. Springer, 2022.
- [83] QHwan Kim, Joon-Hyuk Ko, Sunghoon Kim, Nojun Park, and Wonho Jhe. Bayesian neural network with pretrained protein embedding enhances prediction accuracy of drug-protein interaction. *Bioinformatics*, 37(20):3428–3435, 2021.

- [84] Rakesh Bal, Yijia Xiao, and Wei Wang. Pgraphdta: Improving drug target interaction prediction using protein language models and contact maps. *arXiv preprint arXiv:2310.04017*, 2023.
- [85] Ahmed Elnaggar, Michael Heinzinger, Christian Dallago, Ghaliya Rehawi, Yu Wang, Llion Jones, Tom Gibbs, Tamas Feher, Christoph Angerer, Martin Steinegger, et al. Prottrans: Toward understanding the language of life through self-supervised learning. *IEEE transactions on pattern analysis and machine intelligence*, 44(10): 7112–7127, 2021.
- [86] Zeming Lin, Halil Akin, Roshan Rao, Brian Hie, Zhongkai Zhu, Wenting Lu, Allan dos Santos Costa, Maryam Fazel-Zarandi, Tom Sercu, Sal Candido, et al. Language models of protein sequences at the scale of evolution enable accurate structure prediction. *BioRxiv*, 2022:500902, 2022.
- [87] Nadav Brandes, Dan Ofer, Yam Peleg, Nadav Rappoport, and Michal Linial. Proteinbert: a universal deep-learning model of protein sequence and function. *Bioinformatics*, 38(8):2102–2110, 2022.
- [88] Ehsaneddin Asgari and Mohammad RK Mofrad. Continuous distributed representation of biological sequences for deep proteomics and genomics. *PLoS one*, 10(11):e0141287, 2015.
- [89] Roshan Rao, Nicholas Bhattacharya, Neil Thomas, Yan Duan, Peter Chen, John Canny, Pieter Abbeel, and Yun Song. Evaluating protein transfer learning with tape. *Advances in neural information processing systems*, 32, 2019.
- [90] Ethan C Alley, Grigory Khimulya, Surojit Biswas, Mohammed AlQuraishi, and George M Church. Unified rational protein engineering with sequence-based deep representation learning. *Nature methods*, 16(12):1315–1322, 2019.
- [91] The UniProt Consortium. Uniprot: the universal protein knowledgebase. *Nucleic acids research*, 46(5):2699–2699, 2018.
- [92] Nicolas Hulo, Christian JA Sigrist, Virginie Le Saux, Petra S Langendijk-Genevaux, Lorenza Bordoli, Alexandre Gattiker, Edouard De Castro, Philipp Bucher, and Amos Bairoch. Recent improvements to the prosite database. *Nucleic Acids Research*, 32(suppl\_1):D134–D137, 2004.
- [93] Alex Bateman, Lachlan Coin, Richard Durbin, Robert D Finn, Volker Hollich, Sam Griffiths-Jones, Ajay Khanna, Mhairi Marshall, Simon Moxon, Erik LL Sonnhammer, et al. The pfam protein families database. *Nucleic acids research*, 32(suppl\_1):D138–D141, 2004.
- [94] Christophe N Magnan and Pierre Baldi. Sspro/accpro 5: almost perfect prediction of protein secondary structure and relative solvent accessibility using profiles, machine learning and structural similarity. *Bioinformatics*, 30(18):2592–2597, 2014.
- [95] Mingjian Jiang, Zhen Li, Shugang Zhang, Shuang Wang, Xiaofeng Wang, Qing Yuan, and Zhiqiang Wei. Drug–target affinity prediction using graph neural network and contact maps. *RSC advances*, 10(35):20701–20712, 2020.
- [96] Penglei Wang, Shuangjia Zheng, Yize Jiang, Chengtao Li, Junhong Liu, Chang Wen, Atanas Patronov, Dahong Qian, Hongming Chen, and Yuedong Yang. Structure-aware multimodal deep learning for drug–protein interaction prediction. *Journal of chemical information and modeling*, 62(5):1308–1317, 2022.
- [97] Mirco Michel, David Menéndez Hurtado, and Arne Elofsson. Pcons4: fast, accurate and hassle-free contact predictions. *Bioinformatics*, 35(15):2677–2679, 2019.
- [98] Roshan Rao, Joshua Meier, Tom Sercu, Sergey Ovchinnikov, and Alexander Rives. Transformer protein language models are unsupervised structure learners. *Biorxiv*, pages 2020–12, 2020.
- [99] Laurent Maveyraud and Lionel Mourey. Protein x-ray crystallography and drug discovery. *Molecules*, 25(5): 1030, 2020.
- [100] R Kaptein, R Boelens, RM Scheek, and WF Van Gunsteren. Protein structures from nmr. *Biochemistry*, 27(15): 5389–5395, 1988.
- [101] Juan Esquivel-Rodríguez and Daisuke Kihara. Computational methods for constructing protein structure models from 3d electron microscopy maps. *Journal of structural biology*, 184(1):93–102, 2013.
- [102] Tapio Pahikkala, Antti Airola, Sami Pietilä, Sushil Shakyawar, Agnieszka Szwejda, Jing Tang, and Tero Aittokallio. Toward more realistic drug–target interaction predictions. *Briefings in bioinformatics*, 16(2):325–337, 2015.
- [103] Minghua Zhao, Min Yuan, Yaning Yang, and Steven X Xu. Cppl: Prediction of compound-protein interaction by integrating graph attention network with long short-term memory neural network. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 20(3):1935–1942, 2022.
- [104] Chen Lin, Sheng Ni, Yun Liang, Xiangxiang Zeng, and Xiangrong Liu. Learning to predict drug target interaction from missing not at random labels. *IEEE transactions on nanobioscience*, 18(3):353–359, 2019.



- [105] Yoshihiro Yamanishi, Michihiro Araki, Alex Gutteridge, Wataru Honda, and Minoru Kanehisa. Prediction of drug–target interaction networks from the integration of chemical and genomic spaces. *Bioinformatics*, 24(13): i232–i240, 2008.
- [106] Fangping Wan and Jianyang Zeng. Deep learning with feature embedding for compound-protein interaction prediction. *Biorxiv*, page 086033, 2016.
- [107] Ali Ezzat, Min Wu, Xiao-Li Li, and Chee-Keong Kwoh. Computational prediction of drug–target interactions using chemogenomic approaches: an empirical survey. *Briefings in bioinformatics*, 20(4):1337–1357, 2019.
- [108] Kunal Roy, Supratik Kar, and Rudra Narayan Das. *Understanding the basics of QSAR for applications in pharmaceutical sciences and risk assessment*. Academic press, 2015.
- [109] Pedro J Ballester and John BO Mitchell. A machine learning approach to predicting protein–ligand binding affinity with applications to molecular docking. *Bioinformatics*, 26(9):1169–1175, 2010.
- [110] Hongjian Li, Kwong-Sak Leung, Man-Hon Wong, and Pedro J Ballester. Low-quality structural and interaction data improves binding affinity prediction via random forest. *Molecules*, 20(6):10947–10962, 2015.
- [111] H Tomas Rube, Chaitanya Rastogi, Siqian Feng, Judith F Kribelbauer, Allyson Li, Basheer Becerra, Lucas AN Melo, Bach Viet Do, Xiaoting Li, Hammaad H Adam, et al. Prediction of protein–ligand binding affinity from sequencing data with interpretable machine learning. *Nature biotechnology*, 40(10):1520–1527, 2022.
- [112] Duc Duy Nguyen and Guo-Wei Wei. Agl-score: algebraic graph learning score for protein–ligand binding scoring, ranking, docking, and screening. *Journal of chemical information and modeling*, 59(7):3291–3304, 2019.
- [113] Renxiao Wang, Luhua Lai, and Shaomeng Wang. Further development and validation of empirical scoring functions for structure-based binding affinity prediction. *Journal of computer-aided molecular design*, 16:11–26, 2002.
- [114] Mohamed A Khamis and Walid Gomaa. Comparative assessment of machine-learning scoring functions on pdbbind 2013. *Engineering Applications of Artificial Intelligence*, 45:136–151, 2015.
- [115] Oliver Korb, Thomas Stutzle, and Thomas E Exner. Empirical scoring functions for advanced protein- ligand docking with plants. *Journal of chemical information and modeling*, 49(1):84–96, 2009.
- [116] Thomas Gaillard. Evaluation of autodock and autodock vina on the casf-2013 benchmark. *Journal of chemical information and modeling*, 58(8):1697–1706, 2018.
- [117] Marta M Stepniewska-Dziubinska, Piotr Zielenkiewicz, and Pawel Siedlecki. Development and evaluation of a deep learning model for protein–ligand binding affinity prediction. *Bioinformatics*, 34(21):3666–3674, 2018.
- [118] Demetri T Moustakas, P Therese Lang, Scott Pegg, Eric Pettersen, Irwin D Kuntz, Natasja Brooijmans, and Robert C Rizzo. Development and validation of a modular, extensible docking program: Dock 5. *Journal of computer-aided molecular design*, 20:601–619, 2006.
- [119] David M Lorber and Brian K Shoichet. Hierarchical docking of databases of multiple ligand conformations. *Current topics in medicinal chemistry*, 5(8):739–749, 2005.
- [120] Garrett M Morris, Ruth Huey, William Lindstrom, Michel F Sanner, Richard K Belew, David S Goodsell, and Arthur J Olson. Autodock4 and autodocktools4: Automated docking with selective receptor flexibility. *Journal of computational chemistry*, 30(16):2785–2791, 2009.
- [121] Oleg Trott and Arthur J Olson. Autodock vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of computational chemistry*, 31(2):455–461, 2010.
- [122] Richard A Friesner, Jay L Banks, Robert B Murphy, Thomas A Halgren, Jasna J Klicic, Daniel T Mainz, Matthew P Repasky, Eric H Knoll, Mee Shelley, Jason K Perry, et al. Glide: a new approach for rapid, accurate docking and scoring. 1. method and assessment of docking accuracy. *Journal of medicinal chemistry*, 47(7): 1739–1749, 2004.
- [123] Gareth Jones, Peter Willett, Robert C Glen, Andrew R Leach, and Robin Taylor. Development and validation of a genetic algorithm for flexible docking. *Journal of molecular biology*, 267(3):727–748, 1997.
- [124] Matthias Rarey, Bernd Kramer, Thomas Lengauer, and Gerhard Klebe. A fast flexible docking method using an incremental construction algorithm. *Journal of molecular biology*, 261(3):470–489, 1996.
- [125] Ajay N Jain. Surflex-dock 2.1: robust performance from ligand energetic modeling, ring flexibility, and knowledge-based search. *Journal of computer-aided molecular design*, 21:281–306, 2007.
- [126] Hans FG Velec, Holger Gohlke, and Gerhard Klebe. Drugscorecsd knowledge-based scoring function derived from small molecule crystal data with superior recognition rate of near-native ligand poses and better affinity prediction. *Journal of medicinal chemistry*, 48(20):6296–6303, 2005.

- [127] Sheng-You Huang and Xiaoqin Zou. Inclusion of solvation and entropy in the knowledge-based scoring function for protein- ligand interactions. *Journal of chemical information and modeling*, 50(2):262–273, 2010.
- [128] Alexey V Ishchenko and Eugene I Shakhnovich. Small molecule growth 2001 (smog2001): An improved knowledge-based scoring function for protein- ligand interactions. *Journal of medicinal chemistry*, 45(13): 2770–2780, 2002.
- [129] Chi Zhang, Song Liu, Qianqian Zhu, and Yaoqi Zhou. A knowledge-based energy function for protein- ligand, protein- protein, and protein- dna complexes. *Journal of medicinal chemistry*, 48(7):2325–2335, 2005.
- [130] Ingo Muegge. Pmf scoring revisited. *Journal of medicinal chemistry*, 49(20):5895–5902, 2006.
- [131] Mark A Johnson, Gerald M Maggiora, et al. Concepts and applications of molecular similarity. (*No Title*), 1990.
- [132] Liat Perlman, Assaf Gottlieb, Nir Atias, Eytan Ruppin, and Roded Sharan. Combining drug and gene similarity measures for drug-target elucidation. *Journal of computational biology*, 18(2):133–145, 2011.
- [133] Darko Butina, Matthew D Segall, and Katrina Frankcombe. Predicting adme properties in silico: methods and models. *Drug discovery today*, 7(11):S83–S88, 2002.
- [134] David Ryan Koes, Matthew P Baumgartner, and Carlos J Camacho. Lessons learned in empirical scoring with smina from the csar 2011 benchmarking exercise. *Journal of chemical information and modeling*, 53(8): 1893–1904, 2013.
- [135] Mark J Howard. Protein nmr spectroscopy. *Current biology*, 8(10):R331–R333, 1998.
- [136] Lei Wang, Zhu-Hong You, Xing Chen, Shi-Xiong Xia, Feng Liu, Xin Yan, Yong Zhou, and Ke-Jian Song. A computational-based method for predicting drug–target interactions by using stacked autoencoder deep neural network. *Journal of Computational Biology*, 25(3):361–373, 2018.
- [137] Lingwei Xie, Song He, Xinyu Song, Xiaochen Bo, and Zhongnan Zhang. Deep learning-based transcriptome data classification for drug-target interaction prediction. *BMC genomics*, 19:93–102, 2018.
- [138] Maciej Wójcikowski, Pawel Siedlecki, and Pedro J Ballester. Building machine-learning scoring functions for structure-based prediction of intermolecular binding affinity. *Docking screens for drug discovery*, pages 1–12, 2019.
- [139] Ingoo Lee, Jongsoo Keum, and Hojung Nam. Deepconv-dti: Prediction of drug-target interactions via deep learning with convolution on protein sequences. *PLoS computational biology*, 15(6):e1007129, 2019.
- [140] Muhammed A Yildirim, Kwang-Il Goh, Michael E Cusick, Albert-Laszlo Barabasi, and Marc Vidal. Drug-target network. *Nature biotechnology*, 25(10):1119–1126, 2007.
- [141] Stanley J Opella. Structure determination of membrane proteins by nuclear magnetic resonance spectroscopy. *Annual Review of Analytical Chemistry*, 6(1):305–328, 2013.
- [142] William L Jorgensen and Laura L Thomas. Perspective on free-energy perturbation calculations for chemical equilibria. *Journal of chemical theory and computation*, 4(6):869–876, 2008.
- [143] Süleyman Selim Çınaroğlu and Emel Timuçin. Comprehensive evaluation of the mm-gbsa method on bromodomain-inhibitor sets. *Briefings in Bioinformatics*, 21(6):2112–2125, 2020.
- [144] Akshay R Yadav and Shrinivas K Mohite. Homology modeling and generation of 3d-structure of protein. *Research Journal of Pharmaceutical Dosage Forms and Technology*, 12(4):313–320, 2020.
- [145] Zaynab Mousavian and Ali Masoudi-Nejad. Drug–target interaction prediction via chemogenomic space: learning-based methods. *Expert opinion on drug metabolism & toxicology*, 10(9):1273–1287, 2014.
- [146] Zhisong He, Jian Zhang, Xiao-He Shi, Le-Le Hu, Xiangyin Kong, Yu-Dong Cai, and Kuo-Chen Chou. Predicting drug-target interaction networks based on functional groups and biological features. *PloS one*, 5(3):e9603, 2010.
- [147] Gang Fu, Ying Ding, Abhik Seal, Bin Chen, Yizhou Sun, and Evan Bolton. Predicting drug target interactions using meta-path-based semantic network analysis. *BMC bioinformatics*, 17:1–10, 2016.
- [148] Kexin Huang, Tianfan Fu, Lucas M Glass, Marinka Zitnik, Cao Xiao, and Jimeng Sun. Deeppurpose: a deep learning library for drug–target interaction prediction. *Bioinformatics*, 36(22-23):5545–5547, 2020.
- [149] Qingjun Yuan, Junning Gao, Dongliang Wu, Shihua Zhang, Hiroshi Mamitsuka, and Shanfeng Zhu. Druge-rank: improving drug–target interaction prediction of new candidate drugs or targets by ensemble learning to rank. *Bioinformatics*, 32(12):i18–i27, 2016.
- [150] Ingoo Lee and Hojung Nam. Identification of drug-target interaction by a random walk with restart method on an interactome network. *BMC bioinformatics*, 19:9–18, 2018.

