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CNN-OSBO Encoder-Decoder Architecture for Drug-Target Interaction (DTI) Prediction of Covid-19 Targets

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***Abstract*—Drug Target Interaction (DTI) prediction is an important factor is drug discovery and repositioning (DDR) since it detects the response of a drug over a target protein. The Coronavirus disease 2019 (COVID-19) disease created groups of deadly pneumonia with clinical appearance mostly similar to SARS-CoV.The precise diagnosis of COVID-19 clinical outcome is more challenging, since the diseases has various forms with varying structures. So predicting the interactions between various drugs with the SARS-CoV target protein is very crucial need in these days, which may leads to discovery of new drugs for the deadly disease. Recently, Deep learning (DL) techniques have been applied by the researches for DTI prediction. Since CNN is one of the major DL models which has the ability to create predictive feature vectors or embeddings, CNN–OSBO encoder-decoder architecture for DTI prediction of Covid-19 targets has been designed Given the input drug and Covid-19 target pair of data, they are fed into the Convolution Neural Networks (CNN) with Opposition based Satin Bowerbird Optimizer (OSBO) encoder modules, separately. Here OSBO is utilized for regulating the hyper parameters (HPs) of CNN layers. Both the encoded data are then embedded to create a binding module. Finally the CNN Decoder module predicts the interaction of drugs over the Covid-19 targets by returning an affinity or interaction score. Experimental results state that DTI prediction using CNN+OSBO achieves better accuracy results when compared with the existing techniques.**

Keywords—Drug–Target Interactions (DTI), Covid-19, Encoder Decoder, Convolution Neural Networks (CNN),* Opposition based Satin Bowerbird Optimizer (*OSBO)

I. INTRODUCTION

DTI infer that medicines are associated to the drug by a specific reaction. Drugs consist of chemical substances that will affect our body in a natural way. The target may be any part of the living being which is related to the drug's biological effects. Discovery of new drugs for biological reasons is based on DTI predictions [1].

DTI prediction is an important factor in DDR since it detects the response of a drug over a target protein [2].In-vivo and in-vitro tests taken for DTI prediction are mostly very costly and involve huge delay before powerful medicines are discovered [3]. Hence computational techniques can be used in the present years. A finite number of ML algorithms have been proposed in the literature for DTI prediction such as SVM, Deep Learning (DL) [4]. Such ML methods use features created from molecular fingerprints of drugs and protein structures. Some of the recently proposed DL based techniques for DTI predictions are DeepDTI and GraphDTA [5] [6].

A. Problem Statement and Objectives

COVID-19 which was originated by a new corona virus has infiltrated all over the world since December 2019 [11]. This viral infection created groups of deadly pneumonia with clinical appearance mostly similar to SARS-CoV.The precise diagnosis of COVID-19 clinical outcome is more challenging, since the diseases have various forms with varying structures [12] [13].

So predicting the interactions between various drugs with the SARS-CoV target protein is very crucial need in these days, which may leads to discovery of new drugs for the deadly disease.

Present approaches usually consider minimal number of labeled data and omit the huge unlabelled data.

Hence the our main objectives are

- To design machine learning based algorithm for accurate prediction of drug interactions with the Covid-19 SARS virus.
- To establish the meaningful association among the extracted structures.

II. RELATED WORKS

The DTI prediction model of Heba El-Behery et al [1] utilizes the ability of architectures of proteins and drugs. This model extracts the features from proteins using their characteristics. It uses SMILES string from the drugs by

applying encoding methods. Experimental results show that the prediction is yield more accurate results than the existing methods.

Binary classifiers [2] were used to predict the reactions of the drugs. The ChEMBL database with 11 targets was used for classification. The SMILES strings were converted into binary fingerprints using Extended Connectivity Fingerprints 4 (ECFP4). The 11 drug components have been applied on 11 target proteins for interaction prediction. It was determined that the ML and DL methods yield better results on the ECFP4 data when compared to other molecular descriptors.

The FRnet-DTI classifier [4] has been developed for DTI prediction. The encode and predict CNN models are used to process and classify the features , respectively. The major factors for applying ML have been analyzed in [10]. The specific applications of these models have been summarized and the drawbacks are discussed.

