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A geometric deep learning model for display and prediction of potential drug-virus interactions against SARS-CoV-2

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ABSTRACT

Although the coronavirus epidemic spread rapidly with the Omicron variant, it lost its lethality rate with the effect of vaccine and immunity. The hospitalization and intense demand decreased. However, there is no definite information about when this disease will end or how dangerous the different variants could be. In addition, it is not possible to end the risk of variants that will continue to circulate among animals in nature. After this stage, drug-virus interactions should be examined in order to be able to prepare against possible new types of viruses and variants and to rapidly-produce drugs or vaccines against possible viruses. Despite experimental methods that are expensive, laborious, and time-consuming, geometric deep learning(GDL) is an alternative method that can be used to make this process faster and cheaper. In this study, we propose a new model based on geometric deep learning for the prediction of drug-virus interaction against COVID-19. First, we use the antiviral drug data in the SMILES molecular structure representation to generate too many features and better describe the structure of chemical species. Then the data is converted into a molecular representation and then into a graphical structure that the GDL model can understand. The node feature vectors are transferred to a different space with the Message Passing Neural Network (MPNN) for the training process to take place. We develop a geometric neural network architecture where the graph embedding values are passed through the fully connected layer and the prediction is actualized. The results indicate that the proposed method outperforms existing methods with 97% accuracy in predicting drug-virus interactions.

1. Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV2), which has become a growing pandemic and a global problem, continues to show its effect on the whole world. Since over 433 million cases and over 5.9 million deaths have been reported until March 2022, it is emergent to discover efficient treatment options to prevent coronavirus. SARS-CoV-2 is a virus with different mutations, and besides it does not have a specific drug, treatment algorithms change over time [1]. Developing a new vaccine and antiviral drug in a short time may not be realistic and may not be effective against different mutations of the virus. SARS-CoV-2 is a single-stranded Ribonükleik asid (RNA) virus. The virus follows cell membrane fusion and infects the cell by binding to the ACE II receptor. In order to replicate, the virus hijacks the host cell machinery and infects nearby cells. Now the coronavirus multiplies in the body and causes damage and destruction in the lung and other organs. Understanding the chemical mechanism of SARS-CoV-2 can help identify virus-drug interaction and discover a potential treatment [2].

Remdesivir, favipiravir, ribavirin, lopinavir, ritonavir, hydroxychloroquine chloroquine etc. drug treatments are recommended by health authorities. In addition, all these drugs have many clinically different potential drug-drug interactions. During the pandemic, which is expected to continue for a long time, it is thought that it is important for scientists to have knowledge of the current literature in planning drug treatments, discovering drugs affecting the virus, and determining drug-drug interactions. For this, in this study, the mechanisms of action of hydroxychloroquine, favipiravir, remdesivir, oseltamivir, azithromycin, tocilizumab and similar drugs used in the treatment of Coronavirus disease (COVID-19) on the virus and virus-drug interactions are discussed [3,4]. Geometric deep learning, a very popular method recently, is used to predict virus-drug interactions and to show relationships visually. Because of the 3-dimensional structure of RNA molecules and their critical role in drug discovery, it is difficult to predict them computationally. With geometric deep learning, which effectively learns from even a small amount of data, it is possible to predict the protein structure and drug interaction of the virus and...
visualize the virus-drug relationship [5]. Geometric deep learning (GDL) pushes classical methods into the background in problems such as structure prediction for mRNAs and proteins. GDL increases the performance of the model by increasing the depth with its 3-dimensional molecular structure in drug interaction and drug discovery.

Recently, studies on COVID-19 and drug interaction have been continuing intensively. For this purpose, while experimental studies continue in clinical and laboratory environments, machine learning and deep learning methods have also started to be used frequently in bioinformatics studies. However, studies on the use of geometric deep learning method in drug-virus interaction are very limited in the literature. For this reason, this study proposes a message passing neural network-based (MPNN) model to discover the genomic basis and mechanisms of drug-target interaction for SARS-CoV-2. Thus, this study will contribute to the determination of all drugs related to COVID-19 or other disease viruses and to studies on new drug discoveries.

1.1. Research issues and motivation

There are various methods such as machine learning, deep learning, graph neural networks, similarity-based methods and computational methods applied to extract antiviral drugs against COVID-19. However, these methods either require a very expensive and time-consuming laboratory environment or are insufficient to identify drug interactions affecting the virus. In fact, there is still no proven effective drug targeting SARS-CoV-2. The biggest difference of this study from other studies in the literature is that the MPNN model shows low cost and high accuracy compared to existing methods in determining drug-virus interaction without the need for a laboratory environment. With the proposed MPNN model, visual motifs will be presented for a better understanding of the mechanism of drug-virus interaction, and drugs that directly affect the virus will be revealed together with their effect rates.