- [151] Kevin Bleakley and Yoshihiro Yamanishi. Supervised prediction of drug–target interactions using bipartite local models. *Bioinformatics*, 25(18):2397–2403, 2009.
- [152] Jian-Yu Shi, Jia-Xin Li, Hui-Meng Lu, and Yong Zhang. Predicting drug-target interactions between new drugs and new targets via pairwise k-nearest neighbor and automatic similarity selection. In *Intelligence Science and Big Data Engineering. Big Data and Machine Learning Techniques: 5th International Conference, IScIDE 2015, Suzhou, China, June 14-16, 2015, Revised Selected Papers, Part II 5*, pages 477–486. Springer, 2015.
- [153] Hansaim Lim, Paul Gray, Lei Xie, and Aleksandar Poleksic. Improved genome-scale multi-target virtual screening via a novel collaborative filtering approach to cold-start problem. *Scientific reports*, 6(1):38860, 2016.
- [154] André CA Nascimento, Ricardo BC Prudêncio, and Ivan G Costa. A multiple kernel learning algorithm for drug-target interaction prediction. *BMC bioinformatics*, 17:1–16, 2016.
- [155] Jian-Ping Mei, Chee-Keong Kwoh, Peng Yang, Xiao-Li Li, and Jie Zheng. Drug–target interaction prediction by learning from local information and neighbors. *Bioinformatics*, 29(2):238–245, 2013.
- [156] Jean-Loup Faulon, Milind Misra, Shawn Martin, Ken Sale, and Rajat Sapra. Genome scale enzyme–metabolite and drug–target interaction predictions using the signature molecular descriptor. *Bioinformatics*, 24(2):225–233, 2008.
- [157] Meng-yu Wang, Peng Li, and Pei-li Qiao. The virtual screening of the drug protein with a few crystal structures based on the adaboost-svm. *Computational and Mathematical Methods in Medicine*, 2016(1):4809831, 2016.
- [158] Yuhao Wang and Jianyang Zeng. Predicting drug-target interactions using restricted boltzmann machines. *Bioinformatics*, 29(13):i126–i134, 2013.
- [159] Twan Van Laarhoven, Sander B Nabuurs, and Elena Marchiori. Gaussian interaction profile kernels for predicting drug–target interaction. *Bioinformatics*, 27(21):3036–3043, 2011.
- [160] Zheng Xia, Ling-Yun Wu, Xiaobo Zhou, and Stephen TC Wong. Semi-supervised drug-protein interaction prediction from heterogeneous biological spaces. In *BMC systems biology*, volume 4, pages 1–16. Springer, 2010.
- [161] Lihong Peng, Bo Liao, Wen Zhu, Zejun Li, and Keqin Li. Predicting drug–target interactions with multi-information fusion. *IEEE journal of biomedical and health informatics*, 21(2):561–572, 2015.
- [162] Tong He, Marten Heidemeyer, Fuqiang Ban, Artem Cherkasov, and Martin Ester. Simboost: a read-across approach for predicting drug–target binding affinities using gradient boosting machines. *Journal of cheminformatics*, 9: 1–14, 2017.
- [163] Yaoyao Lu, Junkai Liu, Tengsheng Jiang, Zhiming Cui, and Hongjie Wu. Drug-target binding affinity prediction based on three-branched multiscale convolutional neural networks. *Current Bioinformatics*, 18(10):853–862, 2023.
- [164] Shudong Wang, Zhenzhen Du, Mao Ding, Renteng Zhao, Alfonso Rodriguez-Paton, and Tao Song. Ldcnn-dti: a novel light deep convolutional neural network for drug-target interaction predictions. In *2020 IEEE international conference on bioinformatics and biomedicine (BIBM)*, pages 1132–1136. IEEE, 2020.
- [165] Jeongtae Son and Dongsup Kim. Development of a graph convolutional neural network model for efficient prediction of protein-ligand binding affinities. *PloS one*, 16(4):e0249404, 2021.
- [166] Donglin Wang, Xiangyong Chen, Xin Bao, and Kun Zhou. Agraphdta: An efficient model for drug-target affinity prediction with feature fusion. In *2023 International Conference on New Trends in Computational Intelligence (NTCI)*, volume 1, pages 360–364. IEEE, 2023.
- [167] Timothy Szocinski, Duc Duy Nguyen, and Guo-Wei Wei. Awegnn: Auto-parametrized weighted element-specific graph neural networks for molecules. *Computers in biology and medicine*, 134:104460, 2021.
- [168] Haiou Qi, Ting Yu, Wenwen Yu, and Chenxi Liu. Drug–target affinity prediction with extended graph learning-convolutional networks. *BMC bioinformatics*, 25(1):75, 2024.
- [169] Haiyang Wang, Guangyu Zhou, Siqi Liu, Jyun-Yu Jiang, and Wei Wang. Drug-target interaction prediction with graph attention networks. *arXiv preprint arXiv:2107.06099*, 2021.
- [170] Yan Sun, Yan Yi Li, Carson K Leung, and Pingzhao Hu. ingnn-dti: prediction of drug–target interaction with interpretable nested graph neural network and pretrained molecule models. *Bioinformatics*, 40(3):btac135, 2024.
- [171] Mengying Sun, Sendong Zhao, Coryandar Gilvary, Olivier Elemento, Jiayu Zhou, and Fei Wang. Graph convolutional networks for computational drug development and discovery. *Briefings in bioinformatics*, 21(3): 919–935, 2020.
- [172] Zonghan Wu, Shirui Pan, Fengwen Chen, Guodong Long, Chengqi Zhang, and S Yu Philip. A comprehensive survey on graph neural networks. *IEEE transactions on neural networks and learning systems*, 32(1):4–24, 2020.

- [173] Xiang Yue, Zhen Wang, Jingong Huang, Srinivasan Parthasarathy, Soheil Moosavinasab, Yungui Huang, Simon M Lin, Wen Zhang, Ping Zhang, and Huan Sun. Graph embedding on biomedical networks: methods, applications and evaluations. *Bioinformatics*, 36(4):1241–1251, 2020.
- [174] Xinyi Tu, Zhe Li, and Wenbin Lin. Se-dta: a spatial equivariant network for drug-target binding affinity prediction. In *2024 9th International Conference on Intelligent Computing and Signal Processing (ICSP)*, pages 993–998. IEEE, 2024.
- [175] Rachit Kumar, Joseph D Romano, and Marylyn D Ritchie. Caster-dta: Equivariant graph neural networks for predicting drug-target affinity. *bioRxiv*, pages 2024–11, 2024.
- [176] Ahmet Süreyya Rifaioğlu, Rengül Cetin Atalay, D Cansen Kahraman, Tunca Doğan, Maria Martin, and Volkan Atalay. Mdeepred: novel multi-channel protein featurization for deep learning-based binding affinity prediction in drug discovery. *Bioinformatics*, 37(5):693–704, 2021.
- [177] Mostafa Karimi, Di Wu, Zhangyang Wang, and Yang Shen. Deepaffinity: interpretable deep learning of compound–protein affinity through unified recurrent and convolutional neural networks. *Bioinformatics*, 35(18): 3329–3338, 2019.
- [178] Zhuo Huang, Qiu Xiao, Tuo Xiong, Wanwan Shi, Yide Yang, and Guanghui Li. Predicting drug–protein interactions through branch-chain mining and multi-dimensional attention network. *Computers in Biology and Medicine*, 171:108127, 2024.
- [179] Jiejing Deng, Yijia Zhang, Yaohua Pan, Xiaobo Li, and Mingyu Lu. Multidta: drug-target binding affinity prediction via representation learning and graph convolutional neural networks. *International Journal of Machine Learning and Cybernetics*, pages 1–10, 2024.
- [180] Kyohei Koyama, Kotaro Kamiya, and Koki Shimada. Cross attention dti: Drug-target interaction prediction with cross attention module in the blind evaluation setup. *BIOKDD2020*, 2020.
- [181] Xiaokun Li, Qiang Yang, Gongning Luo, Long Xu, Weihe Dong, Wei Wang, Suyu Dong, Kuanquan Wang, Ping Xuan, and Xin Gao. Sagdti: self-attention and graph neural network with multiple information representations for the prediction of drug–target interactions. *Bioinformatics Advances*, 3(1):vbad116, 2023.
- [182] Xiaoqing Cheng, Xixin Yang, Yuanlin Guan, and Yihan Feng. Ert-gfan: A multimodal drug–target interaction prediction model based on molecular biology and knowledge-enhanced attention mechanism. *Computers in Biology and Medicine*, 180:109012, 2024.
- [183] Huiqing Wang, Jingjing Wang, Chunlin Dong, Yuanyuan Lian, Dan Liu, and Zhiliang Yan. A novel approach for drug-target interactions prediction based on multimodal deep autoencoder. *Frontiers in pharmacology*, 10:1592, 2020.
- [184] Zhixian Liu, Qingfeng Chen, Wei Lan, Haiming Pan, Xinkun Hao, and Shirui Pan. Gadt: graph autoencoder approach for dti prediction from heterogeneous network. *Frontiers in Genetics*, 12:650821, 2021.
- [185] Lingling Zhao, Yan Zhu, Naifeng Wen, Chunyu Wang, Junjie Wang, and Yongfeng Yuan. Drug-target binding affinity prediction in a continuous latent space using variational autoencoders. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 2024.
- [186] Wei Wang, Huiru Liang, Shihao Liang, Dong Liu, Hongjun Zhang, Jiangli Shang, Yun Zhou, and Xianfang Wang. Mdgae-dti: Drug-target interactions prediction based on multi-information integration and graph auto-encoder. In *International Conference on Intelligent Computing*, pages 232–242. Springer, 2024.
- [187] Yijia Wu, Yanmei Lin, Yuzhong Peng, Ru Zhang, and Li Cai. T-graphdta: A drug-target binding affinity prediction framework based on protein pre-training model and hybrid graph neural network. In *International Conference on Applied Intelligence*, pages 113–123. Springer, 2023.
- [188] Jingtao Wang, Xi Li, and Hua Zhang. Gnn-pt: enhanced prediction of compound-protein interactions by integrating protein transformer. *arXiv preprint arXiv:2009.00805*, 2020.
- [189] Jiayue Hu, Wang Yu, Chao Pang, Junru Jin, Nhat Truong Pham, Balachandran Manavalan, and Leyi Wei. Drugormerdti: Drug graphormer for drug–target interaction prediction. *Computers in Biology and Medicine*, 161:106946, 2023.
- [190] Nelson RC Monteiro, José L Oliveira, and Joel P Arrais. Tag-dta: Binding-region-guided strategy to predict drug-target affinity using transformers. *Expert Systems with Applications*, 238:122334, 2024.
- [191] Mengmeng Gao, Daokun Zhang, Yi Chen, Yiwen Zhang, Zhikang Wang, Xiaoyu Wang, Shanshan Li, Yuming Guo, Geoffrey I Webb, Anh TN Nguyen, et al. Graphormerdti: a graph transformer-based approach for drug-target interaction prediction. *Computers in Biology and Medicine*, 173:108339, 2024.

