predicting drug-target binding affinity with graph neural networks

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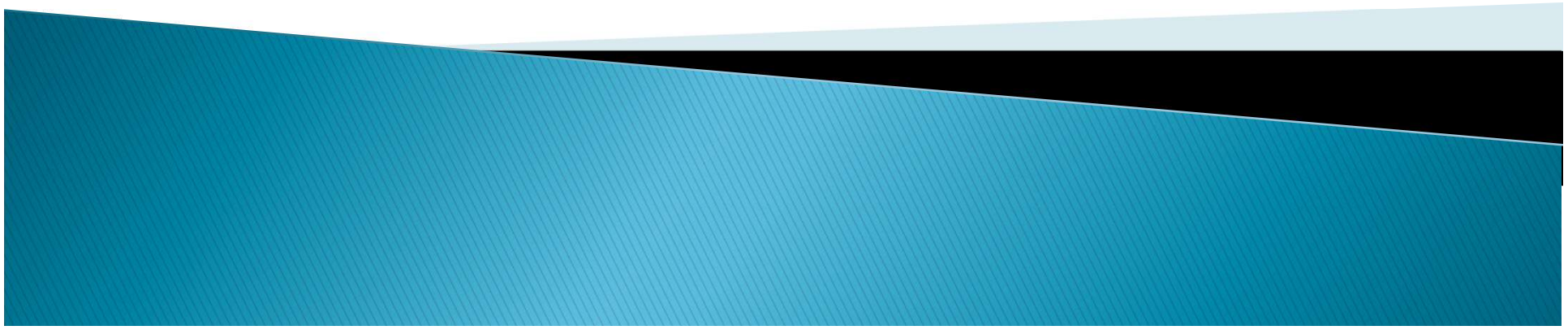
Directed By: Francesc Seratosa



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- Drug and Protein representation
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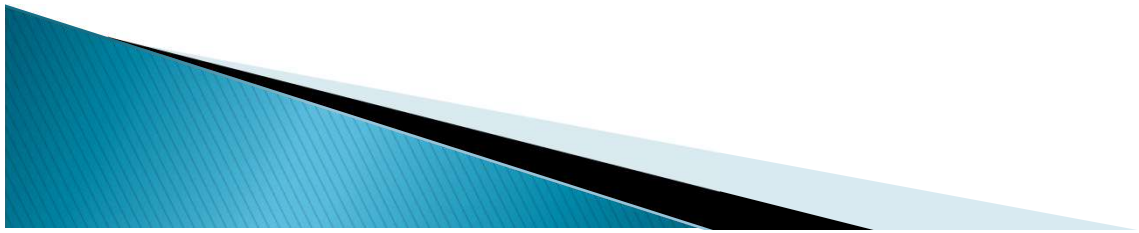
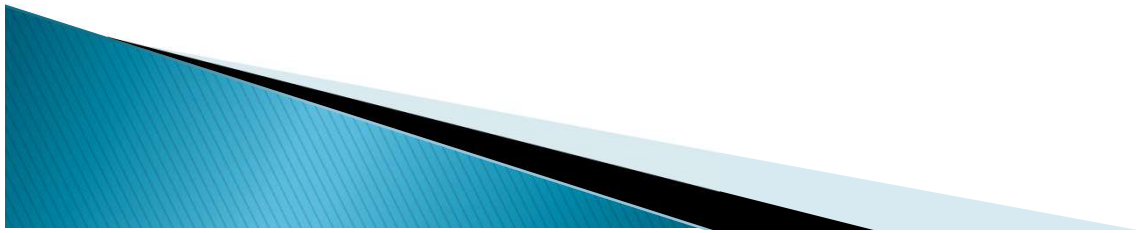


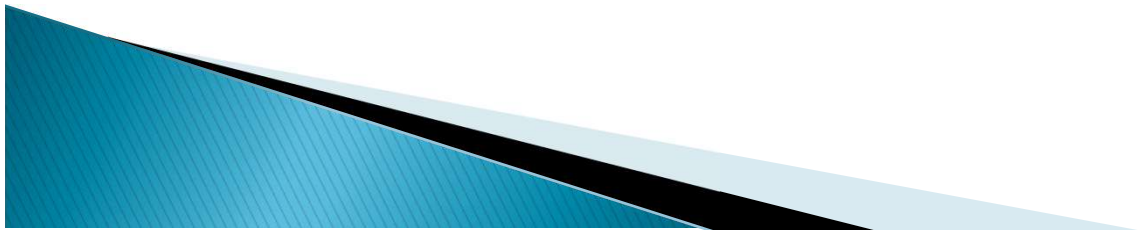
Introduction

- A virus encodes one or more **proteases** which are enzymes that spur the formation of new protein products, thus play crucial roles in virus replication
- **proteases** are important targets for the design and development of potent antiviral agents or **drugs**



Introduction

- **Binding affinity** is the strength of the binding interaction between a single molecule (e.g., a virus protein) to its ligand or binding partner (e.g., a drug)

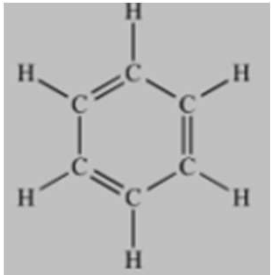


Protein representation

- A protein sequence is the order of amino acids in a protein. Amino acids are the building blocks of proteins
- an example of a protein sequence, representing the first 7 amino acids of the protein insulin (**GIVEQCC ...**):
  - **G**: Glycine
  - **I**: Isoleucine
  - **V**: Valine
  - **E**: Glutamic acid
  - **Q**: Glutamine
  - **C**: Cysteine
  - **C**: Cysteine

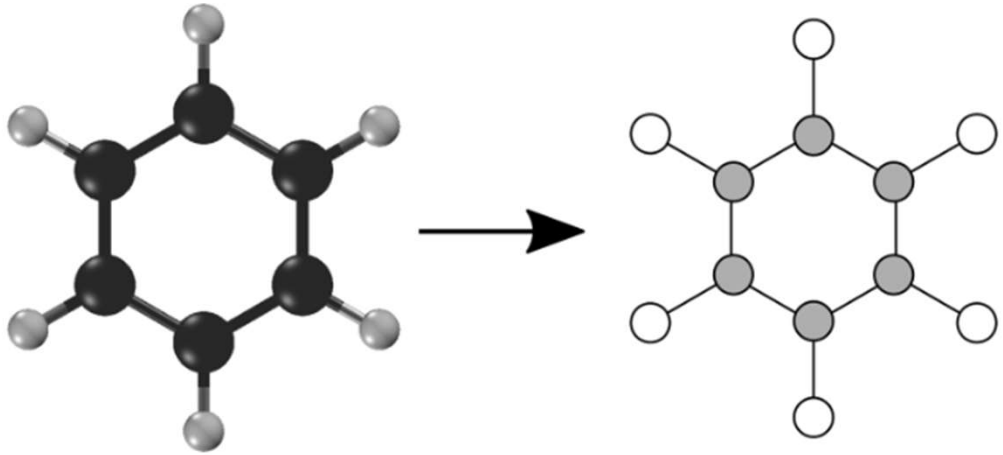
SMILES notation

- “Simplified Molecular-Input Line-Entry System”
- popular method for specifying molecules with text strings.
- invented to represent molecules to be readable by humans and computers
  - Methane: "C"
  - Ethanol: "CCO"
  - Benzene: "c1ccccc1“
  - Glucose: "OC[C@@H]1OC@HC@@HC@H[C@H]1O"



molecular graph

- A molecular graph describes the set of atoms in a molecule and how they are bonded together
- G = (V,E), where V is the set of N nodes and E is the set of edges represented as an adjacency matrix A



An example of converting a benzene molecule into a molecular graph. Note that atoms are converted into nodes and chemical bonds into edges.