1.2. Main contributions

In summary, our main contributions are as follows:

- We handle the task of predicting drug-virus interaction from a network perspective and design a geometric deep learning based on message passing neural network to identify potential drugs against COVID-19.
- In order to predict the interaction between drugs and target proteins in human cells, we not only show the virus-drug interaction with geometric deep learning but also show how the drugs that affect the virus affect the virus.
- To the best of our knowledge, we are the first to use a MPNN model to detect and visually model all drugs that interact with the ACE2 protein, along with their efficacy rates.
- We test the proposed geometric deep learning model, and the experimental results show that the proposed model achieves state-of-the-art new results with substantial improvements in identifying drug targets over other models.

The paper is organized as follows. In the next section, the related works is introduced. In Section 3, we introduce the materials and methods for MPNN model. The experiment results and discussion are provided in Section 4 and Section 5 concludes this paper.

1.3. Novelty

In this section, the novelty in the proposed MPNN model to identify drug-virus interaction against COVID-19 is stated through the following points: (i) Different from the existing methods in the literature, this paper comes across as the optimum integration of methods such as graph neural networks, computational methods, and machine learning methods. (ii) We do not agree to directly use any past model to determine drug-virus interaction for coronavirus. Instead, we create a special version of these techniques and use geometric deep learning, which includes message passing neural networks, for the first time in this field. (iii) Compared to the existing works, the interaction potential of the drug molecule with the COVID-19 virus is measured in this paper using MPNN and a geometric deep learning structure with a fully connected layer.

2. Related works

Recently, many methods have been introduced to predict drug-virus combinations for SARS-CoV-2 throughout the pandemic. These methods are grouped as wet laboratory experiments [6], computational methods [7-9] and chemogenomic methods [10-12]. Laboratory experiments to predict targeted drug interactions require a long time and cost. Computational methods are divided into 3 groups such as ligand methods, insertion methods, and chemogenomic methods. Ligand methods predict the relationships of similar molecules with similar proteins. The biggest disadvantage of this method is that it makes a calculation that increases with the size of the training set, extending the training time considerably [7,12]. Docking methods are incomplete in finding the interaction of three-dimensional proteins such as membrane proteins with drugs [9]. Chemogenomic approaches can overcome the shortcomings of existing ligand and docking methods. They predict target drug interactions using biological data such as large-scale drug and protein omics data from databases [12]. Chemogenomic approaches also include different methods such as machine learning, deep learning, graph methods, and network methods. Among all methods, methods based on deep learning or machine learning are less costly and produce more reliable predictive results [7,12]. Geometric deep learning, based on neural network architectures that contain and process symmetry information, has recently become very popular in molecular biology and genomics studies. GDL, which is based on different symmetry properties and different levels of abstraction, holds promise for applications in DNA, RNA, protein-drug association, drug discovery, and molecular modeling [13,14].

In this section, for a more accurate comparison, studies with deep learning and machine learning were explained. Artificial intelligence-based research plays a very active role in drug-protein discovery for against the COVID-19 in epidemic. Beck et al. [15] proposed a deep learning-based method to identify drugs that predict drug-coronavirus protein interaction. In Ref. [16], Shin et al. conducted a training for drug-target interaction prediction on a sample group containing drug SMILES sequences and amino acid sequences with a deep learning model. In Ref. [17], a deep learning model for predicting drugs was applied to combat SARS-CoV-2. They used current drugs with the influenza virus and approved protease inhibitors to train the model. As a result, they created a model that could identify drugs effective against the coronavirus. Table 1 summarizes studies based on deep learning and machine learning methods and their performance to predict drug-virus interactions in the literature. Based on the methods used in the studies in the literature, in this study, we propose for the first time a geometric deep learning approach to extract new virus-drug associations to identify promising drug candidates against SARS-CoV-2.

3. Materials and methods

In this section, we present the steps of our MPNN model in the prediction of drug-virus interaction against COVID-19 were presented in detail. The proposed model involves 3 steps: (i) dataset collection and preprocessing, (ii) training, and (iii) prediction to potential drug-virus interaction for COVID-19. Fig. 1 shows the flow diagram of the proposed MPNN model.
works on include small molecules and peptides. To simplify the physico-chemical properties that aid absorption, specificity, and low toxicity that are easily produced and processed in the laboratory, in addition to the data format is that the SMILES data format has properties that allow it to represent the sequence and structure of small molecules and peptides, the SMILES format is preferred with the chemical properties. Each node on the graph has its own feature (atomic degree, formal charge, radical electron number, is_in_ring, chirality, valence electrons, the number of n hydrogens, the hybridization state, GDP model are the atomic number of the molecule, the number of interatomic bonds as the edges of this graph. The different types of bonds in the compound have been specifically covered. Fig. 2 shows the transition to molecular representation and graph representation of the drug named Oxaloacetate Ion in SMILES format from the positive sample group.