- [192] Wei Chen, Guanxing Chen, Lu Zhao, and Calvin Yu-Chian Chen. Predicting drug–target interactions with deep-embedding learning of graphs and sequences. *The Journal of Physical Chemistry A*, 125(25):5633–5642, 2021.
- [193] Lesong Wei, Wentao Long, and Leyi Wei. Mdl-cpi: Multi-view deep learning model for compound-protein interaction prediction. *Methods*, 204:418–427, 2022.
- [194] Radheesh Sharma Meda and Amir Barati Farimani. Bapulm: Binding affinity prediction using language models. *arXiv e-prints*, pages arXiv–2411, 2024.
- [195] Yang Hua, Zhenhua Feng, Xiaoning Song, Xiao-Jun Wu, and Josef Kittler. Mmdg-dti: Drug–target interaction prediction via multimodal feature fusion and domain generalization. *Pattern Recognition*, 157:110887, 2025.
- [196] Ying Qian, Xuelian Li, Jian Wu, Aimin Zhou, Zhijian Xu, and Qian Zhang. Picture-word order compound protein interaction: Predicting compound–protein interaction using structural images of compounds. *Journal of computational chemistry*, 43(4):255–264, 2022.
- [197] Ying Qian, Jian Wu, and Qian Zhang. Cat-cpi: Combining cnn and transformer to learn compound image features for predicting compound–protein interactions. *Frontiers in Molecular Biosciences*, 9:963912, 2022.
- [198] Yang Zhang, Zhewei Wei, Wenbing Huang, and Chongxuan Li. Hieraffinity: Predicting protein–ligand binding affinity with hierarchical modeling. In *International Conference on Database Systems for Advanced Applications*, pages 37–52. Springer, 2024.
- [199] Xu Gong, Qun Liu, Jing He, Yike Guo, and Guoyin Wang. Multigrandti: an explainable multi-granularity representation framework for drug–target interaction prediction. *Applied Intelligence*, 55(2):1–19, 2025.
- [200] Peng Lei, Changan Yuan, Hongjie Wu, and Xingming Zhao. Drug–target interaction prediction based on graph neural network and recommendation system. In *International Conference on Intelligent Computing*, pages 66–78. Springer, 2022.
- [201] Qing Ye, Chang-Yu Hsieh, Ziyi Yang, Yu Kang, Jiming Chen, Dongsheng Cao, Shibo He, and Tingjun Hou. A unified drug–target interaction prediction framework based on knowledge graph and recommendation system. *Nature communications*, 12(1):6775, 2021.
- [202] Junwei Hu, Michael Bewong, Selasi Kwashie, Wen Zhang, Vincent M Nofong, Guangsheng Wu, and Zaiwen Feng. A heterogeneous network-based contrastive learning approach for predicting drug–target interaction. *arXiv preprint arXiv:2411.00801*, 2024.
- [203] Zhiqin Zhu, Xin Zheng, Guanqiu Qi, Yifei Gong, Yuanyuan Li, Neal Mazur, Baisen Cong, and Xinbo Gao. Drug–target binding affinity prediction model based on multi-scale diffusion and interactive learning. *Expert Systems with Applications*, 255:124647, 2024.
- [204] Tanya Liyaqat, Tanvir Ahmad, and Chandni Saxena. Tem-dtba: Time-efficient drug target binding affinity prediction using multiple modalities with lasso feature selection. *Journal of Computer-Aided Molecular Design*, 37(12):573–584, 2023.
- [205] Mathijs Boezer, Maryam Tavakol, and Zahra Sajadi. Fastdti: drug–target interaction prediction using multimodality and transformers. In *Proceedings of the northern lights deep learning workshop*, volume 4, page ., 2023.
- [206] Uxía Veleiro, Jesús de la Fuente, Guillermo Serrano, Marija Pizurica, Mikel Casals, Antonio Pineda-Lucena, Silve Vicent, Idoia Ochoa, Olivier Gevaert, and Mikel Hernaez. Gennius: an ultrafast drug–target interaction inference method based on graph neural networks. *Bioinformatics*, 40(1):btad774, 2024.
- [207] Jie Gao, Qiming Fu, Jiacheng Sun, Yunzhe Wang, Youbing Xia, You Lu, Hongjie Wu, and Jianping Chen. Qldti: A novel reinforcement learning-based prediction model for drug–target interaction. *Current Bioinformatics*, 19(4):352–374, 2024.
- [208] Donghua Yu, Guojun Liu, Ning Zhao, Xiaoyan Liu, and Maozu Guo. Fpsc-dti: drug–target interaction prediction based on feature projection fuzzy classification and super cluster fusion. *Molecular Omics*, 16(6):583–591, 2020.
- [209] Dimitrios Iliadis, Bernard De Baets, Tapio Pahikkala, and Willem Waegeman. A comparison of embedding aggregation strategies in drug–target interaction prediction. *BMC bioinformatics*, 25(1):59, 2024.
- [210] Zeyu Yin, Yu Chen, Yajie Hao, Sanjeevi Pandiyan, Jinsong Shao, and Li Wang. Fotf-cpi: A compound–protein interaction prediction transformer based on the fusion of optimal transport fragments. *Iscience*, 27(1), 2024.
- [211] Xixi Yang, Zhangming Niu, Yuansheng Liu, Bosheng Song, Weiqiang Lu, Li Zeng, and Xiangxiang Zeng. Modality-dta: multimodality fusion strategy for drug–target affinity prediction. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 20(2):1200–1210, 2022.
- [212] Hakime Öztürk, Arzucan Özgür, and Elif Ozkirimli. Deepdta: deep drug–target binding affinity prediction. *Bioinformatics*, 34(17):i821–i829, 2018.

- [213] Peter W Rose, Andreas Prlić, Ali Altunkaya, Chunxiao Bi, Anthony R Bradley, Cole H Christie, Luigi Di Costanzo, Jose M Duarte, Shuchismita Dutta, Zukang Feng, et al. The rcsb protein data bank: integrative view of protein, gene and 3d structural information. *Nucleic acids research*, page gkw1000, 2016.
- [214] Hakime Öztürk, Elif Ozkirimli, and Arzucan Özgür. Widedta: prediction of drug-target binding affinity. *arXiv preprint arXiv:1902.04166*, 2019.
- [215] Michał Woźniak, Agnieszka Wołos, Urszula Modrzyk, Rafał L Górski, Jan Winkowski, Michał Bajczyk, Sara Szymkuć, Bartosz A Grzybowski, and Maciej Eder. Linguistic measures of chemical diversity and the “keywords” of molecular collections. *Scientific reports*, 8(1):7598, 2018.
- [216] Christian JA Sigrist, Lorenzo Cerutti, Edouard De Castro, Petra S Langendijk-Genevaux, Virginie Bulliard, Amos Bairoch, and Nicolas Hulo. Prosite, a protein domain database for functional characterization and annotation. *Nucleic acids research*, 38(suppl\_1):D161–D166, 2010.
- [217] Bonggun Shin, Sungsoo Park, Keunsoo Kang, and Joyce C Ho. Self-attention based molecule representation for predicting drug-target interaction. In *Machine learning for healthcare conference*, pages 230–248. PMLR, 2019.
- [218] Tianjiao Li, Xing-Ming Zhao, and Limin Li. Co-vae: Drug-target binding affinity prediction by co-regularized variational autoencoders. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 44(12):8861–8873, 2021.
- [219] Lingling Zhao, Junjie Wang, Long Pang, Yang Liu, and Jun Zhang. Gansdta: Predicting drug-target binding affinity using gans. *Frontiers in genetics*, 10:1243, 2020.
- [220] Karim Abbasi, Parvin Razzaghi, Antti Poso, Massoud Amanlou, Jahan B Ghasemi, and Ali Masoudi-Nejad. Deepcda: deep cross-domain compound–protein affinity prediction through lstm and convolutional neural networks. *Bioinformatics*, 36(17):4633–4642, 2020.
- [221] Kaili Wang, Renyi Zhou, Yaohang Li, and Min Li. Deepdtaf: a deep learning method to predict protein–ligand binding affinity. *Briefings in Bioinformatics*, 22(5):bbab072, 2021.
- [222] Ziduo Yang, Weihe Zhong, Lu Zhao, and Calvin Yu-Chian Chen. Ml-dti: mutual learning mechanism for interpretable drug–target interaction prediction. *The Journal of Physical Chemistry Letters*, 12(17):4247–4261, 2021.
- [223] Yuni Zeng, Xiangru Chen, Yujie Luo, Xuedong Li, and Dezhong Peng. Deep drug-target binding affinity prediction with multiple attention blocks. *Briefings in bioinformatics*, 22(5):bbab117, 2021.
- [224] Jooyong Shim, Zhen-Yu Hong, Insuk Sohn, and Changha Hwang. Prediction of drug–target binding affinity using similarity-based convolutional neural network. *Scientific Reports*, 11(1):4416, 2021.
- [225] Xuekai Zhu, Juan Liu, Jian Zhang, Zhihui Yang, Feng Yang, and Xiaolei Zhang. Fingerdta: a fingerprint-embedding framework for drug-target binding affinity prediction. *Big Data Mining and Analytics*, 6(1):1–10, 2022.
- [226] Haoyang Chen, Dahe Li, Jiaqi Liao, Lesong Wei, and Leyi Wei. Multiscaledta: A multiscale-based method with a self-attention mechanism for drug-target binding affinity prediction. *Methods*, 207:103–109, 2022.
- [227] Ashutosh Ghimire, Hilal Tayara, Zhenyu Xuan, and Kil To Chong. Csatdta: prediction of drug–target binding affinity using convolution model with self-attention. *International journal of molecular sciences*, 23(15):8453, 2022.
- [228] Qichang Zhao, Guihua Duan, Mengyun Yang, Zhongjian Cheng, Yaohang Li, and Jianxin Wang. Attentiondta: Drug–target binding affinity prediction by sequence-based deep learning with attention mechanism. *IEEE/ACM transactions on computational biology and bioinformatics*, 20(2):852–863, 2022.
- [229] Li Zhang, Chun-Chun Wang, and Xing Chen. Predicting drug–target binding affinity through molecule representation block based on multi-head attention and skip connection. *Briefings in Bioinformatics*, 23(6):bbac468, 2022.
- [230] Nelson RC Monteiro, José L Oliveira, and Joel P Arrais. Dtitr: End-to-end drug–target binding affinity prediction with transformers. *Computers in Biology and Medicine*, 147:105772, 2022.
- [231] Junjie Wang, NaiFeng Wen, Chunyu Wang, Lingling Zhao, and Liang Cheng. Electra-dta: a new compound-protein binding affinity prediction model based on the contextualized sequence encoding. *Journal of cheminformatics*, 14(1):14, 2022.
- [232] Weining Yuan, Guanxing Chen, and Calvin Yu-Chian Chen. Fusiondta: attention-based feature polymerizer and knowledge distillation for drug-target binding affinity prediction. *Briefings in Bioinformatics*, 23(1):bbab506, 2022.

- [233] Mengying Wang, Weimin Li, Xiao Yu, Yin Luo, Ke Han, Can Wang, and Qun Jin. Affinityvae: a multi-objective model for protein-ligand affinity prediction and drug design. *Computational Biology and Chemistry*, 107:107971, 2023.
- [234] Mogan Gim, Junseok Choe, Seungheun Baek, Jueon Park, Chaeun Lee, Minjae Ju, Sumin Lee, and Jaewoo Kang. Arkdta: attention regularization guided by non-covalent interactions for explainable drug–target binding affinity prediction. *Bioinformatics*, 39(Supplement\_1):i448–i457, 2023.
- [235] Zhi Jin, Tingfang Wu, Taoning Chen, Deng Pan, Xuejiao Wang, Jingxin Xie, Lijun Quan, and Qiang Lyu. Capla: improved prediction of protein–ligand binding affinity by a deep learning approach based on a cross-attention mechanism. *Bioinformatics*, 39(2):btad049, 2023.
- [236] Mahmood Kalematis, Mojtaba Zamani Emani, and Somayyeh Koohi. Bicmp-dta: Drug-target binding affinity prediction through complementary biological-related and compression-based featurization approach. *PLOS Computational Biology*, 19(3):e1011036, 2023.
- [237] Robert Reams. Hadamard inverses, square roots and products of almost semidefinite matrices. *Linear Algebra and its Applications*, 288:35–43, 1999.
- [238] Rudi Cilibrasi and Paul MB Vitányi. Clustering by compression. *IEEE Transactions on Information theory*, 51(4):1523–1545, 2005.
- [239] Zhiqin Zhu, Zheng Yao, Guanqiu Qi, Neal Mazur, Pan Yang, and Baisen Cong. Associative learning mechanism for drug–target interaction prediction. *CAAI Transactions on Intelligence Technology*, 8(4):1558–1577, 2023.
- [240] Yuanlong Chen, Yan Zhu, Zitong Zhang, Junjie Wang, and Chunyu Wang. Prediction of drug protein interactions based on variable scale characteristic pyramid convolution network. *Methods*, 211:42–47, 2023.
- [241] Haixia Zhai, Hongli Hou, Junwei Luo, Xiaoyan Liu, Zhengjiang Wu, and Junfeng Wang. Dgdta: dynamic graph attention network for predicting drug–target binding affinity. *BMC bioinformatics*, 24(1):367, 2023.
- [242] Yu Rong, Yatao Bian, Tingyang Xu, Weiyang Xie, Ying Wei, Wenbing Huang, and Junzhou Huang. Self-supervised graph transformer on large-scale molecular data. *Advances in neural information processing systems*, 33:12559–12571, 2020.
- [243] Changjian Zhou, Zhongzheng Li, Jia Song, and Wensheng Xiang. Transvae-dta: Transformer and variational autoencoder network for drug-target binding affinity prediction. *Computer Methods and Programs in Biomedicine*, 244:108003, 2024.
- [244] Li Han, Ling Kang, and Quan Guo. Imagedta: A simple model for drug–target binding affinity prediction. *ACS omega*, 9(26):28485–28493, 2024.
- [245] Zongquan Li, Pengxuan Ren, Hao Yang, Jie Zheng, and Fang Bai. Tefdta: a transformer encoder and fingerprint representation combined prediction method for bonded and non-bonded drug–target affinities. *Bioinformatics*, 40(1):btad778, 2024.
- [246] Mahmood Kalematis, Mojtaba Zamani Emani, and Somayyeh Koohi. Dcgan-dta: Predicting drug-target binding affinity with deep convolutional generative adversarial networks. *BMC genomics*, 25(1):411, 2024.
- [247] Tyler Rose, Nicolò Monti, Navvy Anand, and Tianyu Shen. Plapt: Protein-ligand binding affinity prediction using pretrained transformers. *bioRxiv*, pages 2024–02, 2024.
- [248] Xiying Chen, Jinsha Huang, Tianqiao Shen, Houjin Zhang, Li Xu, Min Yang, Xiaoman Xie, Yunjun Yan, and Jinyong Yan. Deattentiondta: Protein-ligand binding affinity prediction based on dynamic embedding and self-attention. *Bioinformatics*, page btae319, 2024.
- [249] Xu Sun, Juanjuan Huang, Yabo Fang, Yixuan Jin, Jiageng Wu, Guoqing Wang, and Jiwei Jia. Mredta: A bert and transformer-based molecular representation encoder for predicting drug-target binding affinity. *The FASEB Journal*, 38(19):e70083, 2024.
- [250] Amit Ranjan, Adam Bess, Chris Alvin, and Supratik Mukhopadhyay. Mdf-dta: A multi-dimensional fusion approach for drug-target binding affinity prediction. *Journal of Chemical Information and Modeling*, 2024.
- [251] Peng-Wei Hu, Keith CC Chan, and Zhu-Hong You. Large-scale prediction of drug-target interactions from deep representations. In *2016 international joint conference on neural networks (IJCNN)*, pages 1236–1243. IEEE, 2016.
- [252] Ming Wen, Zhimin Zhang, Shaoyu Niu, Haozhi Sha, Ruihan Yang, Yonghuan Yun, and Hongmei Lu. Deep-learning-based drug–target interaction prediction. *Journal of proteome research*, 16(4):1401–1409, 2017.
- [253] Geoffrey E Hinton. Deep belief networks. *Scholarpedia*, 4(5):5947, 2009.