binding affinity measures

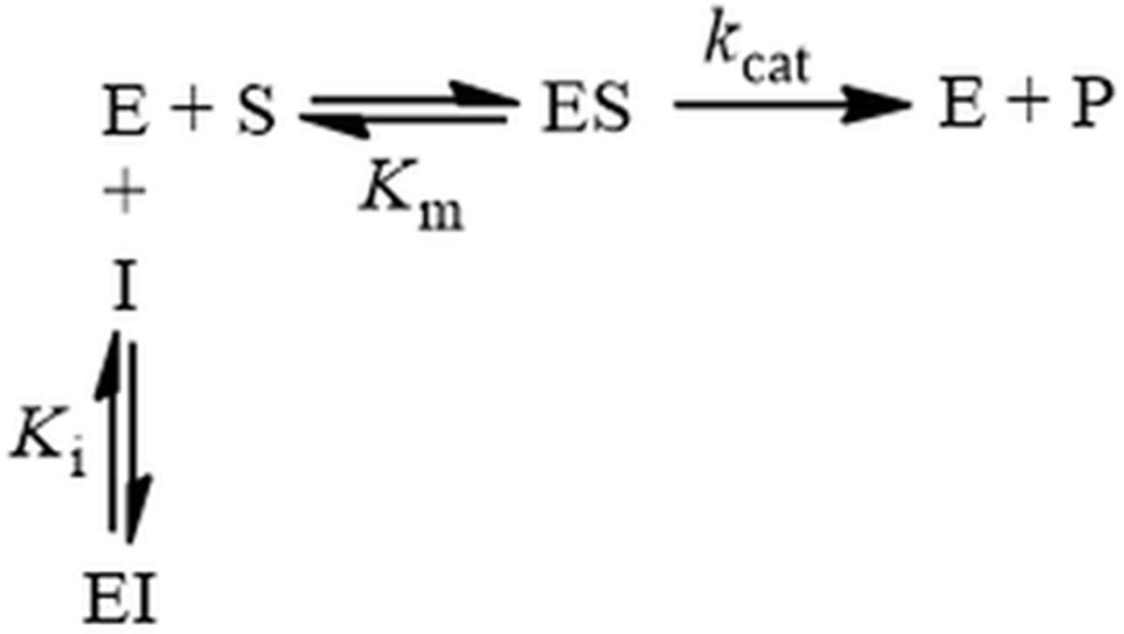
- The kinase dissociation constant(Kd)
  - measures the equilibrium between the ligand(drug)-protein complex and the dissociated components

$$PL \underset{K_d}{\rightleftharpoons} P + L \qquad K_d = \frac{[P][L]}{[PL]}$$

  - Where [P] is the free protein concentration
  - [L] is the free ligand concentration
  - [PL] is the protein-ligand complex

binding affinity measures

- The kinase Inhibition Constant(Ki)
  - represents the affinity of the drug molecule for its target receptor, specifically in the context of **competitive inhibition.**



binding affinity measures

- inhibitory concentration 50% (IC50)
  - the concentration at which the inhibitor causes a 50% inhibition of enzymatic activity
  - less precise than Ki or Kd
  - A lower IC50 value indicates a higher affinity of the drug for the receptor

$$0.5 = \frac{K_m + [S]}{K_m\left(1 + \frac{IC_{50}}{K_i}\right) + [S]} \qquad IC_{50} = K_i\left(1 + \frac{[S]}{K_m}\right)$$

  - [S] is the concentration of the natural substrate that competes with the inhibitor for binding to the target.

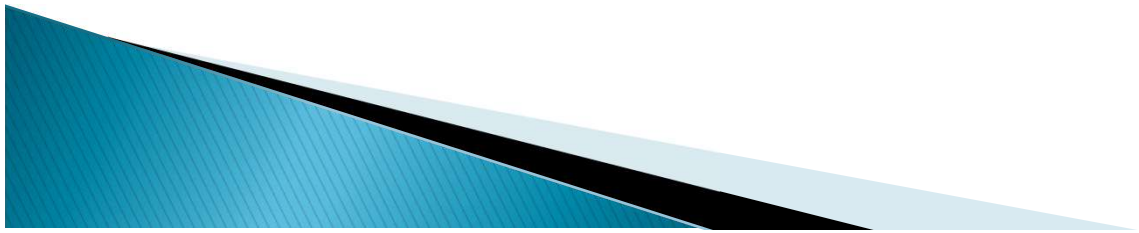
Bioactivity values found from ChEMBL for the imatinib–SRC pair

Drug	Type	Value	Units	Target
IMATINIB	Ki	31000	nM	SRC
IMATINIB	Kd	10000	nM	SRC
IMATINIB	IC50	100000	nM	SRC

Making Sense of Large-Scale Kinase Inhibitor Bioactivity Data Sets: A Comparative and Integrative Analysis, https://pubs.acs.org/doi/10.1021/ci400709d

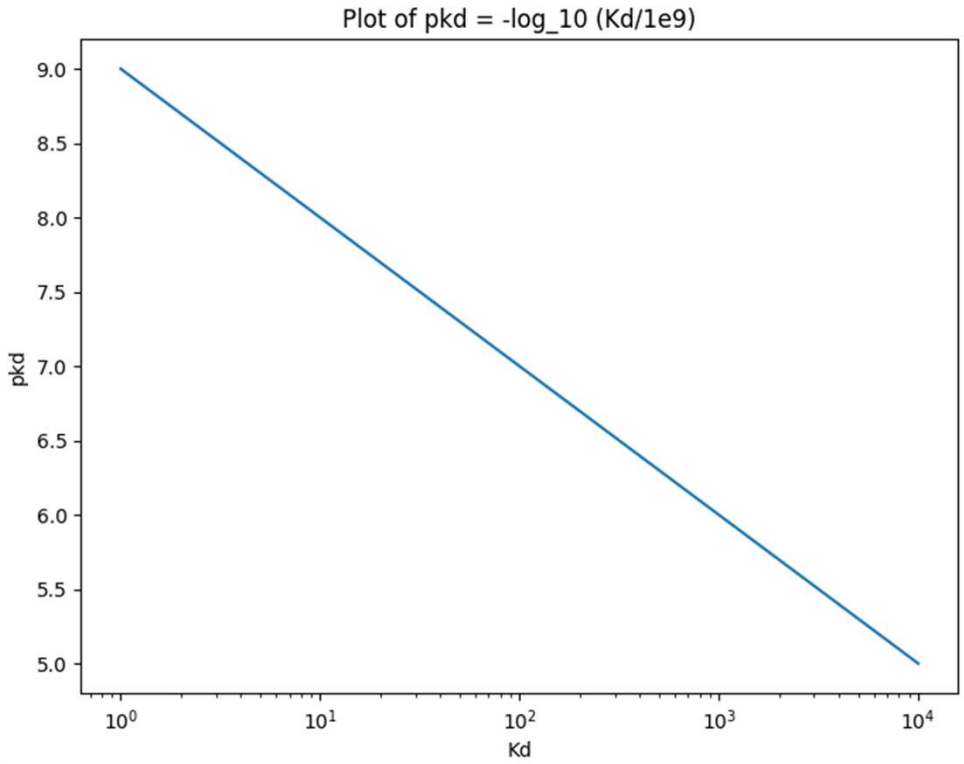
Datasets

- Benchmark dataset davis
- Benchmark dataset kiba
- In house dataset URV



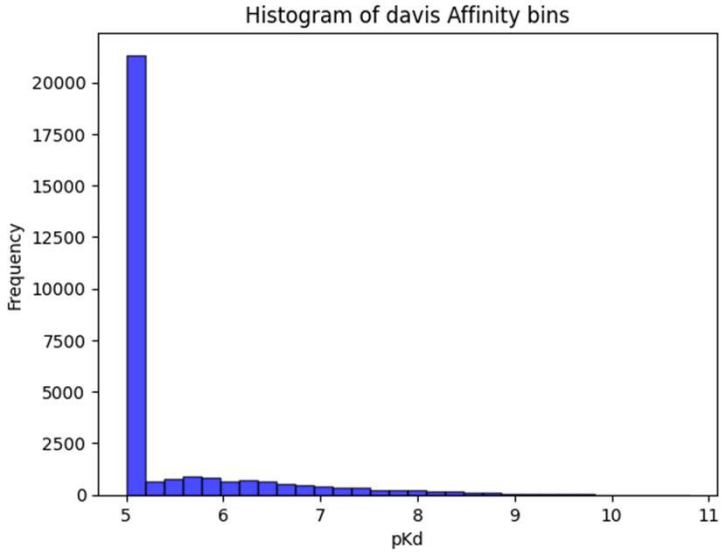
Datasets

- Benchmark dataset **davis**
  - **Kd** values in the Davis dataset were transformed into logspace (**pKd**) as: $\boldsymbol{pkd = -log_{10}(^{Kd}/_{1e9})}$
  - ranging from 5.0 to 10.8



Datasets

- Benchmark dataset **davis**
  - contains the binding affinities for all pairs of 68 drugs and 442 targets, total of 30056 interactions
  - 25047 train set + 5011 test set
  - 69% of which have affinity values of 10000 nM (**pKd**=5) indicating weak or no interaction.