III. PROPOSED METHODOLOGY

A. Overview

The CNN–OSBO encoder-decoder architecture for DTI prediction is depicted in Figure 1

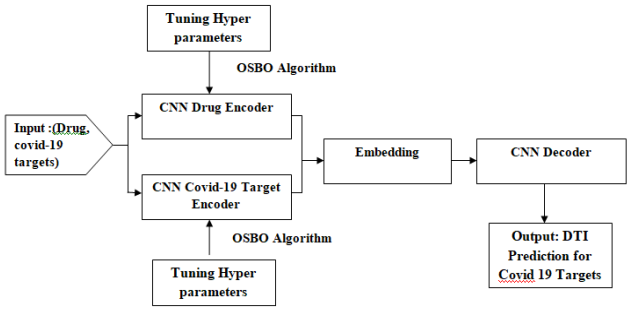

Figure 1 Architecture of CNN–OSBO

Given the input drug and covid-19 target pair of data, they are fed into the CNN+OSBO encoder modules, separately. Here OSBO algorithm is utilized regulating the HPs of CNN layers. Both the encoded data are then embedded to create a binding module. Finally the CNN Decoder module predicts the interaction of drugs over the Covid-19 targets by returning an affinity or interaction score.

B. CNN Encoder for Drugs and Targets

A CNN is a multi-layer 1D neural network with fixed convolutions and more layers. It uses a complex model for data management with faulty mode. CNN has lot of layers which aggregates the feature extraction and grouping method into a learning module. The CNNs proved to useful in diverse domains [7].

During encoding of drugs, the SMILES strings are initially encoded with an embedding layer and then handed over to the CNN convolutions. A global max pooling layer is then included and a latent vector representing the drug is produced.

During encoding of targets, the amino acid sequence is decoupled into separate characters and encoded with an embedding layer. They are then handed over to the CNN convolutions. Next a global max pooling layer is applied. Figure 2 shows the representation of drug and targets.

Ritonavir: C
C(C)C1=NC(=CS1)CN(C)C(=O)NC(C(C)C)C(=O)NC(CC2=CC=CC=C2)CC(C(CC3=CC=CC=C3)NC(=O)OCC4=CN=CS4)O

SARS-CoV2-3CL Protease:
SGFRKMAFPSGKVEGCMVQVTCGTTTLNGLWLDDVV
YCPRHVICTSEDMLNPNYEDLLIRKSNHNFLVQAGNVQ
LRVIGHSMQNCVLKLKVDTANPKTPKYKFVRIQPGQTF
SVLACYNGSPSGVYQCAMRPNFTIKGSFLNGSCGSVGF
NIDYDCVSFCYMHH
MELPTGVHAGTDLEGNFYGPFVDRQTAQAAGTDTTIT
VNVLAWLYAAVINGDRWFLNRFTTTLNDFNLVAMKY
NYEPLTQDHVDILGPLSAQTGIAVLDMCASLKELLQNG
MNGRTILGSALLEDEFTPFDVVRQCSGVTFQ

Figure 2 Representation of Drug and Targets

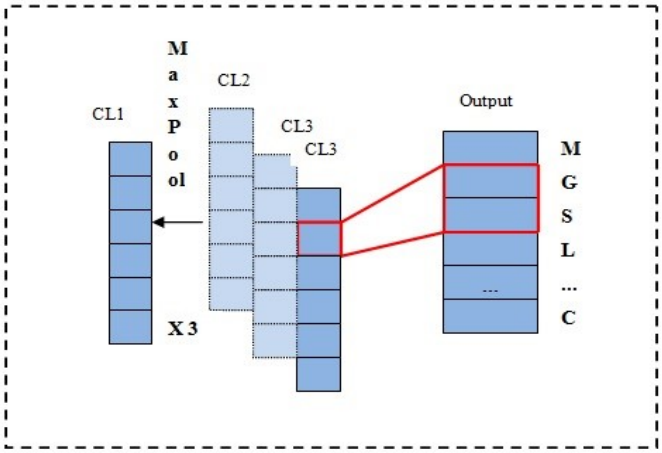

Figure 3 Architecture of CNN Encoder

CNN Parameters	
CL layers	= [1024,1024,512]
Drug filters	= [32,64,96]
Target filters	= [32,64,96]
Drug Kernels	= [4,6,8]
Target Kernels	= [4,8,12]
Learning Rate	= 0.001
Batch Size	= 256

In conventional training method of CNN, the parameters of convolution layer (CL) and Fully Connected Layer (FCL) are fine tuned using Stochastic Gradient Descent (SGD) method. SGD has many HPs which may influence the performance of the network [8].