- [254] GE Hinton. A practical guide to training restricted boltzmann machines. *Neural Networks: Tricks of the Trade/Springer*, 2012.
- [255] ShanShan Hu, Chenglin Zhang, Peng Chen, Pengying Gu, Jun Zhang, and Bing Wang. Predicting drug-target interactions from drug structure and protein sequence using novel convolutional neural networks. *BMC bioinformatics*, 20:1–12, 2019.
- [256] Shuangjia Zheng, Yongjian Li, Sheng Chen, Jun Xu, and Yuedong Yang. Predicting drug–protein interaction using quasi-visual question answering system. *Nature Machine Intelligence*, 2(2):134–140, 2020.
- [257] Kexin Huang, Cao Xiao, Lucas M Glass, and Jimeng Sun. Moltrans: molecular interaction transformer for drug–target interaction prediction. *Bioinformatics*, 37(6):830–836, 2021.
- [258] Po-Yu Kao, Shu-Min Kao, Nan-Lan Huang, and Yen-Chu Lin. Toward drug-target interaction prediction via ensemble modeling and transfer learning. In *2021 IEEE international conference on bioinformatics and biomedicine (BIBM)*, pages 2384–2391. IEEE, 2021.
- [259] Yifan Wu, Min Gao, Min Zeng, Jie Zhang, and Min Li. Bridgedpi: a novel graph neural network for predicting drug–protein interactions. *Bioinformatics*, 38(9):2571–2578, 2022.
- [260] Qichang Zhao, Haochen Zhao, Kai Zheng, and Jianxin Wang. Hyperattentiondti: improving drug–protein interaction prediction by sequence-based deep learning with attention mechanism. *Bioinformatics*, 38(3):655–662, 2022.
- [261] Jackson G De Souza, Marcelo AC Fernandes, and Raquel de Melo Barbosa. A novel deep neural network technique for drug–target interaction. *Pharmaceutics*, 14(3):625, 2022.
- [262] Ying Qian, Xinyi Li, Jian Wu, and Qian Zhang. Mcl-dti: using drug multimodal information and bi-directional cross-attention learning method for predicting drug–target interaction. *BMC bioinformatics*, 24(1):323, 2023.
- [263] Jorg Degen, Christof Wegscheid-Gerlach, Andrea Zaliani, and Matthias Rarey. On the art of compiling and using ‘drug-like’ chemical fragment spaces. *ChemMedChem*, 3(10):1503, 2008.
- [264] Rico Sennrich. Neural machine translation of rare words with subword units. *arXiv preprint arXiv:1508.07909*, 2015.
- [265] Bao-Ming Feng, Yuan-Yuan Zhang, Hao-Yu Zheng, Jin-Long Wang, Wen-Feng Feng, et al. Defusedti: Interpretable drug target interaction prediction model with dual-branch encoder and multiview fusion. *Future Generation Computer Systems*, 161:239–247, 2024.
- [266] Yuqing Ye, Xiao Zhang, Menglin Kong, Haokun Hu, and Zhendong Xu. Phcdti: A multichannel parallel high-order feature crossover model for dtis prediction. *Expert Systems with Applications*, 256:124873, 2024.
- [267] Ying Li, Xingyu Zhang, Zhuo Chen, Hongye Yang, Yuhui Liu, Huiqing Wang, Ting Yan, Jie Xiang, and Bin Wang. Accurate prediction of drug-target interactions in chinese and western medicine by the cwi-dti model. *Scientific Reports*, 14(1):25054, 2024.
- [268] Tri Minh Nguyen, Thin Nguyen, Thao Minh Le, and Truyen Tran. Gefa: early fusion approach in drug-target affinity prediction. *IEEE/ACM transactions on computational biology and bioinformatics*, 19(2):718–728, 2021.
- [269] Jiaqi Liao, Haoyang Chen, Lesong Wei, and Leyi Wei. Gsaml-dta: an interpretable drug-target binding affinity prediction model based on graph neural networks with self-attention mechanism and mutual information. *Computers in biology and medicine*, 150:106145, 2022.
- [270] Zhaoyang Chu, Feng Huang, Haitao Fu, Yuan Quan, Xionghui Zhou, Shichao Liu, and Wen Zhang. Hierarchical graph representation learning for the prediction of drug-target binding affinity. *Information Sciences*, 613: 507–523, 2022.
- [271] Mingjian Jiang, Shuang Wang, Shugang Zhang, Wei Zhou, Yuanyuan Zhang, and Zhen Li. Sequence-based drug-target affinity prediction using weighted graph neural networks. *BMC genomics*, 23(1):449, 2022.
- [272] Dong Ma, Shuang Li, and Zhihua Chen. Drug-target binding affinity prediction method based on a deep graph neural network. *Math. Biosci. Eng.*, 20:269–282, 2022.
- [273] Shudong Wang, Xuanmo Song, Yuanyuan Zhang, Kuijie Zhang, Yingye Liu, Chuanru Ren, and Shanchen Pang. Msgnn-dta: multi-scale topological feature fusion based on graph neural networks for drug–target binding affinity prediction. *International Journal of Molecular Sciences*, 24(9):8326, 2023.
- [274] Alexander Rives, Joshua Meier, Tom Sercu, Siddharth Goyal, Zeming Lin, Jason Liu, Demi Guo, Myle Ott, C Lawrence Zitnick, Jerry Ma, et al. Biological structure and function emerge from scaling unsupervised learning to 250 million protein sequences. *Proceedings of the National Academy of Sciences*, 118(15):e2016239118, 2021.



- [275] Xiangying Zhang, Haotian Gao, Haojie Wang, Zhihang Chen, Zhe Zhang, Xinchong Chen, Yan Li, Yifei Qi, and Renxiao Wang. Planet: a multi-objective graph neural network model for protein–ligand binding affinity prediction. *Journal of Chemical Information and Modeling*, 64(7):2205–2220, 2023.
- [276] Xiangpeng Bi, Shugang Zhang, Wenjian Ma, Huasen Jiang, and Zhiqiang Wei. Hisif-dta: a hierarchical semantic information fusion framework for drug-target affinity prediction. *IEEE Journal of Biomedical and Health Informatics*, 2023.
- [277] Kaili Wang and Min Li. Fusion-based deep learning architecture for detecting drug-target binding affinity using target and drug sequence and structure. *IEEE Journal of Biomedical and Health Informatics*, 2023.
- [278] Wolfgang Kabsch and Christian Sander. Dictionary of protein secondary structure: pattern recognition of hydrogen-bonded and geometrical features. *Biopolymers: Original Research on Biomolecules*, 22(12):2577–2637, 1983.
- [279] Xin Zeng, Kai-Yang Zhong, Bei Jiang, and Yi Li. Fusing sequence and structural knowledge by heterogeneous models to accurately and interpretively predict drug–target affinity. *Molecules*, 28(24):8005, 2023.
- [280] Lok-In Tsui, Te-Cheng Hsu, and Che Lin. Ng-dta: drug-target affinity prediction with n-gram molecular graphs. In *2023 45th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*, pages 1–4. IEEE, 2023.
- [281] Kaili Wang, Renyi Zhou, Jing Tang, and Min Li. Graphscore dta: optimized graph neural network for protein–ligand binding affinity prediction. *Bioinformatics*, 39(6):btad340, 2023.
- [282] Xi Xiao, Wentao Wang, Jiacheng Xie, Lijing Zhu, Gaofer Chen, Zhengji Li, Tianyang Wang, and Min Xu. Hgtdp-dta: Hybrid graph-transformer with dynamic prompt for drug-target binding affinity prediction. *arXiv preprint arXiv:2406.17697*, 2024.
- [283] Chuangchuang Tian, Luping Wang, Zhiming Cui, and Hongjie Wu. Gtamp-dta: Graph transformer combined with attention mechanism for drug-target binding affinity prediction. *Computational Biology and Chemistry*, 108: 107982, 2024.
- [284] Hongjie Wu, Junkai Liu, Tengsheng Jiang, Quan Zou, Shujie Qi, Zhiming Cui, Prayag Tiwari, and Yijie Ding. Attentionmgt-dta: A multi-modal drug-target affinity prediction using graph transformer and attention mechanism. *Neural Networks*, 169:623–636, 2024.
- [285] Qing Ye and Yaxin Sun. Graph neural pre-training based drug-target affinity prediction. *Frontiers in Genetics*, 15:1452339, 2024.
- [286] Ding kai Huang and Jiang Xie. Empdta: An end-to-end multimodal representation learning framework with pocket online detection for drug–target affinity prediction. *Molecules*, 29(12):2912, 2024.
- [287] Wen Torng and Russ B Altman. Graph convolutional neural networks for predicting drug-target interactions. *Journal of chemical information and modeling*, 59(10):4131–4149, 2019.
- [288] Penglei Wang, Shuangjia Zheng, Yize Jiang, Chengtao Li, Junhong Liu, Chang Wen, Atanas Patronov, Dahong Qian, Hongming Chen, and Yuedong Yang. X-dpi: A structure-aware multi-modal deep learning model for drug-protein interactions prediction. *bioRxiv*, pages 2021–06, 2021.
- [289] Mehdi Yazdani-Jahromi, Niloofar Yousefi, Aida Tayebi, Elayaraja Kolanthai, Craig J Neal, Sudipta Seal, and Ozlem Ozmen Garibay. Attentionsitedti: an interpretable graph-based model for drug-target interaction prediction using nlp sentence-level relation classification. *Briefings in Bioinformatics*, 23(4):bbac272, 2022.
- [290] Kyle Ying kai Gao, Achille Fokoue, Heng Luo, Arun Iyengar, Sanjoy Dey, Ping Zhang, et al. Interpretable drug target prediction using deep neural representation. In *IJCAI*, volume 2018, pages 3371–3377, 2018.
- [291] Qingyuan Feng, Evgenia Dueva, Artem Cherkasov, and Martin Ester. Padme: A deep learning-based framework for drug-target interaction prediction. *arXiv preprint arXiv:1807.09741*, 2018.
- [292] Mostafa Karimi, Di Wu, Zhangyang Wang, and Yang Shen. Explainable deep relational networks for predicting compound–protein affinities and contacts. *Journal of chemical information and modeling*, 61(1):46–66, 2020.
- [293] Mohamed Abdel-Basset, Hossam Hawash, Mohamed Elhoseny, Ripon K Chakraborty, and Michael Ryan. Deeph-dta: deep learning for predicting drug-target interactions: a case study of covid-19 drug repurposing. *Ieee Access*, 8:170433–170451, 2020.
- [294] Shuyu Wang, Peng Shan, Yuliang Zhao, and Lei Zuo. Gandti: a multi-task neural network for drug-target interaction prediction. *Computational biology and chemistry*, 92:107476, 2021.
- [295] Yuqian Pu, Jiawei Li, Jijun Tang, and Fei Guo. Deepfusion dta: drug-target binding affinity prediction with information fusion and hybrid deep-learning ensemble model. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 19(5):2760–2769, 2021.

- [296] Balanand Jha, Akshay Deepak, Vikash Kumar, and Gopalakrishnan Krishnasamy. Original research article dfdfa-multiatt: Multi-attention based deep learning ensemble fusion network for drug target affinity prediction. *Journal of Autonomous Intelligence*, 7(5), 2024.
- [297] Shugang Zhang, Mingjian Jiang, Shuang Wang, Xiaofeng Wang, Zhiqiang Wei, and Zhen Li. Sag-dta: prediction of drug–target affinity using self-attention graph network. *International Journal of Molecular Sciences*, 22(16): 8993, 2021.
- [298] Yuan Jin, Jiarui Lu, Runhan Shi, and Yang Yang. Embeddti: enhancing the molecular representations via sequence embedding and graph convolutional network for the prediction of drug-target interaction. *Biomolecules*, 11(12):1783, 2021.
- [299] Asad Ahmed, Bhavika Mam, and Ramanathan Sowdhamini. Deelig: A deep learning approach to predict protein-ligand binding affinity. *Bioinformatics and biology insights*, 15:11779322211030364, 2021.
- [300] Xun Wang, Jiali Liu, Chaogang Zhang, and Shudong Wang. Ssgraphcpi: A novel model for predicting compound-protein interactions based on deep learning. *International Journal of Molecular Sciences*, 23(7):3780, 2022.
- [301] Qingyu Li, Xiaochang Zhang, Lianlian Wu, Xiaochen Bo, Song He, and Shengqi Wang. Pla-more: a protein–ligand binding affinity prediction model via comprehensive molecular representations. *Journal of chemical information and modeling*, 62(18):4380–4390, 2022.
- [302] Ziduo Yang, Weihe Zhong, Lu Zhao, and Calvin Yu-Chian Chen. Mgraphdta: deep multiscale graph neural network for explainable drug–target binding affinity prediction. *Chemical science*, 13(3):816–833, 2022.
- [303] Xin Zeng, Guang-Peng Su, Shu-Juan Li, Shuang-Qing Lv, Meng-Liang Wen, and Yi Li. Drug-online: an online platform for drug-target interaction, affinity, and binding sites identification using deep learning. *BMC bioinformatics*, 25(1):156, 2024.
- [304] Qingyu Tian, Mao Ding, Hui Yang, Caibin Yue, Yue Zhong, Zhenzhen Du, Dayan Liu, Jiali Liu, and Yufeng Deng. Predicting drug-target affinity based on recurrent neural networks and graph convolutional neural networks. *Combinatorial Chemistry & High Throughput Screening*, 25(4):634–641, 2022.
- [305] Huu Ngoc Tran Tran, J Joshua Thomas, and Nurul Hashimah Ahamed Hassain Malim. Deepnc: a framework for drug-target interaction prediction with graph neural networks. *PeerJ*, 10:e13163, 2022.
- [306] Shrimon Mukherjee, Madhusudan Ghosh, and Partha Basuchowdhuri. Deepglstm: deep graph convolutional network and lstm based approach for predicting drug-target binding affinity. In *Proceedings of the 2022 SIAM international conference on data mining (SDM)*, pages 729–737. SIAM, 2022.
- [307] Lyu Zhijian, Jiang Shaohua, Liang Yigao, and Gao Min. Gdgru-dta: predicting drug-target binding affinity based on gnn and double gru. *arXiv preprint arXiv:2204.11857*, 2022.
- [308] Mohit Pandey, Mariia Radaeva, Hazem Mslati, Olivia Garland, Michael Fernandez, Martin Ester, and Artem Cherkasov. Ligand binding prediction using protein structure graphs and residual graph attention networks. *Molecules*, 27(16):5114, 2022.
- [309] Huiwen Wang, Haoquan Liu, Shangbo Ning, Chengwei Zeng, and Yunjie Zhao. Dlssaffinity: protein–ligand binding affinity prediction via a deep learning model. *Physical Chemistry Chemical Physics*, 24(17):10124–10133, 2022.
- [310] Shaofu Lin, Chengyu Shi, and Jianhui Chen. Generalizeddta: combining pre-training and multi-task learning to predict drug-target binding affinity for unknown drug discovery. *BMC bioinformatics*, 23(1):367, 2022.
- [311] Chelsea Finn, Pieter Abbeel, and Sergey Levine. Model-agnostic meta-learning for fast adaptation of deep networks. In *International conference on machine learning*, pages 1126–1135. PMLR, 2017.
- [312] Kejie Fang, Yiming Zhang, Shiyu Du, and Jian He. Coldtata: utilizing data augmentation and attention-based feature fusion for drug-target binding affinity prediction. *Computers in Biology and Medicine*, 164:107372, 2023.
- [313] Yan Zhu, Lingling Zhao, Naifeng Wen, Junjie Wang, and Chunyu Wang. Datadta: a multi-feature and dual-interaction aggregation framework for drug–target binding affinity prediction. *Bioinformatics*, 39(9):btad560, 2023.
- [314] Yang Hua, Xiaoning Song, Zhenhua Feng, and Xiaojun Wu. Mfr-dta: a multi-functional and robust model for predicting drug–target binding affinity and region. *Bioinformatics*, 39(2):btad056, 2023.
- [315] Leiming Xia, Lei Xu, Shourun Pan, Dongjiang Niu, Beiyi Zhang, and Zhen Li. Drug-target binding affinity prediction using message passing neural network and self supervised learning. *BMC genomics*, 24(1):557, 2023.
- [316] Mingjian Jiang, Yunchang Shao, Yuanyuan Zhang, Wei Zhou, and Shunpeng Pang. A deep learning method for drug-target affinity prediction based on sequence interaction information mining. *PeerJ*, 11:e16625, 2023.