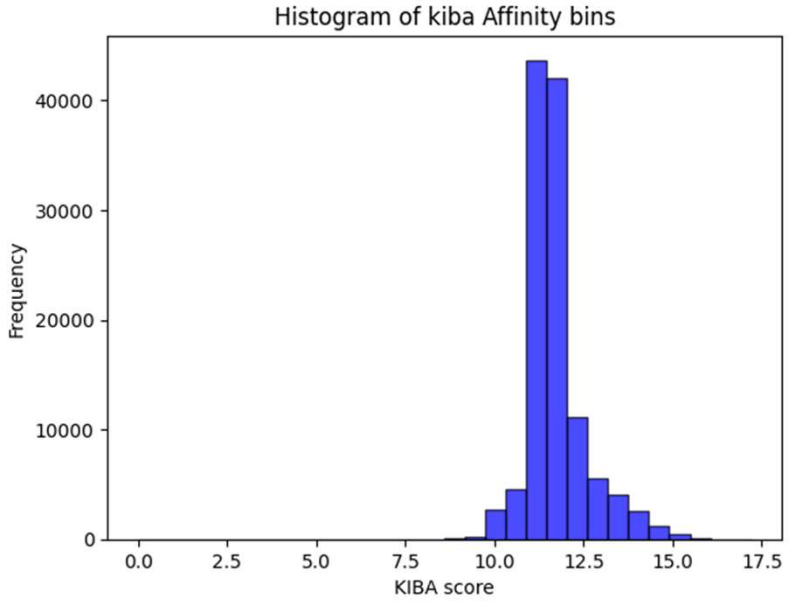
Datasets

- Benchmark dataset **kiba**
  - Kinase Inhibitor Bioactivity Data Set
  - binding affinity might be measured by **Kd**, Ki or IC50
  - integrates the information from IC50, Ki , and Kd measurements into a single bioactivity score

$$\mathrm{KIBA} = \begin{cases} K_i.\ \mathrm{adj} & \text{if } IC_{50} \text{ and } K_i \text{ are present} \\ K_d.\ \mathrm{adj} & \text{if } IC_{50} \text{ and } K_d \text{ are present} \\ (K_i.\ \mathrm{adj} + K_d.\ \mathrm{adj})/2 & \text{if } IC_{50},\ K_i, \text{ and } K_d \text{ are present} \end{cases}$$

Datasets

- Benchmark dataset kiba
  - measured as KIBA scores and ranging from 0.0 to 17.2
  - Total of118257 interactions(98547 train set + 19710 test set)
  - most interactions between 10 and 15 kiba score

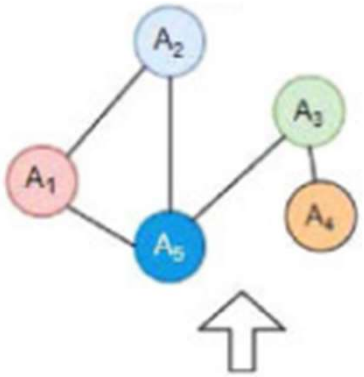


Previous Work

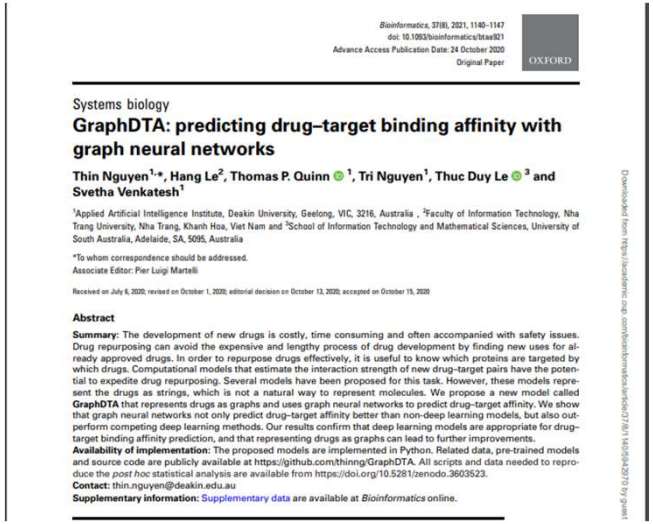
- **collaborative filtering (2017)**: utilizes a similarity measure to identify drugs and targets that are similar to the query drug and target. This allows the model to leverage existing data on similar compounds and targets to make predictions for new ones
- **DeepDTA model (2018)**: uses a deep neural network architecture with two branches
  - (CNNs):for capturing local patterns in SMILES notation of drugs
  - (RNNs):for capturing sequential information in protein sequences.
- **WideDTA model (2019)**: uses CNNs to learn complex patterns from both the drug SMILES notation and target protein sequence representations.

GraphDTA paper overview(2020)

- a new neural network architecture capable of directly modeling drugs as **molecular graphs**
- tests the hypothesis that a graph structure could yield a better representation for drugs
- outperforms previous deep learning models



'O=C(NC1CCNCC1)c1[nH]ncc1NC(=O)c1c(Cl)cccc1Cl'



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Original Paper

OXFORD

Systems biology

GraphDTA: predicting drug–target binding affinity with graph neural networks

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Abstract

Summary: The development of new drugs is costly, time consuming and often accompanied with safety issues. Drug repurposing can avoid the expensive and lengthy process of drug development by finding new uses for already approved drugs. In order to repurpose drugs effectively, it is useful to know which proteins are targeted by which drugs. Computational models that estimate the interaction strength of new drug–target pairs have the potential to expedite drug repurposing. Several models have been proposed for this task. However, these models represent the drugs as strings, which is not a natural way to represent molecules. We propose a new model called **GraphDTA** that represents drugs as graphs and uses graph neural networks to predict drug–target affinity. We show that graph neural networks not only predict drug–target affinity better than non-deep learning models, but also outperform competing deep learning methods. Our results confirm that deep learning models are appropriate for drug–target binding affinity prediction, and that representing drugs as graphs can lead to further improvements.

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

Contact: thin.nguyen@deakin.edu.au

Supplementary information: Supplementary data are available at *Bioinformatics* online.

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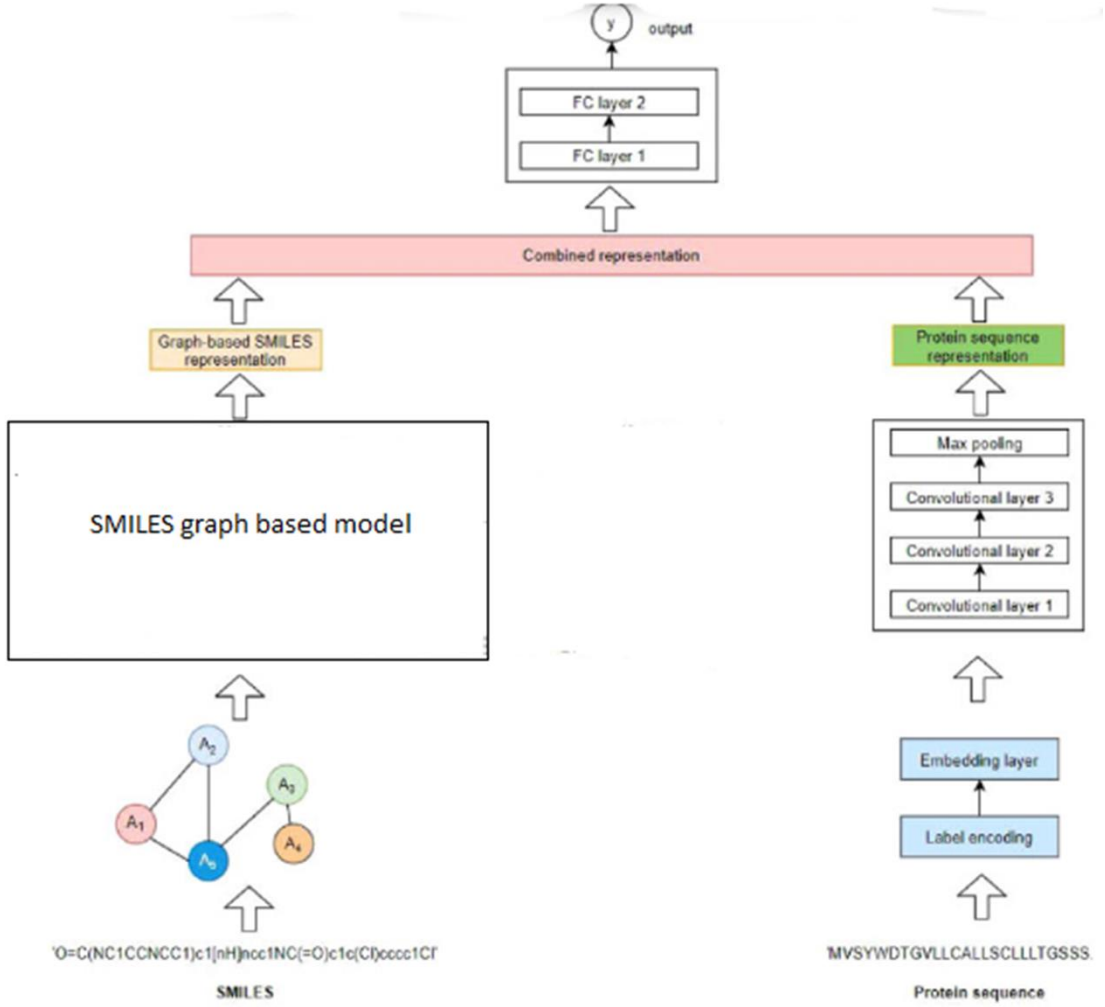
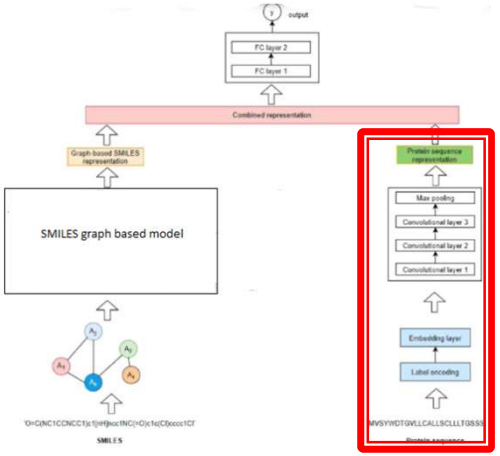
GraphDTA architecture