In this work, Here OSBO algorithm is utilized regulating the HPs of CNN layers.

(i) HP tuning of CNN using OSBO Algorithm

This section describes the OSBO algorithm which is used to optimize the HPs of CNN:

The hyper parameters learning rate and regularization constant should be enhanced for a maximum number of epochs. Hence the fitness function is defined based on these parameters as

$$\text{Fitness}() = (\alpha.LR + \beta.E + \gamma.RC) \quad (1)$$

Where Learning rate (LR), number of epochs (E) and Regularization Coefficient (RC).

The OSBO is an effective algorithm, since it avoids the sorting process and enhances the computational efficiency.

The OSBO algorithm for HP optimization in SGD training is presented below:

(ii) OSBO Algorithm

Satin bowerbirds are fruitlet and insect-eating group of birds which exist in deep jungle and tropical forest in eastern Australia. Usually they reside at specific regions of forests. During winter season, they go away from their home jungle and shift into exposed forests to eat for fruitlet and pests. In any circumstance, with the advent of the spring propagation period they meet organized in tiny clusters, occupying terrains which they obviously include every year [9].

Masculine satin bowerbirds produce specific twig edifices, known as arbours, where wooing and coupling occur. Bowers are highlighted with floras, quills, berries etc. These improvements are necessary for in feminine choice and masculine coupling attainment. Men contest by captivating enhancements from diverse men and will abolish the bowers of adjoins. Masculine wooing conduct includes outline of improvements and poignant cabinets combined by flamboyant languages and women favour men that demonstrate at extraordinary strength. One more sign of robust voluptuous rivalry is that not each single adult man are fruitful at making, upholding and shielding bowers, and consequently, there is important unpredictability in masculine breeding attainment. In simple words, masculine bowerbirds appeal pals by emerging a bower, an edifice constructed from firewood and sticks, and beautifying the nearby zone. Women go and have a look at some bowers in advance for selecting a coupling companion and recurring to its bower.

In SBO procedure [11], adult men twitch to construct bower with numerous resources on their terrain in the midst of breeding period. They utilize a collection of things like floras, fruitlets, glittering substances, twigs and also theatrical signals that are all part of aspects to attract women. Ladies, because of the prettiness of the bower and theatrical signals of men gets fascinated to bower. Mark that masculine birds u use their usual character and mock of diverse men for constructing the bower. Depending on the values of the bird life, SBO procedure is prearranged in the following steps.

(a) Random Bower Generation

SBO algorithm starts with randomly generating an initial population. Actually, early inhabitants include a group of locations for bowers. Every location is considered as a N-D vector of strictures that need to be enhanced. The blend of parameters determines the prettiness of the bower.

Randomly generate initial solution by utilizing number of solution length 1 and range of solution from 0 to 5.

$$I_i = I_1, I_2, \ldots I_n \quad (2)$$

$$O\mathbf{i} = x + y - I\mathbf{i} \quad (3)$$

$I_i \epsilon I_1$, I_2, I_3 …. NP are randomly produced opposition based solutions, x and y are lower and upper bounds

(b) Probability Estimation

The probability indicates the prettiness of a bower, based on which a female bird chooses a built bower. In the same way, the male imitator bird chooses a bower based on the allotted probability, which is determined by Eq. (4).

$$prob_i = \frac{fit_i}{\sum_{n=1}^{NB} fit_n} \quad (4)$$

In this equation, NB is the No. of bowers, fit_i is fitness of i^{th} solution given by

$$fit_i = \begin{cases} \frac{1}{1+f(y_i)} & f(y_i) \geq 0 \\ 1+\left|f(y_i)\right| & f(y_i) < 0 \end{cases} \quad (5)$$

In Eq. (5), $f(y_i)$ is the fitness function (given in Eq.(1)) of i^{th} position or i^{th} bower.