- [317] Zhiqin Zhu, Zheng Yao, Xin Zheng, Guanqiu Qi, Yuanyuan Li, Neal Mazur, Xinbo Gao, Yifei Gong, and Baisen Cong. Drug–target affinity prediction method based on multi-scale information interaction and graph optimization. *Computers in Biology and Medicine*, 167:107621, 2023.
- [318] Li Zhang, Chun-Chun Wang, Yong Zhang, and Xing Chen. Gpcndta: prediction of drug-target binding affinity through cross-attention networks augmented with graph features and pharmacophores. *Computers in Biology and Medicine*, 166:107512, 2023.
- [319] Taras Voitsitskyi, Roman Stratiichuk, Ihor Koleiev, Leonid Popryho, Zakhar Ostrovsky, Pavlo Henitsoi, Ivan Khropachov, Volodymyr Vozniak, Roman Zhytar, Diana Nechepurenko, et al. 3dprottdta: a deep learning model for drug-target affinity prediction based on residue-level protein graphs. *RSC advances*, 13(15):10261–10272, 2023.
- [320] Haohuai He, Guanxing Chen, and Calvin Yu-Chian Chen. Nghnn-dta: a node-adaptive hybrid graph neural network for interpretable drug–target binding affinity prediction. *Bioinformatics*, 39(6):btad355, 2023.
- [321] Xinxing Yang, Genke Yang, and Jian Chu. Graphcl-dta: a graph contrastive learning with molecular semantics for drug-target binding affinity prediction. *IEEE Journal of Biomedical and Health Informatics*, 2024.
- [322] Jing Zhang, Zhi Liu, Yaohua Pan, Hongfei Lin, and Yijia Zhang. Imaen: An interpretable molecular augmentation model for drug–target interaction prediction. *Expert Systems with Applications*, 238:121882, 2024.
- [323] Minghui Li, Zikang Guo, Yang Wu, Peijin Guo, Yao Shi, Shengshan Hu, Wei Wan, and Shengqing Hu. Vidta: Enhanced drug-target affinity prediction via virtual graph nodes and attention-based feature fusion. *arXiv preprint arXiv:2412.19589*, 2024.
- [324] Guishen Wang, Hangchen Zhang, Mengting Shao, Yuncong Feng, Chen Cao, and Xiaowen Hu. Deeptgin: a novel hybrid multimodal approach using transformers and graph isomorphism networks for protein-ligand binding affinity prediction. *Journal of Cheminformatics*, 16:147, 2024.
- [325] Long Zhao, Hongmei Wang, and Shaoping Shi. Pocketdta: an advanced multimodal architecture for enhanced prediction of drug- target affinity from 3d structural data of target binding pockets. *Bioinformatics*, 40(10): btae594, 2024.
- [326] Youzhi Liu, Linlin Xing, Longbo Zhang, Hongzhen Cai, and Maozu Guo. Geformerdta: drug target affinity prediction based on transformer graph for early fusion. *Scientific Reports*, 14(1):7416, 2024.
- [327] Wenjing Qiu, Qianle Liang, Liyi Yu, Xuan Xiao, Wangren Qiu, and Weizhong Lin. Lstm-sagdta: Predicting drug-target binding affinity with an attention graph neural network and lstm approach. *Current Pharmaceutical Design*, 30(6):468, 2024.
- [328] Yongqing Wu, Yao Jin, Peng Sun, and Zhichen Ding. Hbdta: Hierarchical bi-lstm networks for drug-target binding affinity prediction. *Engineering Letters*, 32(2), 2024.
- [329] Xihe Qiu, Haoyu Wang, Xiaoyu Tan, and Zhijun Fang. Gk bertdta: a graph representation learning and semantic embedding-based framework for drug-target affinity prediction. *Computers in Biology and Medicine*, 173:108376, 2024.
- [330] Yuansheng Liu, Xinyan Xia, Yongshun Gong, Bosheng Song, and Xiangxiang Zeng. Ssr-dta: Substructure-aware multi-layer graph neural networks for drug–target binding affinity prediction. *Artificial Intelligence in Medicine*, 157:102983, 2024.
- [331] Lifan Chen, Xiaoqin Tan, Dingyan Wang, Feisheng Zhong, Xiaohong Liu, Tianbiao Yang, Xiaomin Luo, Kaixian Chen, Hualiang Jiang, and Mingyue Zheng. Transformerpci: improving compound–protein interaction prediction by sequence-based deep learning with self-attention mechanism and label reversal experiments. *Bioinformatics*, 36(16):4406–4414, 2020.
- [332] Zhongjian Cheng, Cheng Yan, Fang-Xiang Wu, and Jianxin Wang. Drug-target interaction prediction using multi-head self-attention and graph attention network. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 19(4):2208–2218, 2021.
- [333] Lei Huang, Jiecong Lin, Rui Liu, Zetian Zheng, Lingkuan Meng, Xingjian Chen, Xiangtao Li, and Ka-Chun Wong. Coadti: multi-modal co-attention based framework for drug–target interaction annotation. *Briefings in bioinformatics*, 23(6):bbac446, 2022.
- [334] Xiaoli Lin, Shuai Xu, Xuan Liu, Xiaolong Zhang, and Jing Hu. Detecting drug–target interactions with feature similarity fusion and molecular graphs. *Biology*, 11(7):967, 2022.
- [335] Yang Hua, Xiaoning Song, Zhenhua Feng, Xiao-Jun Wu, Josef Kittler, and Dong-Jun Yu. Cpinformer for efficient and robust compound-protein interaction prediction. *IEEE/ACM transactions on computational biology and bioinformatics*, 20(1):285–296, 2022.

- [336] Peiliang Zhang, Ziqi Wei, Chao Che, and Bo Jin. Deepmgt-dti: Transformer network incorporating multilayer graph information for drug–target interaction prediction. *Computers in biology and medicine*, 142:105214, 2022.
- [337] Yaohua Pan, Yijia Zhang, Jing Zhang, and Mingyu Lu. Csditi: an interpretable cross-attention network with gnn-based drug molecule aggregation for drug-target interaction prediction. *Applied Intelligence*, 53(22): 27177–27190, 2023.
- [338] Zhangli Lu, Chuqi Lei, Kaili Wang, Libo Qin, Jing Tang, and Min Li. Dtiam: A unified framework for predicting drug-target interactions, binding affinities and activation/inhibition mechanisms. *arXiv preprint arXiv:2312.15252*, 2023.
- [339] Peizhen Bai, Filip Miljković, Bino John, and Haiping Lu. Interpretable bilinear attention network with domain adaptation improves drug–target prediction. *Nature Machine Intelligence*, 5(2):126–136, 2023.
- [340] Yunfei He, Chenyuan Sun, Li Meng, Yiwen Zhang, Rui Mao, and Fei Yang. Flexible drug-target interaction prediction with interactive information extraction and trade-off. *Expert Systems with Applications*, 249:123821, 2024.
- [341] Hailong Yang, Yue Chen, Yun Zuo, Zhaohong Deng, Xiaoyong Pan, Hong-Bin Shen, Kup-Sze Choi, and Dong-Jun Yu. Mindg: a drug–target interaction prediction method based on an integrated learning algorithm. *Bioinformatics*, 40(4):btac147, 2024.
- [342] JunJie Wee and Kelin Xia. Forman persistent ricci curvature (fprc)-based machine learning models for protein–ligand binding affinity prediction. *Briefings in Bioinformatics*, 22(6):bbab136, 2021.
- [343] Zixuan Cang, Lin Mu, and Guo-Wei Wei. Representability of algebraic topology for biomolecules in machine learning based scoring and virtual screening. *PLoS computational biology*, 14(1):e1005929, 2018.
- [344] Marc A Moesser, Dominik Klein, Fergus Boyles, Charlotte M Deane, Andrew Baxter, and Garrett M Morris. Protein-ligand interaction graphs: Learning from ligand-shaped 3d interaction graphs to improve binding affinity prediction. *BioRxiv*, pages 2022–03, 2022.
- [345] Shuo Zhang, Yang Liu, and Lei Xie. Efficient and accurate physics-aware multiplex graph neural networks for 3d small molecules and macromolecule complexes. *arXiv preprint arXiv:2206.02789*, 2022.
- [346] Yang Zhang, Gengmo Zhou, Zhewei Wei, and Hongteng Xu. Predicting protein-ligand binding affinity via joint global-local interaction modeling. In *2022 IEEE International Conference on Data Mining (ICDM)*, pages 1323–1328. IEEE, 2022.
- [347] Ziduo Yang, Weihe Zhong, Qiujie Lv, Tiejun Dong, and Calvin Yu-Chian Chen. Geometric interaction graph neural network for predicting protein–ligand binding affinities from 3d structures (gign). *The journal of physical chemistry letters*, 14(8):2020–2033, 2023.
- [348] Dejun Jiang, Chang-Yu Hsieh, Zhenxing Wu, Yu Kang, Jike Wang, Ercheng Wang, Ben Liao, Chao Shen, Lei Xu, Jian Wu, et al. Interactiongraphnet: A novel and efficient deep graph representation learning framework for accurate protein–ligand interaction predictions. *Journal of medicinal chemistry*, 64(24):18209–18232, 2021.
- [349] Evan N Feinberg, Debnil Sur, Zhenqin Wu, Brooke E Husic, Huanghao Mai, Yang Li, Saisai Sun, Jianyi Yang, Bharath Ramsundar, and Vijay S Pande. Potentialnet for molecular property prediction. *ACS central science*, 4(11):1520–1530, 2018.
- [350] Kristof Schütt, Pieter-Jan Kindermans, Huziel Enoc Saucedo Felix, Stefan Chmiela, Alexandre Tkatchenko, and Klaus-Robert Müller. Schnet: A continuous-filter convolutional neural network for modeling quantum interactions. *Advances in neural information processing systems*, 30, 2017.
- [351] Lina Dong, Shuai Shi, Xiaoyang Qu, Ding Luo, and Binju Wang. Ligand binding affinity prediction with fusion of graph neural networks and 3d structure-based complex graph. *Physical Chemistry Chemical Physics*, 25(35): 24110–24120, 2023.
- [352] Kathryn Tunyasuvunakool, Jonas Adler, Zachary Wu, Tim Green, Michal Zielinski, Augustin Židek, Alex Bridgland, Andrew Cowie, Clemens Meyer, Agata Laydon, et al. Highly accurate protein structure prediction for the human proteome. *Nature*, 596(7873):590–596, 2021.
- [353] Josh Abramson, Jonas Adler, Jack Dunger, Richard Evans, Tim Green, Alexander Pritzel, Olaf Ronneberger, Lindsay Willmore, Andrew J Ballard, Joshua Bambrick, et al. Accurate structure prediction of biomolecular interactions with alphafold 3. *Nature*, pages 1–3, 2024.
- [354] Minkyung Baek, Frank DiMaio, Ivan Anishchenko, Justas Dauparas, Sergey Ovchinnikov, Gyu Rie Lee, Jue Wang, Qian Cong, Lisa N Kinch, R Dustin Schaeffer, et al. Accurate prediction of protein structures and interactions using a three-track neural network. *Science*, 373(6557):871–876, 2021.