- Protein branch
- Drug branch
  - 4 models
- Combined representation



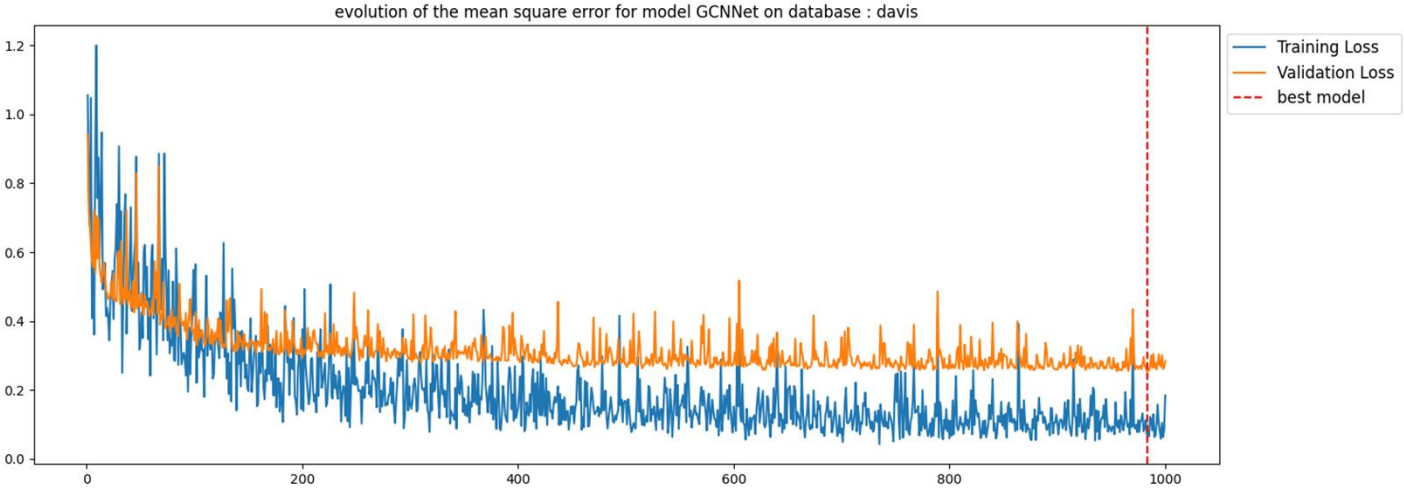
Protein Branch

- Label encoding [e.g. Alanine (A) is 1, Cystine (C) is 3, Aspartic Acid (D) is 4 and so on]
-



Results

- train and test GCN-based model with davis dataset



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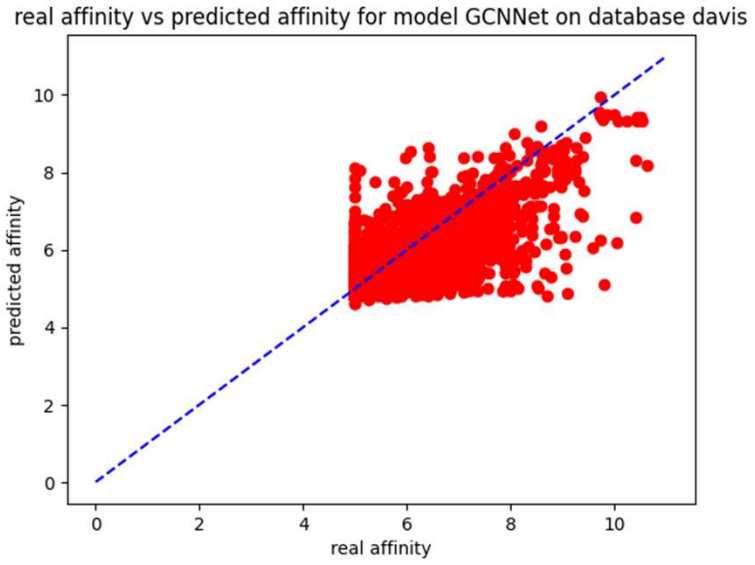
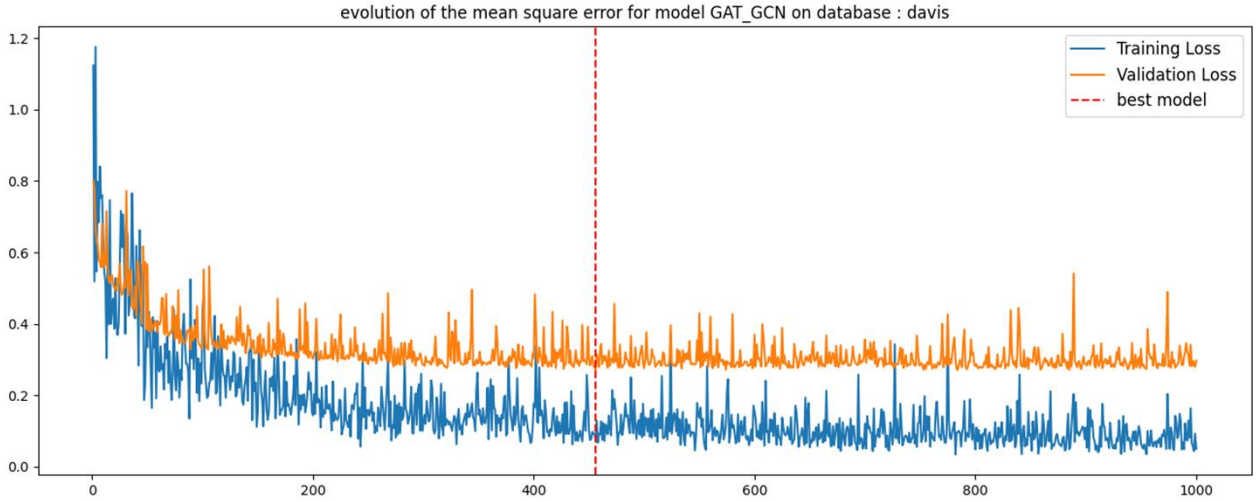
epochs	1000
train batch size	512
train size	20036
validation size	5010
validation percentage	20.0 %
MSE	0.25293395



Results

- train and test GATGCN-based model with davis



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validation size	5010
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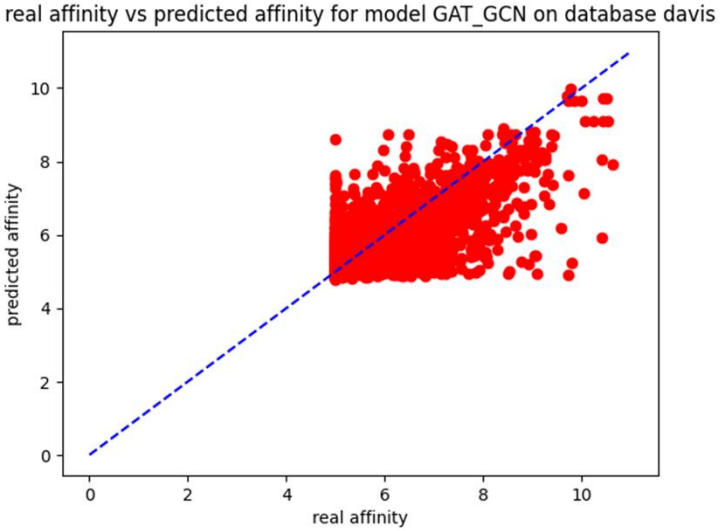
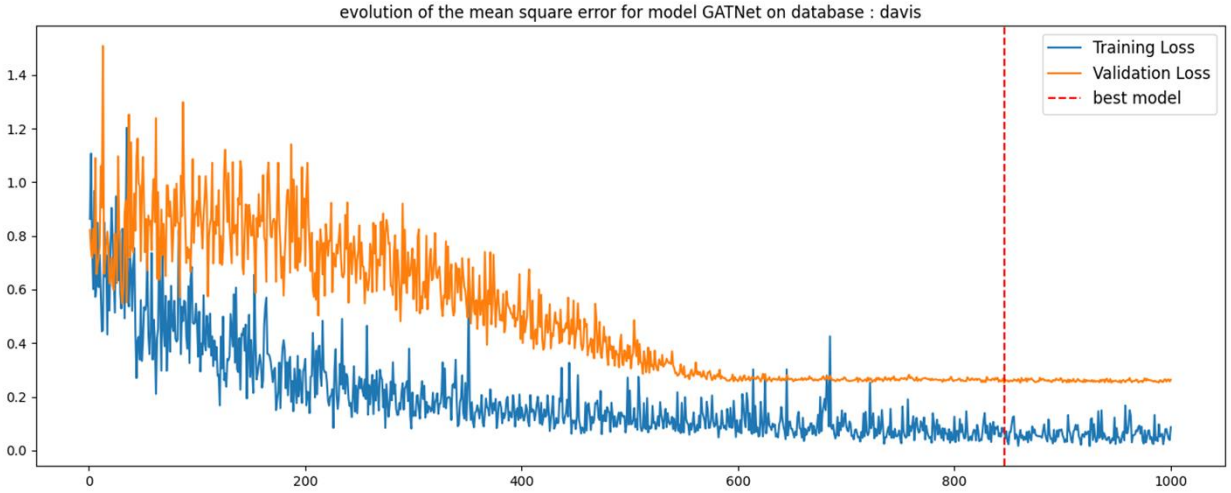