Eq. (5) has two sections. The section 1 computes the final fitness for values ≥ 0, while the section2 computes the fitness for values < 0.

This Eqn has two basic qualities:

1. For $f(y_i)=0$, the fitness value becomes one, for both sections of Eq.(5)
2. Fitness is usually a +ve value.

(c) Elitism

It is one of the major properties of optimization algorithms. It permits the optimum solutions to be stored at each iteration of the algorithm. Each bird usually constructs its nest using natural objects. The male bird follows all other birdies in the breeding time and adjusts its normal behaviour to aggregate his bower and enhance it. The Elite indicates the position of the optimum bower has the maximum fitness. Hence it needs to have to choice to impact various positions.

(d) Determining Position Updates

In each cycle of the algorithm, the positions of each bower are updated by Eq. (6).

$$y_{ik}(new) = y_{ik}(old) + \lambda_k \left(\left(\frac{y_{jk} + y_{elite,k}}{2} \right) - y_{ik}(old) \right) \quad (6)$$

In Eq. (6), y_i is i^{th} vector and y_{ik} is its k^{th} member. y_j is the optimum solution from other solutions in the present iteration. The value j is determined based on the probabilities obtained from the positions. The solution with higher possibility will gain opportunity to be selected as y_j. y_{elite} is the Elite position, which is stored in each iteration of the algorithm.

λ_k fixes the attraction term in the objective bower and decides the measure which is determined for every factor.

(e) Mutation

During the ending of each iteration, random modifications are done to y_{ik} with a given probability. The mutation step is utilized with an average of y_{ik} and variance of σ^2, as shown in Eq. (7).

$$y_{ik}^{new} \sim N\left(y_{ik}^{old}, \sigma^2\right) \quad (7)$$

$$N\left(y_{ik}^{old}, \sigma^2\right) = y_{ik}^{old} + (\sigma * N(0,1)) \quad (8)$$

σ is determined as in Eq. (9):

$$\sigma = Z * \left(\text{var}_{max} - \text{var}_{min} \right) \quad (9)$$

where var_{max} and var_{min} are maximum and minimum bounds of variables, correspondingly. Z is the % of the difference between the maximum and minimum bounds.

(f) Integration of Old and Updated population

\During the termination of each iteration, the old population and the updated population are checked. Once checked., they are integrated together and the resulting population is arrived by the last marked number while the others are deleted.

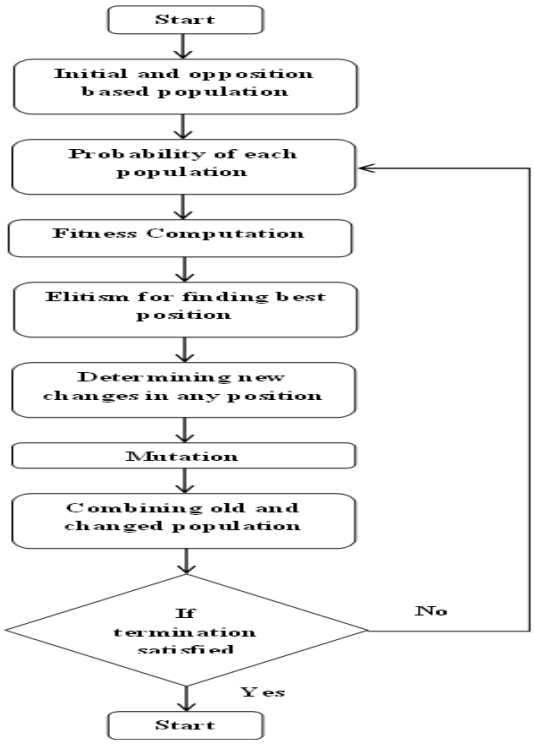

Figure 4 Flowchart for OSBO algorithm

(iii) Training Process of CNN+OSBO Encoder

The steps involved in the training process are listed below:

1) Load the benchmark dataset of <drug, target> pairs.
2) Invoke the CNN encoder for Drug and targets, separately.
3) Split the dataset into training, validation and testing sets,
4) Determine the optimal values of the hyper-parameters using OSBO algorithm.
5) Initialize the model using the configuration
6) Train the model using train function
7) Perform embedding of drug and target hidden features

C. Embedding

The content embedding $Cont_D$ and $Cont_T$ for each drug-target pair is generated using Learnable Lookup Dictionary (LLD) as

$$Cont_{iD} = MCont_D \cdot M_{iD}$$
$$Cont_{jT} = MCont_T \cdot M_{jT} \quad (10)$$

Where $MCont_D$ and $MCont_T$ are matrices of LLD and M_{iD} and M_{jT} represent the ith vector of drug and j^{th} vector of target.