- [355] Izhar Wallach, Michael Dzamba, and Abraham Heifets. Atomnet: a deep convolutional neural network for bioactivity prediction in structure-based drug discovery. *arXiv preprint arXiv:1510.02855*, 2015.
- [356] Joseph Gomes, Bharath Ramsundar, Evan N Feinberg, and Vijay S Pande. Atomic convolutional networks for predicting protein-ligand binding affinity. *arXiv preprint arXiv:1703.10603*, 2017.
- [357] José Jiménez, Miha Skalic, Gerard Martinez-Rosell, and Gianni De Fabritiis. K deep: protein–ligand absolute binding affinity prediction via 3d-convolutional neural networks. *Journal of chemical information and modeling*, 58(2):287–296, 2018.
- [358] Zixuan Cang and Guo-Wei Wei. Topologynet: Topology based deep convolutional and multi-task neural networks for biomolecular property predictions. *PLoS computational biology*, 13(7):e1005690, 2017.
- [359] Yanjun Li, Mohammad A Rezaei, Chenglong Li, and Xiaolin Li. Deepatom: A framework for protein-ligand binding affinity prediction. In *2019 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, pages 303–310. IEEE, 2019.
- [360] Jaechang Lim, Seongok Ryu, Kyubyong Park, Yo Joong Choe, Jiyeon Ham, and Woo Youn Kim. Predicting drug–target interaction using a novel graph neural network with 3d structure-embedded graph representation. *Journal of chemical information and modeling*, 59(9):3981–3988, 2019.
- [361] Liangzhen Zheng, Jingrong Fan, and Yuguang Mu. Onionnet: a multiple-layer intermolecular-contact-based convolutional neural network for protein–ligand binding affinity prediction. *ACS omega*, 4(14):15956–15965, 2019.
- [362] Zechen Wang, Liangzhen Zheng, Yang Liu, Yuanyuan Qu, Yong-Qiang Li, Mingwen Zhao, Yuguang Mu, and Weifeng Li. Onionnet-2: a convolutional neural network model for predicting protein-ligand binding affinity based on residue-atom contacting shells. *Frontiers in chemistry*, 9:753002, 2021.
- [363] Haiping Zhang, Linbu Liao, Konda Mani Saravanan, Peng Yin, and Yanjie Wei. Deepbindrg: a deep learning based method for estimating effective protein–ligand affinity. *PeerJ*, 7:e7362, 2019.
- [364] Yongbeom Kwon, Woong-Hee Shin, Junsu Ko, and Juyong Lee. Ak-score: accurate protein-ligand binding affinity prediction using an ensemble of 3d-convolutional neural networks. *International journal of molecular sciences*, 21(22):8424, 2020.
- [365] Derek Jones, Hyojin Kim, Xiaohua Zhang, Adam Zemla, Garrett Stevenson, WF Drew Bennett, Daniel Kirshner, Sergio E Wong, Felice C Lightstone, and Jonathan E Allen. Improved protein–ligand binding affinity prediction with structure-based deep fusion inference. *Journal of chemical information and modeling*, 61(4):1583–1592, 2021.
- [366] Shuangli Li, Jingbo Zhou, Tong Xu, Liang Huang, Fan Wang, Haoyi Xiong, Weili Huang, Dejing Dou, and Hui Xiong. Structure-aware interactive graph neural networks for the prediction of protein-ligand binding affinity. In *Proceedings of the 27th ACM SIGKDD conference on knowledge discovery & data mining*, pages 975–985, 2021.
- [367] Hong Yuan, Jing Huang, and Jin Li. Protein-ligand binding affinity prediction model based on graph attention network. *Math. Biosci. Eng.*, 18(6):9148–9162, 2021.
- [368] Qinqing Liu, Peng-Shuai Wang, Chunjiang Zhu, Blake Blumenfeld Gaines, Tan Zhu, Jinbo Bi, and Minghu Song. Octsurf: Efficient hierarchical voxel-based molecular surface representation for protein-ligand affinity prediction. *Journal of Molecular Graphics and Modelling*, 105:107865, 2021.
- [369] Gernot Riegler, Ali Osman Ulusoy, and Andreas Geiger. Octnet: Learning deep 3d representations at high resolutions. In *Proceedings of the IEEE conference on computer vision and pattern recognition*, pages 3577–3586, 2017.
- [370] Sangmin Seo, Jonghwan Choi, Sanghyun Park, and Jaegyeon Ahn. Binding affinity prediction for protein–ligand complex using deep attention mechanism based on intermolecular interactions. *BMC bioinformatics*, 22:1–15, 2021.
- [371] Huimin Shen, Youzhi Zhang, Chunhou Zheng, Bing Wang, and Peng Chen. A cascade graph convolutional network for predicting protein–ligand binding affinity. *International journal of molecular sciences*, 22(8):4023, 2021.
- [372] Filippo Maria Bianchi, Daniele Grattarola, Lorenzo Livi, and Cesare Alippi. Graph neural networks with convolutional arma filters. *IEEE transactions on pattern analysis and machine intelligence*, 44(7):3496–3507, 2021.
- [373] Justin Gilmer, Samuel S Schoenholz, Patrick F Riley, Oriol Vinyals, and George E Dahl. Neural message passing for quantum chemistry. In *International conference on machine learning*, pages 1263–1272. PMLR, 2017.

- [374] Yu Wang, Zhengxiao Wei, and Lei Xi. Sfcnn: a novel scoring function based on 3d convolutional neural network for accurate and stable protein–ligand affinity prediction. *BMC bioinformatics*, 23(1):222, 2022.
- [375] Debby D Wang and Moon-Tong Chan. Protein-ligand binding affinity prediction based on profiles of intermolecular contacts. *Computational and Structural Biotechnology Journal*, 20:1088–1096, 2022.
- [376] Ruiqiang Lu, Jun Wang, Pengyong Li, Yuquan Li, Shuoyan Tan, Yiting Pan, Huanxiang Liu, Peng Gao, Guotong Xie, and Xiaojun Yao. Improving drug-target affinity prediction via feature fusion and knowledge distillation. *Briefings in Bioinformatics*, 24(3):bbad145, 2023.
- [377] Shuke Zhang, Yanzhao Jin, Tianmeng Liu, Qi Wang, Zhaohui Zhang, Shuliang Zhao, and Bo Shan. Ss-gnn: a simple-structured graph neural network for affinity prediction. *ACS omega*, 8(25):22496–22507, 2023.
- [378] Nedra Mekni, Hosein Fooladi, Ugo Perricone, and Thierry Langer. Encoding protein-ligand interactions: binding affinity prediction with multigraph-based modeling and graph convolutional network. ., 2023.
- [379] Jiaxian Yan, Zhaofeng Ye, Ziyi Yang, Chengqiang Lu, Shengyu Zhang, Qi Liu, and Jiezhong Qiu. Multi-task bioassay pre-training for protein-ligand binding affinity prediction. *Briefings in Bioinformatics*, 25(1):bbad451, 2024.
- [380] Rawan S Olayan, Haitham Ashoor, and Vladimir B Bajic. Ddr: efficient computational method to predict drug–target interactions using graph mining and machine learning approaches. *Bioinformatics*, 34(7):1164–1173, 2018.
- [381] Ming Hao, Stephen H Bryant, and Yanli Wang. Predicting drug-target interactions by dual-network integrated logistic matrix factorization. *Scientific reports*, 7(1):40376, 2017.
- [382] Nansu Zong, Hyeoneui Kim, Victoria Ngo, and Olivier Harismendy. Deep mining heterogeneous networks of biomedical linked data to predict novel drug–target associations. *Bioinformatics*, 33(15):2337–2344, 2017.
- [383] Xiao-Ying Yan, Shao-Wu Zhang, and Chang-Run He. Prediction of drug-target interaction by integrating diverse heterogeneous information source with multiple kernel learning and clustering methods. *Computational biology and chemistry*, 78:460–467, 2019.
- [384] Yang Yue and Shan He. Dti-hene: a novel method for drug-target interaction prediction based on heterogeneous network embedding. *BMC bioinformatics*, 22:1–20, 2021.
- [385] Ping Xuan, Bingxu Chen, Tiangang Zhang, and Yan Yang. Prediction of drug–target interactions based on network representation learning and ensemble learning. *IEEE/ACM transactions on computational biology and bioinformatics*, 18(6):2671–2681, 2020.
- [386] Qiao Ning, Yue Wang, Yaomiao Zhao, Jiahao Sun, Lu Jiang, Kaidi Wang, and Minghao Yin. Dmghnn: Double multi-view heterogeneous graph neural network framework for drug-target interaction prediction. *Artificial Intelligence in Medicine*, 159:103023, 2025.
- [387] Ming Chen, Yajian Jiang, Xiujuan Lei, Yi Pan, Chunyan Ji, Wei Jiang, and Hongkai Xiong. Drug-target interactions prediction based on signed heterogeneous graph neural networks. *Chinese Journal of Electronics*, 33(1):231–244, 2024.
- [388] Liyi Yu, Wangren Qiu, Weizhong Lin, Xiang Cheng, Xuan Xiao, and Jiexia Dai. Hgdti: predicting drug–target interaction by using information aggregation based on heterogeneous graph neural network. *BMC bioinformatics*, 23(1):126, 2022.
- [389] Lihong Peng, Zongzheng Bai, Longlong Liu, Long Yang, Xin Liu, Min Chen, and Xing Chen. Dti-mvsca: An anti-over-smoothing multi-view framework with negative sample selection for predicting drug-target interactions. *IEEE Journal of Biomedical and Health Informatics*, 2024.
- [390] Ran Zhang, Zhanjie Wang, Xuezhi Wang, Zhen Meng, and Wenjuan Cui. Mhtan-dti: Metapath-based hierarchical transformer and attention network for drug–target interaction prediction. *Briefings in Bioinformatics*, 24(2):bbad079, 2023.
- [391] Zhixian Liu, Qingfeng Chen, Wei Lan, Huihui Lu, and Shichao Zhang. Ssldti: A novel method for drug-target interaction prediction based on self-supervised learning. *Artificial Intelligence in Medicine*, 149:102778, 2024.
- [392] Yunan Luo, Xinbin Zhao, Jingtian Zhou, Jinglin Yang, Yanqing Zhang, Wenhua Kuang, Jian Peng, Ligong Chen, and Jianyang Zeng. A network integration approach for drug-target interaction prediction and computational drug repositioning from heterogeneous information. *Nature communications*, 8(1):573, 2017.
- [393] Xiangxiang Zeng, Siyi Zhu, Weiqiang Lu, Zehui Liu, Jin Huang, Yadi Zhou, Jiansong Fang, Yin Huang, Huimin Guo, Lang Li, et al. Target identification among known drugs by deep learning from heterogeneous networks. *Chemical Science*, 11(7):1775–1797, 2020.

- [394] Yifan Shang, Lin Gao, Quan Zou, and Liang Yu. Prediction of drug-target interactions based on multi-layer network representation learning. *Neurocomputing*, 434:80–89, 2021.
- [395] Qi An and Liang Yu. A heterogeneous network embedding framework for predicting similarity-based drug-target interactions. *Briefings in bioinformatics*, 22(6):bbab275, 2021.
- [396] Deshan Zhou, Zhijian Xu, WenTao Li, Xiaolan Xie, and Shaoliang Peng. Multidti: drug–target interaction prediction based on multi-modal representation learning to bridge the gap between new chemical entities and known heterogeneous network. *Bioinformatics*, 37(23):4485–4492, 2021.
- [397] Runze Wang, Zehua Zhang, Yueqin Zhang, Zhongyuan Jiang, Shilin Sun, and Chenwei Zhang. Sparse imbalanced drug-target interaction prediction via heterogeneous data augmentation and node similarity. In *Pacific-Asia Conference on Knowledge Discovery and Data Mining*, pages 548–561. Springer, 2022.
- [398] Lu Jiang, Jiahao Sun, Yue Wang, Qiao Ning, Na Luo, and Minghao Yin. Heterogeneous graph convolutional network integrates multi-modal similarities for drug-target interaction prediction. In *2021 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, pages 137–140. IEEE, 2021.
- [399] Fangping Wan, Lixiang Hong, An Xiao, Tao Jiang, and Jianyang Zeng. Neodti: neural integration of neighbor information from a heterogeneous network for discovering new drug–target interactions. *Bioinformatics*, 35(1): 104–111, 2019.
- [400] Jin Li, Jingru Wang, Hao Lv, Zhuoxuan Zhang, and Zaixia Wang. Imchgan: inductive matrix completion with heterogeneous graph attention networks for drug-target interactions prediction. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 19(2):655–665, 2021.
- [401] Yang Li, Guanyu Qiao, Keqi Wang, and Guohua Wang. Drug–target interaction predication via multi-channel graph neural networks. *Briefings in Bioinformatics*, 23(1):bbab346, 2022.
- [402] Yang Li, Guanyu Qiao, Xin Gao, and Guohua Wang. Supervised graph co-contrastive learning for drug–target interaction prediction. *Bioinformatics*, 38(10):2847–2854, 2022.
- [403] Xinyu Fu, Jiani Zhang, Ziqiao Meng, and Irwin King. Magnn: Metapath aggregated graph neural network for heterogeneous graph embedding. In *Proceedings of the web conference 2020*, pages 2331–2341, 2020.
- [404] Mei Li, Xiangrui Cai, Sihan Xu, and Hua Ji. Metapath-aggregated heterogeneous graph neural network for drug–target interaction prediction. *Briefings in Bioinformatics*, 24(1):bbac578, 2023.
- [405] Qianwen Lu, Zhiheng Zhou, and Qi Wang. Multi-layer graph attention neural networks for accurate drug-target interaction mapping. *Scientific Reports*, 14(1):26119, 2024.
- [406] Haitao Fu, Feng Huang, Xuan Liu, Yang Qiu, and Wen Zhang. Mvgn: data integration through multi-view graph convolutional network for predicting links in biomedical bipartite networks. *Bioinformatics*, 38(2):426–434, 2022.
- [407] Zhen Tian, Xiangyu Peng, Haichuan Fang, Wenjie Zhang, Qiguo Dai, and Yangdong Ye. Mhadt: predicting drug–target interactions via multiview heterogeneous information network embedding with hierarchical attention mechanisms. *Briefings in Bioinformatics*, 23(6):bbac434, 2022.
- [408] Yansen Su, Zhiyang Hu, Fei Wang, Yannan Bin, Chunhou Zheng, Haitao Li, Haowen Chen, and Xiangxiang Zeng. Amgdti: drug–target interaction prediction based on adaptive meta-graph learning in heterogeneous network. *Briefings in Bioinformatics*, 25(1):bbad474, 2024.
- [409] Donghua Yu, Huawen Liu, and Shuang Yao. Drug–target interaction prediction based on improved heterogeneous graph representation learning and feature projection classification. *Expert Systems with Applications*, 252:124289, 2024.
- [410] Jiajie Peng, Jingyi Li, and Xuequn Shang. A learning-based method for drug-target interaction prediction based on feature representation learning and deep neural network. *BMC bioinformatics*, 21(Suppl 13):394, 2020.
- [411] Hafez Eslami Manoochehri and Mehrdad Nourani. Drug-target interaction prediction using semi-bipartite graph model and deep learning. *BMC bioinformatics*, 21:1–16, 2020.
- [412] Tianyi Zhao, Yang Hu, Linda R Valsdottir, Tianyi Zang, and Jiajie Peng. Identifying drug–target interactions based on graph convolutional network and deep neural network. *Briefings in bioinformatics*, 22(2):2141–2150, 2021.
- [413] Jiajie Peng, Yuxian Wang, Jiaojiao Guan, Jingyi Li, Ruijiang Han, Jianye Hao, Zhongyu Wei, and Xuequn Shang. An end-to-end heterogeneous graph representation learning-based framework for drug–target interaction prediction. *Briefings in bioinformatics*, 22(5):bbaa430, 2021.