3.2. Training

The second step of our proposed geometric deep learning-based model to identify new virus-drug relationships for COVID-19 is training. The training step of the proposed model consists of 2 parts. The first part is the Message Passing Neural Network (MPNN) and the second part is the Fully Connected Network (FCN).

3.2.1. Message passing neural network

Message Passing Neural Networks (MPNN) is a type of neural network model designed to work on graphs that predict the quantum properties of an organic molecule. MPNN helps to convert the information on the graph data structure into a vector, this vector is called graph embedding. The embedding vector is updated according to the messages from other nodes on the graph. With MPNN, node feature vectors are transferred to a different space. The properties we use in the GDP model are the atomic number of the molecule, the number of valence electrons, the number of n hydrogens, the hybridization state, atomic degree, formal charge, radical electron number, is_in_ring, chirality, bond type and conjugated state. The MPNN model takes as input the node features (xv) and bond features (euv) of the models. The model has two phases such as the message passing phase and the reading phase. In the message transition phase, t represents the time steps. Also, while message functions are defined as mt, vertex update functions are defined in ut. MPNN framework has 3 formula on graphs [29]. Equation (1) shows the message obtained from neighboring nodes.

\[ m_{v(t)}^{i+1} = \sum_{e \in \text{edge}} m_{e}^{t} \]  

\[ m_{e}^{t} = \frac{1}{2} (m_{v}^{t-1} + m_{v}^{t}) \]  

\[ m_{v}^{t+1} = U_{v}(h_{v}^{t}, m_{v}^{t+1}) \]  

The hidden state of the vt node is obtained by updating the old hidden state with the newly obtained \( Mv \) vector. The update function of ut indicates an average between the previous hidden state and the message. This message passing algorithm is repeated a certain number of times and finally the reading stage is reached in Equation (3).

\[ \hat{y} = R \left( \{ h_{v}^{t+1} \} | \text{edge} \right) \]  

In the final step, all newly updated latent states are extracted and a final feature vector describing the entire graph is generated. It is used in GRU (Gated Recurrent Unit) in the MPNN structure used in the message passing stage. GRU simply updates an embedding vector based on the previous values of that embedding vector. GRU finds an optimal path in graph. The updated function of message passing is shown in Equation (4) [30].

\[ U_{v} = \text{GRU} \left( h_{v}^{t}, m_{v}^{t+1} \right) \]  

Briefly, the message passing neural network stage puts related data on the graph close to each other in a different space. The more similar the graph data (nodes) are, the closer they are to each other in the embedding space.

| Reference | Dataset | Method | AUC/ACC (Area Under Curve/Accuracy) |
|-----------|---------|--------|----------------------------------|
| El-Behery et al. [18] | DrugBank database | Machine learning methods (SVM, RF) Deep learning methods (CNN, ANN) Ensemble methods (Light-Boost, Extra-tree) | ACC = 0.98 |
| Wang et al. [19] | Matador database | Similarity method, DrugBank database | ACC = 0.82 |
| Beephi et al. [20] | Deep learning ensemble approach | ACC = 0.8897 |
| Ban et al. [21] | Benchmark dataset | Similarity matrices and NRLMF score | ACC = 0.8571 |
| Su et al. [22] | DrugBank database | SAN: Sequence combined attentive network embedding model | ACC = 0.8198 |
| Monterio et al. [23] | DrugBank database | Lasso model and DNN | ACC = 0.89 |
| Long et al. [24] | DrugVirus and MDAD database | HGATDVA framework | ACC = 0.8895 |
| Chen et al. [25] | Benchmark database | Cluster sampling, ENSFEE, XG Boost classifier | ACC = 0.91 |
| MingWen et al. [26] | DrugBank database | RDKit tools, DBN technique | ACC = 0.86 |
3.2.2. Fully connected network

In the study, it is not enough just to position the information on the node close to the embedding space because as the output of the study, whether or not a whole graph is an interaction molecule on the COVID-19 virus is examined. In this case, a graph embedding is obtained starting from the node embeddings on a molecule, and after obtaining the node embedding vectors with the message passing step, a graph embedding is obtained by average pooling on the nodes. Then, this graph embedding value obtained is passed through the fully connected layer and the prediction is actualized. Also, graph embedding vector has exchange invariance. In the fully connected layer stage, as seen in Fig. 3, three dense layers were used and the dropout value of the first two layers was determined as 20% to prevent overfitting. In the fully connected network part, there are 72 neurons in the first Dense layer. There are 36 neurons in the 2nd Dense layer and 1 neuron as output in the last layer. Fig. 3 shows the architecture used in the fully connected network part.