The final embedding $BCont_D$ and $BCont_T$ are generated as

$$BCont_D = Cont_{iD} + Pos_{iD}$$
$$BCont_T = Cont_{jT} + Pos_{jT} \quad (11)$$

Where Pos_{iD} and Pos_{jT} are positional bindings determined from LLD.

D. CNN Decoderfor DTI Prediction

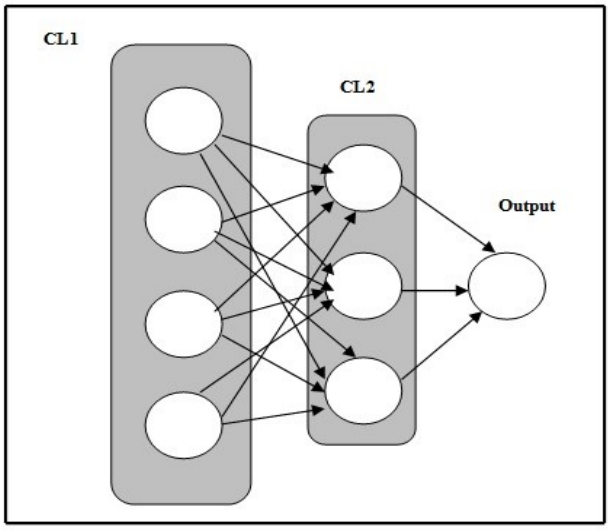

Figure 5 Architecture of CNN Decoder

Once the drug and targets are embedded together, they are given into the multi-layer CNN decoder. The DTI prediction yields two classes of results: The first one is the affinity or interaction score and the other one is a binary label which indicates **Yes** if they can bind or **No** if they could not bind. Figure 5 shows the architecture of CNN decoder.

For the similarity score estimation, it uses Mean Squared Error (MSE) loss and for binary interaction prediction, it uses Binary Cross Entropy (BCE) which are derived in the following equations:

$$MSE_{loss} = \frac{1}{n}\sum_{i=1}^{n}(y_i - y_i')^2 \quad (12)$$

$$BCE_{loss} = \frac{1}{n}\sum_{i=1}^{n} y_i \log(y_i') + (1 - y_i)\log(1 - y_i') \quad (13)$$

Where y_i and y_i' are the true and predicted labels, respectively, for the i^{th} drug-target pair.

IV. EXPERIMENTAL RESULTS

A. Specification of Dataset

The CNN-OSBO Encoder-Decoder architecture is implemented in the DeepPurpose toolkit of Python, which is a DL based tool for DTI prediction.

The BindingDB dataset was utilized in the experiments. The drug-target pairs are considered as input to the model where the drug (d) has form of molecular-input line-entry system

(SMILES) and the target has the form of Amino acid sequence. The output is the binding affinity of the drug-target pair. y is a binary value which indicates interaction result or is a real number which denotes the affinity value