Results

- train and test GAT-based model with davis dataset



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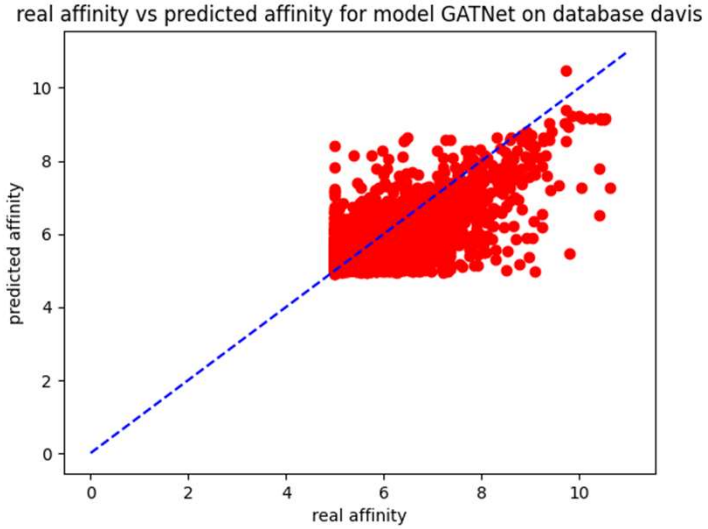
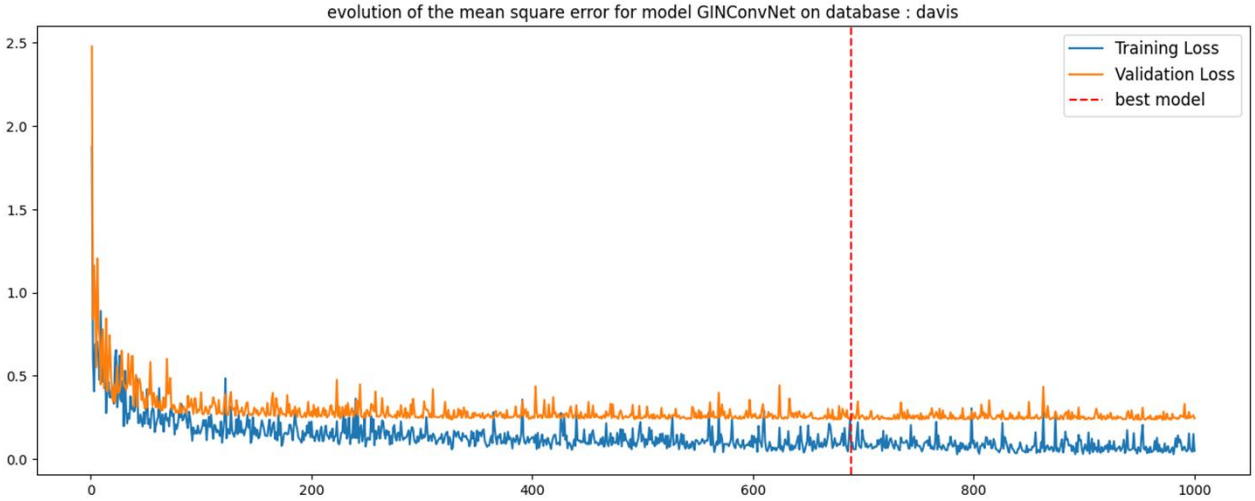


Results

- train and test GinConv-based model with davis



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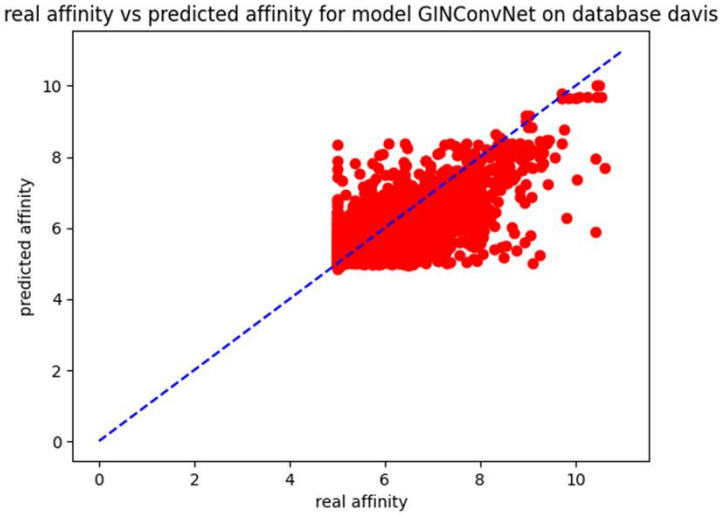
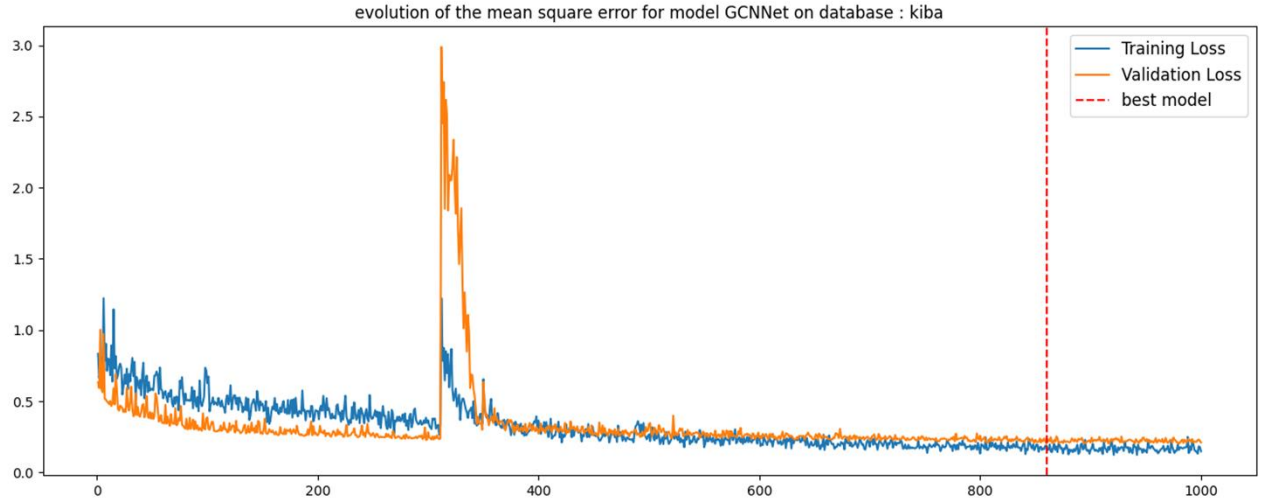