- [414] Maha A Thafar, Mona Alshahrani, Somayah Albaradei, Takashi Gojobori, Magbubah Essack, and Xin Gao. Affinity2vec: drug-target binding affinity prediction through representation learning, graph mining, and machine learning. *Scientific reports*, 12(1):4751, 2022.
- [415] Shudong Wang, Zhenzhen Du, Mao Ding, Alfonso Rodriguez-Paton, and Tao Song. Kg-dti: a knowledge graph based deep learning method for drug-target interaction predictions and alzheimer’s disease drug repositions. *Applied Intelligence*, 52(1):846–857, 2022.
- [416] Alireza Dehghan, Parvin Razzaghi, Karim Abbasi, and Sajjad Gharaghani. Tripletmultidti: multimodal representation learning in drug-target interaction prediction with triplet loss function. *Expert Systems with Applications*, 232:120754, 2023.
- [417] Fatemeh Rafiei, Hojjat Zeraati, Karim Abbasi, Jahan B Ghasemi, Mahboubeh Parsaeian, and Ali Masoudi-Nejad. Deeptrasynergy: drug combinations using multimodal deep learning with transformers. *Bioinformatics*, 39(8):btad438, 2023.
- [418] Wenjian Ma, Shugang Zhang, Zhen Li, Mingjian Jiang, Shuang Wang, Nianfan Guo, Yuanfei Li, Xiangpeng Bi, Huasen Jiang, and Zhiqiang Wei. Predicting drug-target affinity by learning protein knowledge from biological networks. *IEEE Journal of Biomedical and Health Informatics*, 27(4):2128–2137, 2023.
- [419] Yongna Yuan, Yuhao Zhang, Xiangbo Meng, Zhenyu Liu, Bohan Wang, Ruidong Miao, Ruisheng Zhang, Wei Su, and Lei Liu. Edc-dti: an end-to-end deep collaborative learning model based on multiple information for drug-target interactions prediction. *Journal of Molecular Graphics and Modelling*, 122:108498, 2023.
- [420] Yuanyuan Zhang, Yingdong Wang, Chaoyong Wu, Lingmin Zhan, Aoyi Wang, Caiping Cheng, Jinzhong Zhao, Wuxia Zhang, Jianxin Chen, and Peng Li. Drug–target interaction prediction by integrating heterogeneous information with mutual attention network. *BMC bioinformatics*, 25(1):361, 2024.
- [421] E Zixuan, Guanyu Qiao, Guohua Wang, and Yang Li. Gsl-dti: Graph structure learning network for drug-target interaction prediction. *Methods*, 223:136–145, 2024.
- [422] Beiyi Zhang, Dongjiang Niu, Lianwei Zhang, Qiang Zhang, and Zhen Li. Msh-dti: multi-graph convolution with self-supervised embedding and heterogeneous aggregation for drug-target interaction prediction. *BMC bioinformatics*, 25(1):275, 2024.
- [423] Jiahao Wei, Linzhang Lu, and Tie Shen. Predicting drug–protein interactions by preserving the graph information of multi source data. *BMC bioinformatics*, 25(1):10, 2024.
- [424] Alireza Dehghan, Karim Abbasi, Parvin Razzaghi, Hossein Banadkuki, and Sajjad Gharaghani. Ccl-dti: contributing the contrastive loss in drug–target interaction prediction. *BMC bioinformatics*, 25(1):48, 2024.
- [425] Yong Liu, Min Wu, Chunyan Miao, Peilin Zhao, and Xiao-Li Li. Neighborhood regularized logistic matrix factorization for drug-target interaction prediction. *PLoS computational biology*, 12(2):e1004760, 2016.
- [426] Tomohiro Ban, Masahito Ohue, and Yutaka Akiyama. Nrlmf $\beta$ : Beta-distribution-rescored neighborhood regularized logistic matrix factorization for improving the performance of drug–target interaction prediction. *Biochemistry and biophysics reports*, 18:100615, 2019.
- [427] Mehmet Gönen. Predicting drug–target interactions from chemical and genomic kernels using bayesian matrix factorization. *Bioinformatics*, 28(18):2304–2310, 2012.
- [428] Liang-Yong Xia, Zi-Yi Yang, Hui Zhang, and Yong Liang. Improved prediction of drug–target interactions using self-paced learning with collaborative matrix factorization. *Journal of chemical information and modeling*, 59(7):3340–3351, 2019.
- [429] Hiroyuki Kurata and Sho Tsukiyama. Ican: interpretable cross-attention network for identifying drug and target protein interactions. *Plos one*, 17(10):e0276609, 2022.
- [430] Niloofar Yousefi, Mehdi Yazdani-Jahromi, Aida Tayebi, Elayaraja Kolanthai, Craig J. Neal, Tanumoy Banerjee, Agnivo Gosai, Ganesh Balasubramanian, Sudipta Seal, and Ozlem Ozmen Garibay. Bindingsiteaugmenteddti: Enabling a next-generation pipeline for interpretable prediction models in drug-repurposing. *bioRxiv*, 2022. doi:10.1101/2022.08.30.505897. URL <https://www.biorxiv.org/content/early/2022/08/30/2022.08.30.505897>.
- [431] Xiaoqing Ru, Quan Zou, and Chen Lin. Optimization of drug–target affinity prediction methods through feature processing schemes. *Bioinformatics*, 39(11):btad615, 2023.
- [432] Mindy I Davis, Jeremy P Hunt, Sanna Herrgard, Pietro Ciceri, Lisa M Wodicka, Gabriel Pallares, Michael Hocker, Daniel K Treiber, and Patrick P Zarrinkar. Comprehensive analysis of kinase inhibitor selectivity. *Nature biotechnology*, 29(11):1046–1051, 2011.



- [433] Jing Tang, Agnieszka Sz wajda, Sushil Shakyawar, Tao Xu, Petteri Hintsanen, Krister Wennerberg, and Tero Aittokallio. Making sense of large-scale kinase inhibitor bioactivity data sets: a comparative and integrative analysis. *Journal of Chemical Information and Modeling*, 54(3):735–743, 2014.
- [434] Renxiao Wang, Xu eliang Fang, Yipin Lu, Chao-Yie Yang, and Shaomeng Wang. The pdbind database: methodologies and updates. *Journal of medicinal chemistry*, 48(12):4111–4119, 2005.
- [435] Tiqing Liu, Yuhmei Lin, Xin Wen, Robert N Jorissen, and Michael K Gilson. Bindingdb: a web-accessible database of experimentally determined protein–ligand binding affinities. *Nucleic acids research*, 35(suppl\_1):D198–D201, 2007.
- [436] James T Metz, Eric F Johnson, Niru B Soni, Philip J Merta, Lemma Kifle, and Philip J Hajduk. Navigating the kinome. *Nature chemical biology*, 7(4):200–202, 2011.
- [437] Hui Liu, Jianjiang Sun, Jihong Guan, Jie Zheng, and Shuigeng Zhou. Improving compound–protein interaction prediction by building up highly credible negative samples. *Bioinformatics*, 31(12):i221–i229, 2015.
- [438] Richard Judson. Us epa–toxcast and the tox21 program: Perspectives. *Toxicology Letters*, -(211):S2, 2012.
- [439] Michael M Mysinger, Michael Carchia, John J Irwin, and Brian K Shoichet. Directory of useful decoys, enhanced (dud-e): better ligands and decoys for better benchmarking. *Journal of medicinal chemistry*, 55(14):6582–6594, 2012.
- [440] Jing Tang, Balaguru Ravikumar, Zaid Alam, Anni Rebane, Markus Vähä-Koskela, Gopal Peddinti, Arjan J van Adrichem, Janica Wakkinen, Alok Jaiswal, Ella Karjalainen, et al. Drug target commons: a community effort to build a consensus knowledge base for drug–target interactions. *Cell chemical biology*, 25(2):224–229, 2018.
- [441] TS Keshava Prasad, Renu Goel, Kumaran Kandasamy, Shivakumar Keerthikumar, Sameer Kumar, Suresh Mathivanan, Deepthi Telikicherla, Rajesh Raju, Beema Shafreen, Abhilash Venugopal, et al. Human protein reference database—2009 update. *Nucleic acids research*, 37(suppl\_1):D767–D772, 2009.
- [442] Michael Kuhn, Ivica Letunic, Lars Juhl Jensen, and Peer Bork. The sider database of drugs and side effects. *Nucleic acids research*, 44(D1):D1075–D1079, 2016.
- [443] Allan Peter Davis, Cynthia J Grondin, Robin J Johnson, Daniela Sciaky, Roy McMorran, Jolene Wieggers, Thomas C Wieggers, and Carolyn J Mattingly. The comparative toxicogenomics database: update 2019. *Nucleic acids research*, 47(D1):D948–D954, 2019.
- [444] . Uniprot: the universal protein knowledgebase. *Nucleic acids research*, 45(D1):D158–D169, 2017.
- [445] Baris E Suzek, Yuqi Wang, Hongzhan Huang, Peter B McGarvey, Cathy H Wu, and UniProt Consortium. Uniref clusters: a comprehensive and scalable alternative for improving sequence similarity searches. *Bioinformatics*, 31(6):926–932, 2015.
- [446] Helen M Berman, John Westbrook, Zukang Feng, Gary Gilliland, Talapady N Bhat, Helge Weissig, Ilya N Shindyalov, and Philip E Bourne. The protein data bank. *Nucleic acids research*, 28(1):235–242, 2000.
- [447] Michael Kuhn, Christian von Mering, Monica Campillos, Lars Juhl Jensen, and Peer Bork. Stitch: interaction networks of chemicals and proteins. *Nucleic acids research*, 36(suppl\_1):D684–D688, 2007.
- [448] Thomas Sterling and John J. Irwin. Zinc15: A free database of commercially available compounds for virtual screening. <http://zinc15.docking.org/>, 2015.
- [449] Yan Li, Li Han, Zhihai Liu, and Renxiao Wang. Comparative assessment of scoring functions on an updated benchmark: 2. evaluation methods and general results. *Journal of chemical information and modeling*, 54(6):1717–1736, 2014.
- [450] Minyi Su, Qifan Yang, Yu Du, Guoqin Feng, Zhihai Liu, Yan Li, and Renxiao Wang. Comparative assessment of scoring functions: the casf-2016 update. *Journal of chemical information and modeling*, 59(2):895–913, 2018.
- [451] Marinka Zitnik, Rok Sosic, and Jure Leskovec. Biosnap datasets: Stanford biomedical network dataset collection. *Note: <http://snap.stanford.edu/biodata>* Cited by, 5(1), 2018.
- [452] Wallace KB Chan, Hongjiu Zhang, Jianyi Yang, Jeffrey R Brender, Junguk Hur, Arzucan Özgür, and Yang Zhang. Glass: a comprehensive database for experimentally validated gpcr–ligand associations. *Bioinformatics*, 31(18):3035–3042, 2015.
- [453] Regina Z Cer, Uma Mudunuri, R Stephens, and Frank J Lebeda. Ic 50-to-k i: a web-based tool for converting ic 50 to k i values for inhibitors of enzyme activity and ligand binding. *Nucleic acids research*, 37(suppl\_2):W441–W445, 2009.
- [454] Albert L Lehninger, David L Nelson, and Michael M Cox. *Lehninger principles of biochemistry*. Macmillan, 2005.

- [455] Kunal Roy, Pratim Chakraborty, Indrani Mitra, Probir Kumar Ojha, Supratik Kar, and Rudra Narayan Das. Some case studies on application of “rm2” metrics for judging quality of quantitative structure–activity relationship predictions: emphasis on scaling of response data. *Journal of computational chemistry*, 34(12):1071–1082, 2013.

## A Abbreviations

**CNN**: Convolutional Neural Network  
**Adaboost**: Adaptive Boost  
**ADDA**: Adversarial discriminative domain adaptation  
**AG-FP**: algebraic graph-based fingerprints  
**AGL-Score** : Algebraic Graph Learning Score  
**AI**: Artificial Intelligence  
**Att**: Attention  
**BERT**: Bidirectional Encoder Representations from Transformer  
**Bi**: Bidirectional  
**BiGRU**: Bidirectional Gated recurrent unit  
**BiLSTM**: Bi directional Long short term memory network  
**BLA**: Biologics License Application  
**BLM**: Bipartite local model  
**BPE**: Byte Pair Encoding  
**CA**: Cross Attention  
**CNN**: Convolutional Neural Network  
**Comb**: Combinator  
**Conv**: Convolution  
**CPA**: component-protein affinity prediction  
**CPI**: component-protein interaction prediction  
**CS**: Character-based slicing  
**CTD**: Composition, Transition and Distribution  
**DBN**: Deep Belief Network  
**Dda**: Drug-drug association  
**DDI**: Drug-drug interaction  
**DDi**: Drug-disease  
**DNA**: Deoxyribonucleic Acid  
**DPA**: Drug-protein affinity prediction  
**DPI**: Drug-protein interaction prediction  
**DPP**: Drug-protein pair  
**Dside**: Drug side effect  
**DTA**: Drug-target affinity prediction  
**DTI**: Drug-target interaction prediction  
**E**: Enzyme  
**ECFP**: Extended-Connectivity Fingerprint  
**EF**: Early fusion  
**EGCL**: Equivariant Graph Convolutional Layer  
**EGNN**: Equivariant graph neural network  
**ErG**: ElectroRetinoGraphy  
**ESM**: Evolutionary Scale Modeling  
**FC**: Fully Connected  
**FCFP**: Functional-Class Fingerprint  
**FDA**: Food and Drug Administration  
**FEP**: Free-Energy Perturbation  
**FNN**: Feed forward neural network  
**FP**: Fingerprint  
**GAN**: Generative Adversarial Network  
**GAT**: Graph Attention Network  
**GCN**: Graph Convolutional Network  
**GIN**: Graph Isomorphism Network  
**GIP**: Gaussian Interaction Profile  
**GNN**: graph neural network

**GPCR**: G-protein-coupled receptor  
**Grad-AAM/Grad-CAM**: Gradient-weighted Affinity/Class Activation Mapping  
**GRU**: Gated recurrent unit  
**HMM**: Hidden Markov Matrix  
**IC**: Ion-Channel  
**ID**: Identification Number  
**IND**: Investigational New Drug Application  
**KNN**: K-nearest neighbour  
**KronRLS**: Kronecker Regularized Least Square  
**LapRLS**: Laplacian Regularized Least Square  
**LM**: Language model  
**LMCS**: Ligand Maximum Common Substructure  
**LSTM**: Long short term memory network  
**LZMA**: Lempel Ziv Markov chain algorithm  
**MAB**: Multihead Attention Block  
**MACCS** : MELCOR Accident Consequence Code System  
**MCA**: Multihead cross attention  
**MFA**: Multiview Fusion Attention  
**MGC**: Molecular Graph Convolution  
**MHSA/MSA**: Multihead Self Attention Block  
**MLP** : Multi Layer Perceptron  
**MM/GBSA**: Molecular Mechanics/Generalized Born Surface Area  
**MM/PBSA**: Molecular Mechanics Poisson-Boltzmann Surface Area  
**MPNN**: Message Passing Neural Network  
**MSA**: Multiple sequence alignment  
**N/A**: Not Applicable  
**NDA**: New Drug Application  
**NFM**: Neural factorization machine  
**NLP**: Natural Language Processing  
**NMR**: Nuclear Magnetic Resonance  
**NNL**: Neural network layer  
**NR**: Nuclear receptor  
**NTN**: Neural Tensor Network  
**PDi**: Preotein-disease  
**PDM**: Protein Domain profiles or Motif  
**PLA**: Protein-ligand affinity prediction  
**PLI**: Protein-ligand interaction prediction  
**PPa**: Protein-protein assosiation  
**PPI**: Protein-protein interaction  
**PSC**: Protein Sequence Composition  
**Pside**: Protein side effect  
**PSSM**: Position-specific score matrix  
**QSAR**: Quantitative StructureActivity Relationship  
**RBM**: Restricted Boltzmann machine  
**ResGCN**: Residual GCN  
**RGCN**: Relational GCN  
**RNN**: recurrent neural network  
**SA**: Self Attention  
**SC**: Skip Connection  
**SDG**: structure diagram generation  
**SE**: Squeeze-and-excitation  
**SELFIES**: SELF-referencIng Embedded String  
**SHAP**: SHapley Additive exPlanation  
**SMARTS**: SMILES Arbitrary Target Specification  
**SMILES**: Simplified Molecular Input Line Entry System  
**SPS**: Structural Property String  
**SSE**: Secondary Structure Element  
**SVM**: Support Vector machine  
**S-W**: Smith-Waterman

**TAPE:** Tasks Assessing Protein Embedding

**TSR:** Triangular Spatial Relationship

## B Available official codes of models

Table 7: Available official codes of Models. Models which do not have official codes are not mentioned here. In order to access the codes click on the corresponding models.