B. Training and Prediction

```
Training on your own customized data...
in total: 26640 drug-target pairs
encoding drug...
unique drugs: 13763
drug encoding finished...
encoding protein...
unique target sequence: 1
protein encoding finished...
splitting dataset...
Done.
Training from scrtach...
Begin to train model 0 with drug encoding MPNN and target encoding CNN
Let's use 1 GPU!
--- Data Preparation ---
--- Go for Training ---
Training at Epoch 1 iteration 0 with loss 0.69219. Total time 0.00055 hours
Training at Epoch 1 iteration 100 with loss 0.67406. Total time 0.01333 hours
Validation at Epoch 1 , AUROC: 0.70764 , AUPRC: 0.08025 , F1: 0.09424
Training at Epoch 2 iteration 0 with loss 0.62362. Total time 0.02305 hours
Training at Epoch 2 iteration 100 with loss 0.52807. Total time 0.03611 hours
Validation at Epoch 2 , AUROC: 0.72531 , AUPRC: 0.16038 , F1: 0.10389
Training at Epoch 3 iteration 0 with loss 0.47976. Total time 0.04583 hours
Training at Epoch 3 iteration 100 with loss 0.46717. Total time 0.05861 hours
Validation at Epoch 3 , AUROC: 0.73128 , AUPRC: 0.16780 , F1: 0.13793
Training at Epoch 4 iteration 0 with loss 0.47900. Total time 0.06833 hours
Training at Epoch 4 iteration 100 with loss 0.40212. Total time 0.08138 hours
Validation at Epoch 4 , AUROC: 0.73826 , AUPRC: 0.19690 , F1: 0.12826
Training at Epoch 5 iteration 0 with loss 0.40222. Total time 0.09111 hours
Training at Epoch 5 iteration 100 with loss 0.23715. Total time 0.10416 hours
```

```
Training at Epoch 10 iteration 0 with loss 0.17836. Total time 0.20416 hours
Training at Epoch 10 iteration 100 with loss 0.08284. Total time 0.21722 hours
Validation at Epoch 10 , AUROC: 0.72196 , AUPRC: 0.20493 , F1: 0.25490
--- Go for Testing ---
Testing AUROC: 0.794694459119799 , AUPRC: 0.29236629647158663 , F1: 0.30630630630630634
--- Training Finished ---
model training finished, now repurposing
repurposing...
in total: 82 drug-target pairs
encoding drug...
unique drugs: 81
drug encoding finished...
encoding protein...
unique target sequence: 1
protein encoding finished...
Done.
predicting...
--------------
```

Figure 6 Output of training process

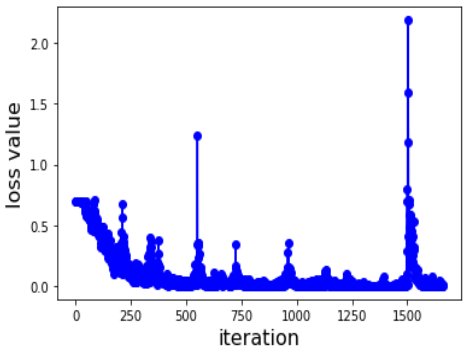

Figure 7 Training and Validation graph

The dataset is split as 70% and 30% for training and testing, respectively.

The training time taken by the proposed CNN-OSBO algorithm is 2.5 seconds.

C. Prediction Results of CNN-OSBO

A set of DT pairs from the dataset that contain high binding attraction are illustrated in Figure 8:

Rank	Drug Name	Target Name	Interaction	Probability
1	Efavirenz	SARS-CoV 3CL Protease	YES	0.57
2	Remdesivir	SARS-CoV 3CL Protease	NO	0.23
3	Zanamivir	SARS-CoV 3CL Protease	NO	0.20
4	Letermovir	SARS-CoV 3CL Protease	NO	0.13
5	Podophyllotoxin	SARS-CoV 3CL Protease	NO	0.11
6	Methisazone	SARS-CoV 3CL Protease	NO	0.06
7	Tipranavir	SARS-CoV 3CL Protease	NO	0.02
8	Atazanavir	SARS-CoV 3CL Protease	NO	0.01
9	Elvitegravir	SARS-CoV 3CL Protease	NO	0.01
10	Loviride	SARS-CoV 3CL Protease	NO	0.01
11	Baloxavir	SARS-CoV 3CL Protease	NO	0.01
12	Enfuvirtide	SARS-CoV 3CL Protease	NO	0.00
13	Nitazoxanide	SARS-CoV 3CL Protease	NO	0.00
14	Indinavir	SARS-CoV 3CL Protease	NO	0.00
15	Darunavir	SARS-CoV 3CL Protease	NO	0.00
16	Dolutegravir	SARS-CoV 3CL Protease	NO	0.00
17	Amprenavir	SARS-CoV 3CL Protease	NO	0.00
18	Pyrimidine	SARS-CoV 3CL Protease	NO	0.00
19	Doravirine	SARS-CoV 3CL Protease	NO	0.00
20	Vicriviroc	SARS-CoV 3CL Protease	NO	0.00
21	Foscarnet	SARS-CoV 3CL Protease	NO	0.00
22	Fosamprenavir	SARS-CoV 3CL Protease	NO	0.00
23	Delavirdine	SARS-CoV 3CL Protease	NO	0.00
24	Pleconaril	SARS-CoV 3CL Protease	NO	0.00