Results

- train and test GCN-based model with kiba dataset



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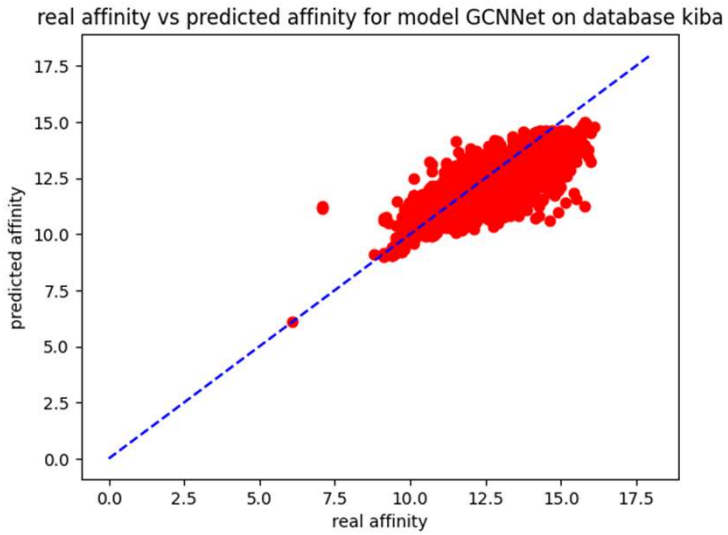
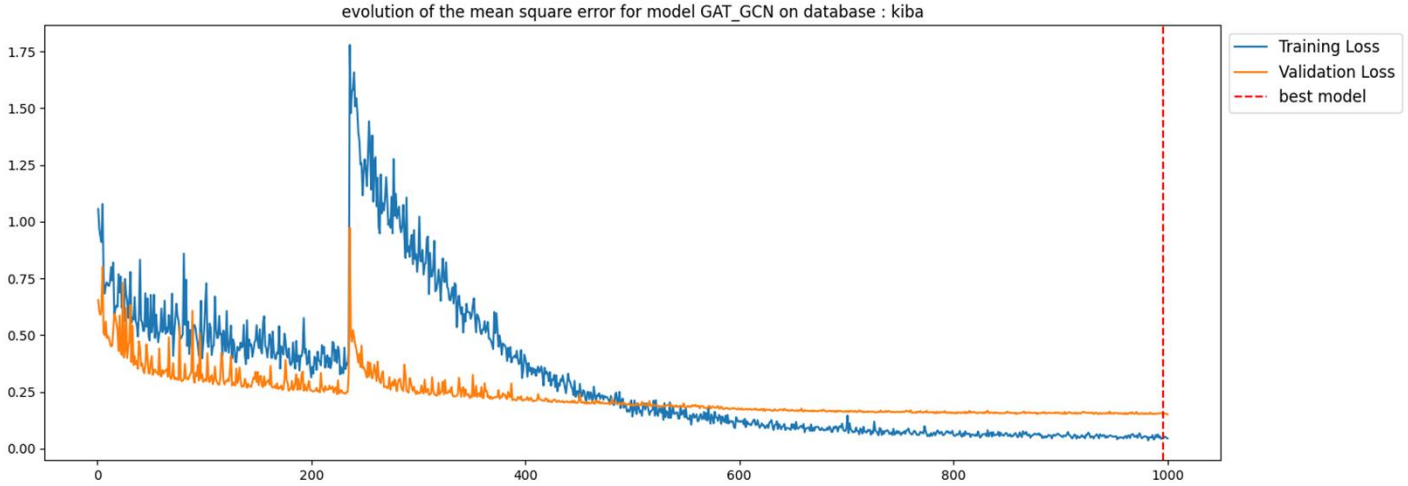
train size	78836
validation size	19709
validation percentage	20.0 %
MSE	0.2024536



Results

- train and test GATGCN-based model with kiba



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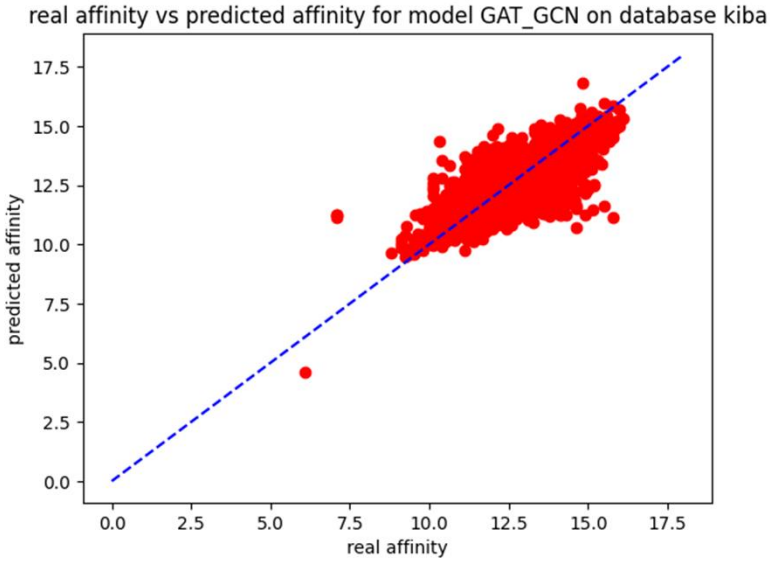
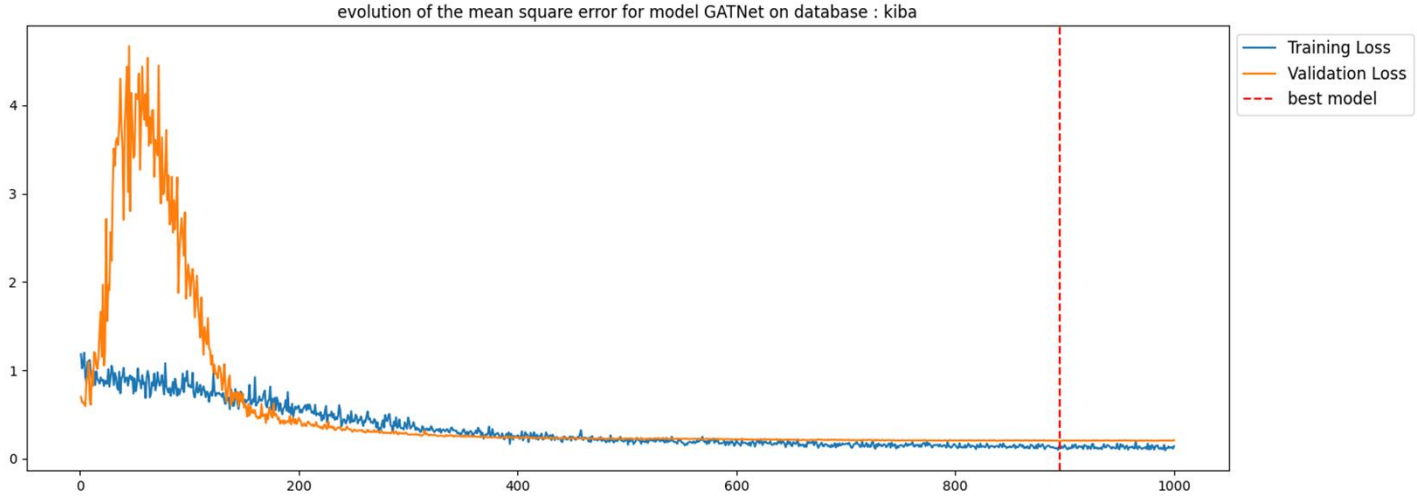
validation size	19709
validation percentage	20.0 %
MSE	0.15026996



Results

- train and test GAT-based model with kiba dataset



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epochs	1000
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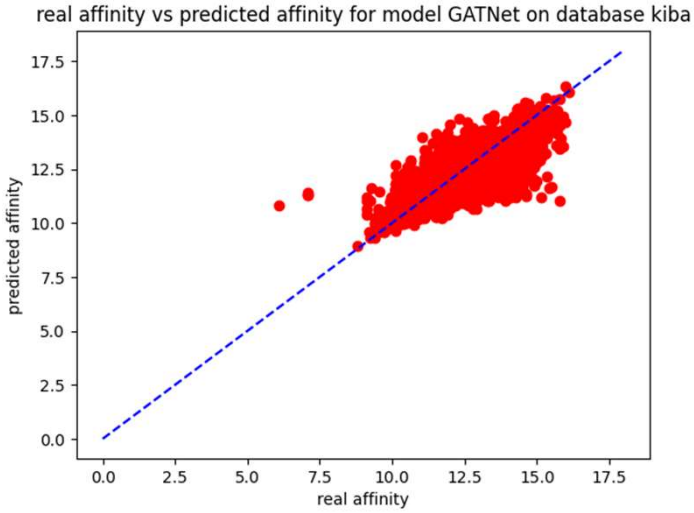
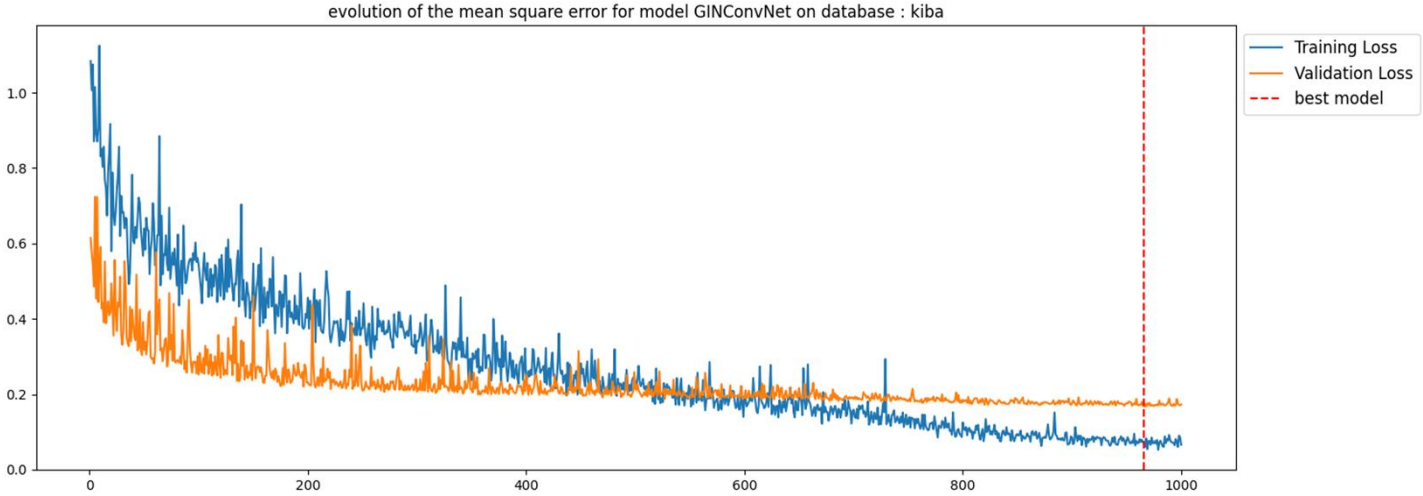
train size	78836
validation size	19709
validation percentage	20.0 %
MSE	0.19964518