	Official code links	
3DProtDTA	DrugBAN	MCL-DTI
Affinity2Vec	DrugMAN	MDF-DTA
AMMVF-DTI	DrugormerDTI	MFR-DTA
ArkDTA	DTIAM	MGraphDTA
AttentionMGT-DTA	DTI-CNN	MHGNN
AttentionSiteDTI	DTINet	MHTAN-DTI
BACPI	DTITR	MINDG
BAPA	EDC-DTI	ML-DTI
BiComp-DTA	EEG-DTI	MolTrans
BridgeDPI	ELECTRA-DTA	MONN
CaoDTI	EmbedDTI	MRBDTA
CAPLA	EMPDTA	MSGNN-DTA
CCL-DTI	FingerDTA	MSH-DTI
CGraphDTA	FOTF-CPI	MT-DTA
ColdDTA	FusionDTA	NeoDTI
CPGL	GanDTI	NHGNN-DTA
CWI-DTI	GCN-DTI	OctSurf
DataDTA	GEFA	Onionnet
DCGAN-DTA	GEFormerDTA	PADME
DEAttentionDTA	GeneralizedDTA	PGraphDTA
DEELIG	GK-BertDTA	PHCDTI
DeepAffinity	GNPDTA	PLA-MoRe
DeepBindRG	GPCNDTA	PLANET
DeepCDA	GraphDTA	PLAPT
DeepConv-DTI	GraphScoreDTA	PocketDTA
DeepCPI/GNN-CPI	GSL-DTI	PSG-BAR
DeepDTA	HGRL-DTA	S2DTA
DeepDTAF	HyperAttentionDTI	Sfcnn
DeepDTI	ICAN	SGCL-DTI
DeepFusionDTA	IIFDTI	SIGN
DeepGLSTM	IMAEN	SS-GNN
DeepGS	ImageDTA	SSR-DTA
DeepH-DTA	IMCP-SF	SubMDTA
DeepMGT-DTI	InterGraph	TDGraphDTA
DeepNC	Jones et al.	TEFDTA
DeepTGIN	KC-DTA	TransformerCPI
DeepTraSynergy	KGE-NFM	TripletMultiDTI
DeFuseDTI	KIDA	UCMPNN-DTA
DGDTA	Kim et al.	WGNN-DTA
DGraphDTA	LSTM-SAGDTA	
DLSSAffinity	MBP	

## C Other tables and figures

Table 8: Summary of sequence-based models input representations

Model	Drug/Ligand representation	Protein/Target representation	Extra representation/input
DeepAffinity	SMILES	Structural property strings	N/A
DeepCDA	SMILES	Protein sequences	N/A
BridgeDPI	SMILES, Morgan FP, Physiochemical features	Protein sequences, onehot, 1/2/3-mer features	Bridge graph
DeepDTA	SMILES	Protein sequences	N/A
WideDTA	SMILES (8 words)	Protein sequences (3 words)	LMCS, Protein Domains and Motifs
MATT-DTI	SMILES	FASTA	N/A
ML-DTI	SMILES	Protein sequences	N/A
Co-VAE	SMILES	Protein sequences	N/A
FusionDTA	SMILES	Protein sequences	N/A
ELECTRA-DTA	SMILES	FASTA	N/A
AttentionDTA	SMILES	Protein sequences	N/A
DTITR	SMILES	Protein sequences, FCS+BPE	N/A
CSatDTA	SMILES	Protein sequences	N/A
MRBDTA	SMILES	FASTA	N/A
FingerDTA	SMILES onehot	AminoAcid onehot	Drug and target fingerprints (ECFP4)
PCNN-DTA	SMILES	Protein sequences	N/A
MT-DTA	SMILES	Protein sequences	N/A
ArkDTA	SMILES and Morgan FP	FASTA with ESM	N/A
DGDTA	SMILES	Protein sequences	N/A
TEFDTA	SMILES to MACCS FP	FASTA	N/A
TransVAE-DTA	SMILES	Protein sequences	N/A
DCGAN-DTA	SMILES	Protein sequences	N/A
DEAttentionDTA	SMILES	Protein Sequences	Pocket sequences
ImageDTA	SMILES	Protein Sequences	N/A
TC-DTA	SMILES	Protein Sequences	N/A
MultiscaleDTA	SMILES	Amino Acid strings	N/A
GANsDTA	SMILES	Protein Sequences	N/A
SimCNN-DTA	Tanimoto drug-drug similarity	Smith Waterman similarity	N/A
BiComp-DTA	SMILES	Protein sequences with LZMA, Smith-Waterman and BiCOMP encoding	N/A
MFDR	881 dim fingerprints	Protein Sequences	N/A
DeepDTI	Extended-Connectivity Fingerprints (ECFP)	Protein sequence composition descriptors (PSC)	N/A
DeepConv-DTI	Morgan/Circular drug fingerprints	Protein Sequences	N/A
MolTrans	SMILES	Protein Sequences	N/A
EnsembleDLM	Daylight, ErG, Morgan FP, SMILES 1-char embeddings	AAC, character-based embedding of FASTA	N/A
MT-DTI	SMILES	FASTA	N/A
DeepDTAF	SMILES	Protein Sequences	SSE, physicochemical chars, sequence+structural property
CAPLA	SMILES	AA sequences, SSEs, physicochemical of residues of protein and pockets	pocket input
AffinityVAE	SMILES	Protein Sequences	N/A
PLAPT	SMILES	Amino Acid strings	N/A
Hu et al.	PaDEL-Descriptor	Physicochemical properties of Amino Acids	data augmentation
DrugVQA	SMILES	2D pairwise distance map	N/A
CA-DTI	Compound feature from molecular graph	Protein Sequences	N/A
HyperAttentionDTI	SMILES	Amino Acid sequences	N/A
MPS2IT-DTI	SMILES	Protein Sequences	N/A
FastDTI	Chemical properties, Grover, ChemBERTa	Protein properties, ProtBert	Yes
MCL-DTI	Image and the chemical features text	FASTA k-gram	Yes
AMMVF-DTI	SMILES	Protein Sequences	N/A
FOTF-CPI	Fragmented SMILES	Fragmented Protein Sequences	N/A
MDF-DTA	SMILES	Protein Sequences	N/A
DeFuseDTI	Molecular graph from SMILES	Protein Sequences	N/A
PHCDTI SMILES	FASTA	N/A	N/A
MREDTA	SMILES	Protein Sequences	N/A
CWI-DTI	SMILES and FPs	protein sequences	Similarity of drug and target structures

Table 9: Summary of structural-based models input representations

Model	Drug/Ligand representation	Protein/Target representation	Extra representation/input
Graph-CNN	Molecular graph from SMILES	Protein pocket graph	N/A
STAMP-DPI/X-DPI	Molecular graph+Mol2vec embedding	Contact map graph+TAPE embedding	N/A
AttentionSiteDTI	Molecular graph from SMILES	Binding pocket graphs	N/A
DGraphDTA	Molecular graph from SMILES	Protein Graph from contact maps	N/A
GEFA	Molecular graph from SMILES	TAPE embeddings and Protein Graph from contact maps	N/A
WGNN-DTA	Molecular graph from SMILES	Weighted Protein Graph from contact maps	N/A
HGRL-DTA	Molecular graph from SMILES	Graph from contact maps	Affinity graph
Ma et al.	Molecular graph from SMILES	Graph of contact maps (Pconsc4) and PSSM features	N/A
GSAML-DTA	Molecular graph from SMILES	Graph from contact maps	N/A
MSGNN-DTA	Drug Atom-Level Graph from SMILES	Weighted Protein Graph from contact maps	Drug Motif-Level Graph
GraphScoreDTA	Molecular graphs	Graph from Contact maps	subgraphs from contact maps, Vina terms
PLANET	Graph in 2D space	Protein pocket graph	N/A
CGraphDTA	Molecular graph	PSSM and HMM graphs	Secondary structure features using DSSP
AttentionMGT-DTA	Molecular graphs	Protein pocket graphs	N/A
GTAMP-DTA	Molecular graphs	Protein pocket graph	N/A
S2DTA	Graphs	Protein graphs (PSSM and HMM)	Pocket graphs
NG-DTA	Molecular graphs from SMILES	N-gram graphs from protein sequences	N/A
EMPDTA	Molecular graphs	Protein structures from ALPHAFOLD	Pocket graphs
HGTDTP-DTA	Molecular graph from SMILES	Contact map graphs	Affinity graph
GNPDTA	Graphs	Graphs	N/A
CASTER-DTA	Molecular SMILES	Protein graphs from PDBank or AlphaFOLD2	N/A

Table 10: Summary of structural-sequence-based models input representations

Model	Drug/Ligand representation	Protein/Target representation	Extra representation/input
DTIAM	Substructures of Molecular graphs	Protein sequences	N/A
DeepCPI	R-radius subgraphs	Protein sequences	N/A
GraphCPI	Molecular graph from SMILES	3-gram encoding with pretrained Word2Vec	N/A
TransformerCPI	Molecular graph from SMILES	Amino Acid sequence	N/A
Kim et al.	molecular graphs	Protein sequences	N/A
DeepMGT-DTI	Molecular graphs	Sequence embeddings	N/A
CPInformer	Molecular graphs, FCFPs from SMILES	Protein sequences	yes
CaoDTI	R-radius subgraphs from SMILES	Protein sequence	N/A
CPGL	R-radius subgraphs	3-gram from Protein sequences	N/A
DrugormerDTI	Molecular graphs	Residual2vec embeddings	N/A
CSDTI	Molecular graphs from SMILES	Protein sequences	N/A
MINDG	SMILES,	Protein sequences	Binding affinity graph
FDTHIT	Molecular graphs from SMILES	FASTA	N/A
PADME	SMILES, ECFP/graphs	Protein sequences (PSC)	N/A
Wang et al.	Molecular graphs	Protein sequences	N/A
DeepGS	SMILES (Smi2Vec), Molecular graph from SMILES	Amino Acid sequences (Prot2vec)	yes
DeepH-DTA	SMILES	Protein sequences	Molecular graphs
GraphDTA	Molecular graph from SMILES	Protein sequences-Onehot encoding	N/A
DeepRelations	Molecular graphs	Protein sequences	Predicted solvent exposure, intermediate predicted k-mer binding residues, intermediate predicted binding residues, predicted protein contact map
GanDTI	Molecular graph from SMILES	Protein sequences (3 words)	N/A
DEELIG	PaDEL-Descriptor, FPs, QikProp to get ADMET	Atomic level, Amino acid level protein-pocket 3D	N/A
DeepFusionDTA	SMILES	Protein sequences	Protein secondary structures, Molecular fingerprints
SAG-DTA	Molecular graph from SMILES	Amino Acid sequences	N/A
EmbedDTI	Atom graph and substructure graph	Protein sequences	Substructure network for drugs
MGraphDTA	Molecular graph from SMILES	Protein sequences-integer encoding	N/A
BACPI	Molecular graph from SMILES, ECFPs	Protein sequences (3 word)	N/A
Tian et al.	Molecular structures	Protein sequences	Chemical background sequences
SSGraphCPI	SMILES, Molecular graph from SMILES	Structure property sequences	yes
DLSSAffinity	SMILES	Complete Protein sequences	Pocket-ligand structural pairs
DeepGLSTM	Molecular graphs	Amino Acid sequences	Molecular graphs paths
GDGRU-DTA	Molecular graph from SMILES	Protein sequences	N/A
DeepNC	Molecular graph from SMILES	Protein sequences-one hot	N/A
Lin et al.	constructed DDI graphs	similarity graph with TEXTCNN	N/A
IIFDTI	Molecular graph from SMILES	Protein sequences	Smi2Vec, Prot2Vec
PSG-BAR	Attributed graphs	Attributed graphs from contact maps	ESM with Protein sequences
Xia et al.	Molecular graphs	Amino Acid sequence	N/A
PLA-MoRe	Molecular graph	Protein sequences	Bioactive propriety of drugs
MFR-DTA	FCFPs and GNN features	Amino Acid embedding (AAE) and word embedding (WE)	yes
DrugBAN	Molecular graph from SMILES	Protein sequences	N/A
3DProtDTA	Graph, Morgan FP	Graphs from AlphaFold	N/A
NHGNN-DTA	SMILES, Molecular graphs	Protein sequences, Pconsc4 graphs	yes
ColdDTA	Graph	Protein sequences	N/A
SubMDTA	Molecular graph from SMILES	Protein sequences (2,3,4 grams)	N/A
DataDTA	AG-FP(3D structures), SMILES	Pockets, Protein sequences	yes
UCMPNN-DTA	Molecular graph from SMILES	Protein sequences	N/A
GPCNDTA	Molecular graph from SMILES	Protein graphs from distances	Pharmacophore, SMILES, protein FASTA
PGraphDTA	Molecular graph from SMILES	Protein sequences	Contactmaps with Pconsc4 and DiffDock
IMAEN	Molecular graph from SMILES	Protein sequences	N/A
TDGraphDTA	Molecular graph from SMILES	Protein sequences	N/A
KC-DTA	Molecular graph from SMILES	2D and 3D Protein sequences	yes
GraphCL-DTA	Molecular graph	Protein sequences	N/A
AGraphDTA	Graph	Graph, sequences	yes
HBDTA	molecular graph from SMILES	Protein sequences	N/A
LSTM-SAGDTA	Molecular graph from SMILES	SeqVec model (ELMo)	N/A
T-GraphDTA	Molecular graph from SMILES	Protein sequences	N/A
GEFormerDTA	ESC from SMILES, graph	Graph from distance map	N/A
GK BertDTA	Molecular structures using SMILES	Amino Acid sequence	SMILES
SSR-DTA	Molecular fingerprints and molecular maps, ECFP	3D-structural information of proteins	yes
PocketDTA	Molecular Morgan fingerprint, 2D molecular graphs from SMILES	Protein sequences with ESM-2, pocket graphs	yes
ViDTA	Molecular graph from SMILES with virtual node	Protein sequences	N/A
DeepTGIN	molecular graph	Protein residue sequences	pocket residue sequences