Figure 8Results of BindingDB dataset

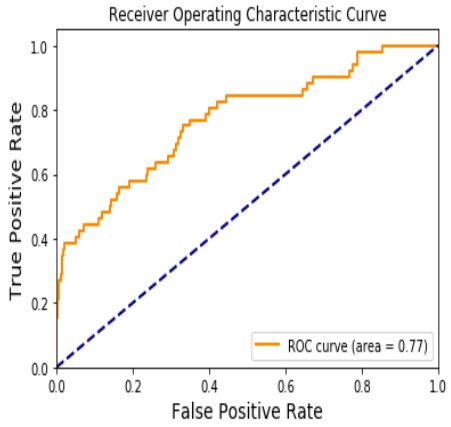

Figure 9 False and True Positive curves for Transformer-CNN-OSBO. The blue line corresponds to the correct predictions.

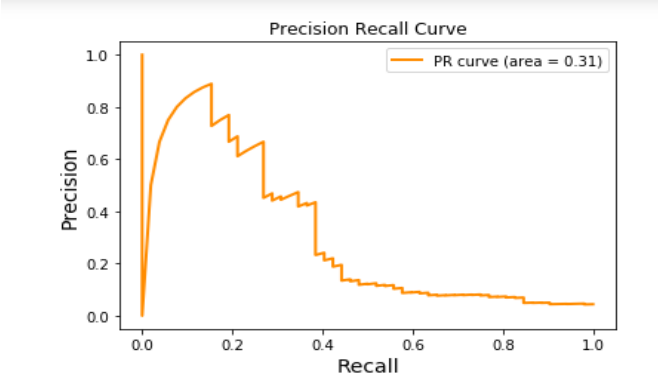

Figure 10 Precision and Recall curves for Transformer-CNN-OSBO

D. Comparison with Other algorithms

The performance of CNN-OSBO is analyzed through Transformer CNN, MPNN-CNN techniques. The performance metrics accuracy, precision, recall and F1-Score are measured.

Table 1 Performance Comparison with other algorithms

Metrics	CNN+OSBO	Transformer + CNN	MPNN+CNN
Recall	0.92	0.91	0.89
Precision	0.46	0.43	0.41
Accuracy	0.87	0.81	0.79
F1 score	0.65	0.60	0.59

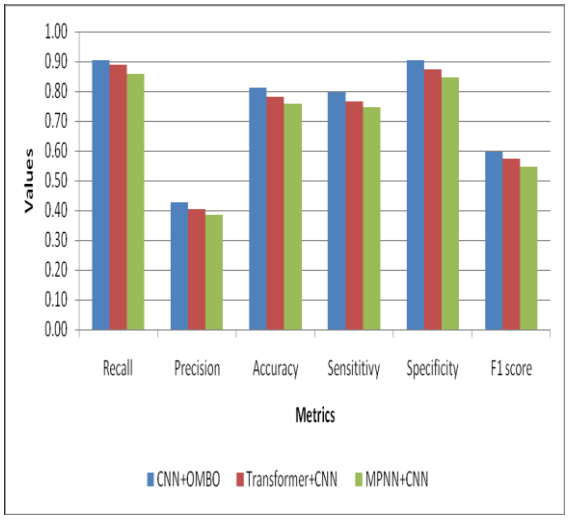

Figure 11 Performance comparison of CNN+OSBO

V. CONCLUSION

ACNN+OSBO encoder-decoder architecture for DTI prediction is designed for Covid-19 targets. Given the input drug and Covid-19 target pair of data, they are fed into the CNN with OSBO encoder modules, separately. Here OSBO algorithm is utilized for regulating the HPs of CNN. Both the encoded data are then embedded to create a binding module. Finally the CNN Decoder module predicts the interaction of drugs over the Covid-19 targets by returning an affinity or interaction score. From the performance results, it has been shown that the CNN-OSBO architecture has higher accuracy metrics over the existing models.

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