Results

- train and test GINCONV-based model with kiba



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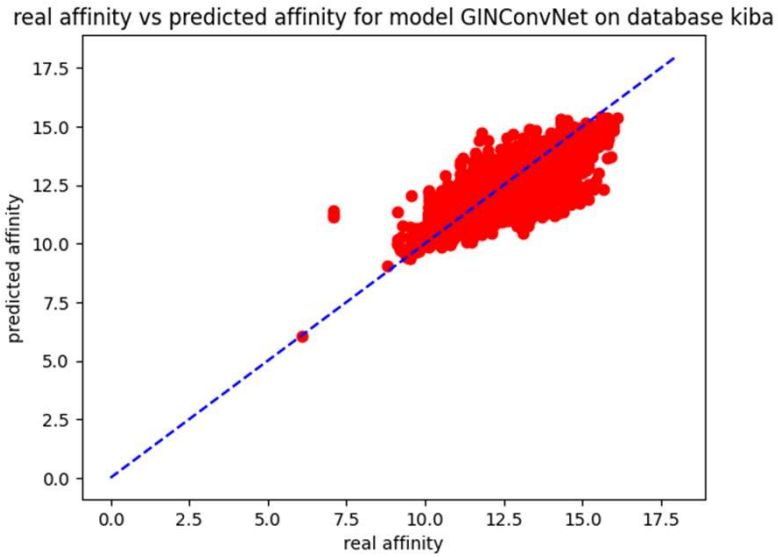
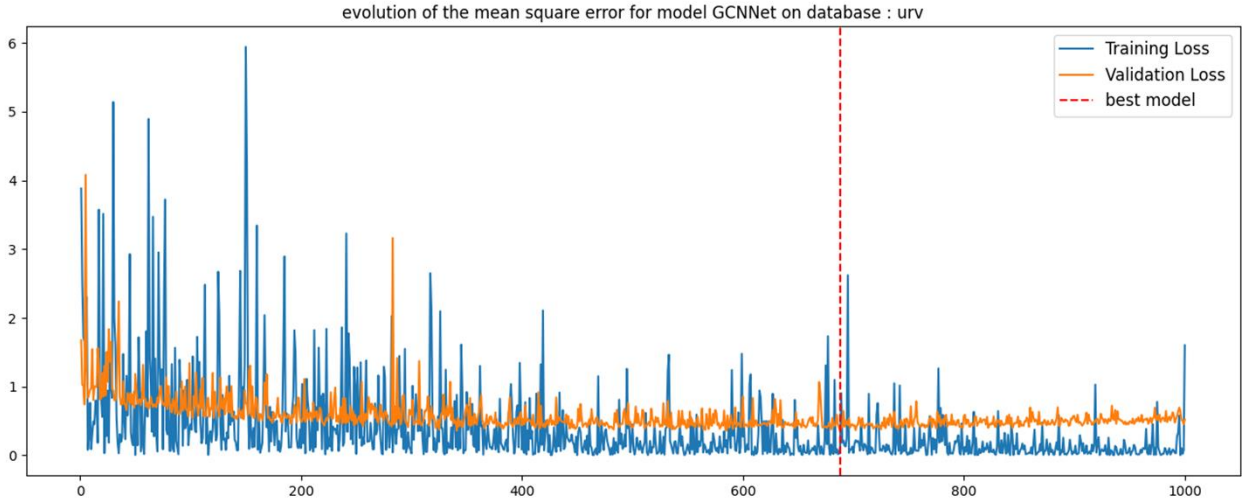
train size	78836
validation size	19709
validation percentage	20.0 %
MSE	0.1673416

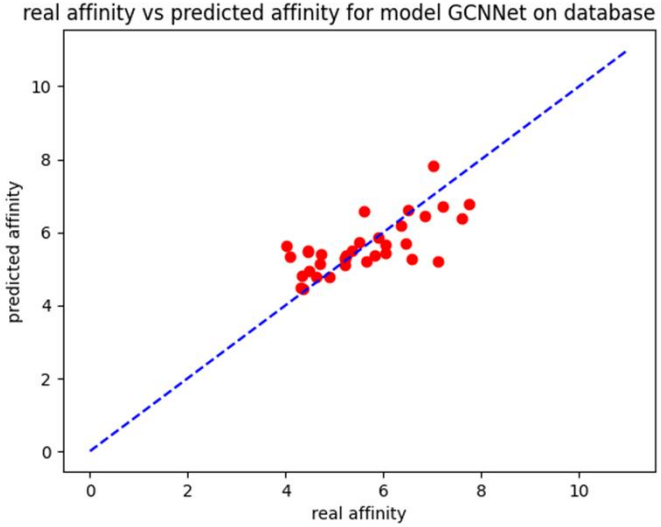


Results

- train and test GCN-based model with URV dataset

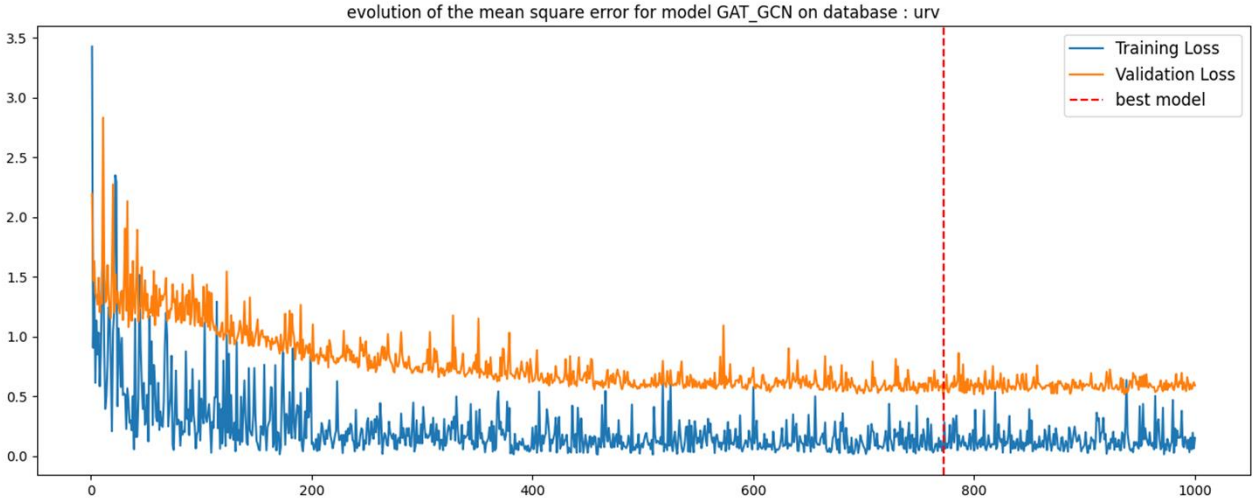


optimizer	ADAM
learning rate	0.0005
epochs	1000
train batch size	4
train size	238
validation size	60
validation percentage	20.0 %
MSE	0.35485



Results

- train and test GATGCN-based model with URV



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epochs	1000
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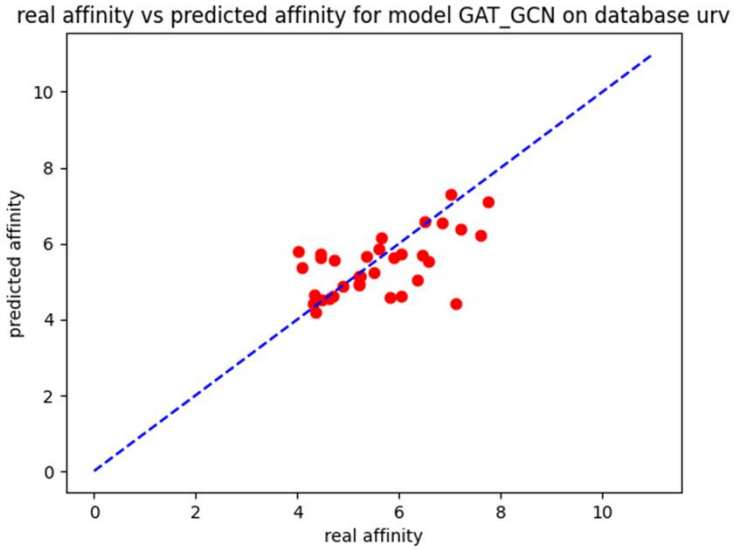
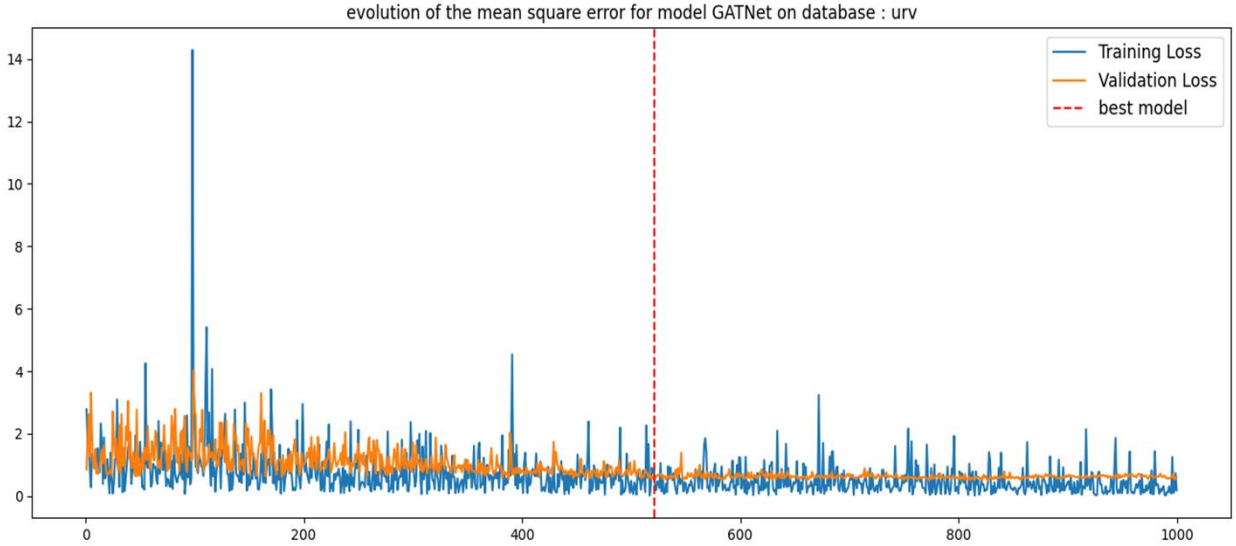
train size	238
validation size	60
validation percentage	20.0 %
MSE	0.51364166

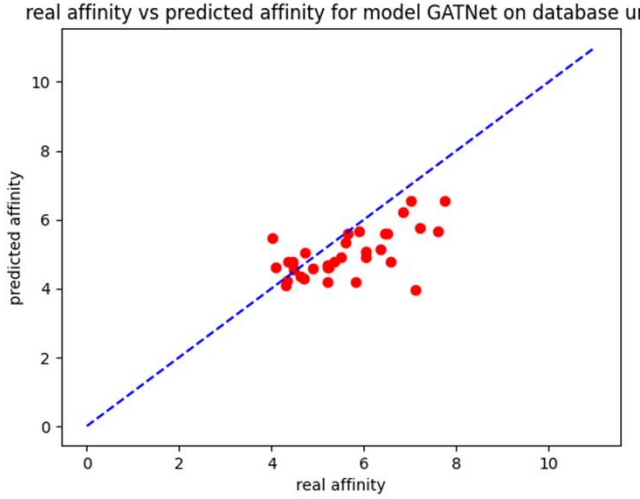


Results

- train and test GAT-based model with kiba dataset

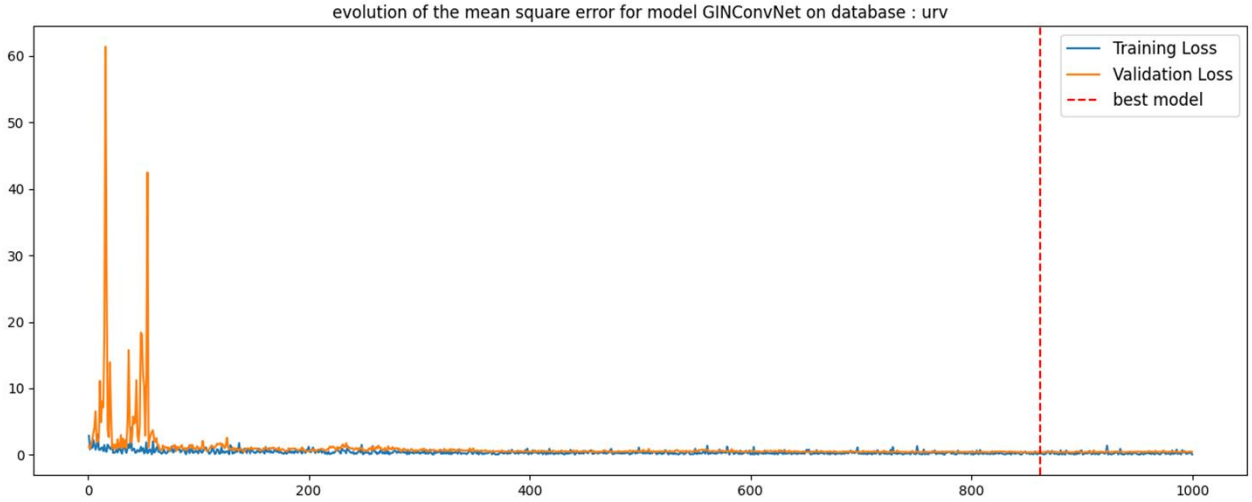


optimizer	ADAM
learning rate	0.0005
epochs	1000
train batch size	4
train size	208
validation size	90
validation percentage	30.0 %
MSE	0.50838196

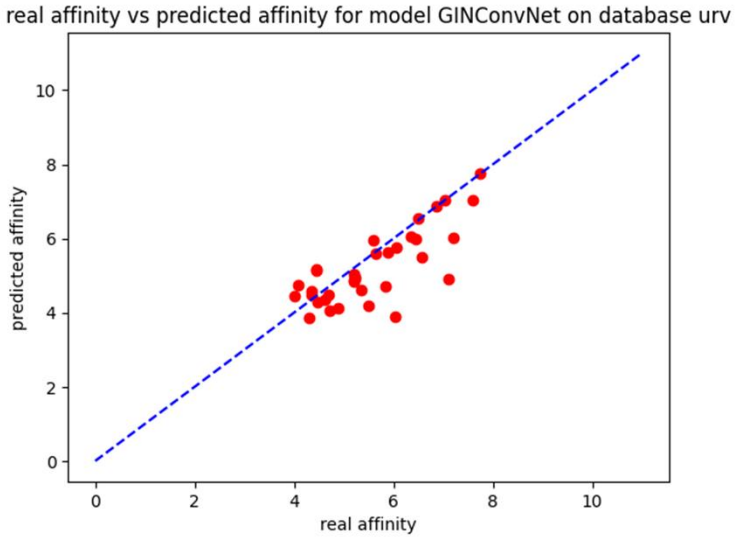


Results

- train and test GINCONV-based model with kiba



optimizer	ADAM
learning rate	0.0001
epochs	1000
train batch size	8
train size	238
validation size	60
validation percentage	20.0 %
MSE	0.3247614



Summary of results

model	dataset	MSE in paper	MSE obtained
GCN-based	davis	0.254	0.25
GATGCN-based	davis	0.245	0.27
GAT-based	davis	0.232	0.25
GINCONV-based	davis	0.229	0.24
GCN-based	kiba	0.179	0.2
GATGCN-based	kiba	0.147	0.15
GAT-based	kiba	0.139	0.2
GINCONV-based	kiba	0.139	0.17
GCN-based	URV	-	0.35
GATGCN-based	URV	-	0.51
GAT-based	URV	-	0.51
GINCONV-based	URV	-	0.32

Conclusion

- the sample size of the data including train and test sets is largest in kiba then davis followed by URV.
- kiba dataset has the best diversity specially for the target proteins as it integrates different bioactivity scores