3.3. Prediction

The last step of our proposed geometric deep learning-based model to predict virus-drug relationships with COVID-19 is training. At this stage, quantitative estimates of drug-likeness (QED) are used to evaluate drug-virus interactions. QED is an index that was proposed in 2012 and shows the range of [0–1] by modeling drug-virus interaction using available information. This index is used in computational methods in small molecule drug discovery, in demonstrating drug-virus interactions, and in evaluating similarity features with existing drugs [31]. Fig. 4 shows the predicted possibilities of interaction between COVID-19 and drugs at the end of the proposed model.

The presented geometric deep learning model is shown in Algorithm 1.

**Algorithm 1.** The algorithm of the proposed geometric deep learning model

| Procedure: | The geometric deep learning model |
|---|---|
| **Input:** | Drugs in SMILES format |
| **Output:** | Quantitative estimate of drug-likeness |
| **Step 1:** | Upload the Drug dataset in csv format |
| **Step 2:** | Perform the passing of the data in Smiles format to the rdkit molecule object to easily use the data on the node and edge. |
| **Step 3:** | Perform the passing from rdkit molecule objects to graph structured data |
| **Step 4:** | Perform the train test split |
| **Step 5:** | Batch the data |
| **Step 6:** | Perform the Message Passing part |
| **Step 7:** | Perform the Readout |
| **Step 8:** | Perform the Fully connected network part |
| **Step 9:** | Estimate the potential for a molecule to become a drug on a scale of [0–1]. |
| **Step 10:** | Evaluate performance of the model with performance metrics and ROC-curves |
4. Experimental results and discussion

In this study, 5-fold cross validation was used on the dataset to verify the effectiveness of our proposed MPNN model in predicting drug-virus interaction for COVID-19. From the positive and negative data sample, drug-virus relationship pairs were randomly divided into five groups. 80% of the dataset was used for training, 10% was used for validation and 10% for testing. For each fold, the group of positive samples that interacted with the virus for training, as well as the group of drugs that did not interact with the virus, known as negative samples, were randomly sampled in equal size. Similarly, the number of samples of negative samples were selected along with the positive samples for testing. All the codes and data set of the experiment in the study have been uploaded to the Github service. It could be accessed with [link]. The AUC performance of the GDL model as the average of 5-fold cross validation is 97.31%. The area under the curve (AUC) is calculated based on ROC curve for proposed GDL model to describe the quality of the study, which provides more accurate visual interpretation for the prediction of the drug-virus interaction for coronavirus. Fig. 5 show the ROC curve of the proposed MPNN model.

Fig. 6 shows the performance curve for Accuracy and Fig. 7 shows the performance curve for F1-score.

4.1. Baseline methods based on graphs for drug-virus interaction

Prediction of drug-virus interaction is a new and very important issue and some methods based on deep graph networks and computational have been developed for this important task. Thus, we compare our proposed GDL model with other existing models in the literature. Baseline methods based on deep graphs are introduced as follows:

- HGATMDA [32]: is a heterogeneous graph attention network-based model to identify drug-virus association.
- HMDAKATZ [33]: is a KATZ measure-based model to identify drug-virus association.
- GCNMDA [34]: is a novel graph convolutional network-based model to predict drug-microbe association.
- WMGHMDA [35]: is a meta graph-based model to identify drug-target interaction.
- WNN-GIP [36]: is a weighted nearest neighbor-Gaussian based model to predict drug-virus association.
- NTSHMDA [37]: is a random walk-based model by integrating network topological similarity to predict drug-microbe associations.
- GCMDAR [38]: is a graph convolutional network-based model to predict drug-virus associations.
- IMCMDA [39]: is an inductive matrix completion-based model to predict disease-mRNA associations.
- SANE [40]: is a sequence attentive network embedding model to predict virus-drug interaction.
- LASSO-DNN [41]: is a least absolute shrinkage and selection operator and deep neural network-based model to predict drug-virus interaction.

Table 2 shows the results that our proposed MPNN model outperformed the 10 baseline methods by 97.31% in terms of AUC. In particular, our proposed GDL model achieves 7.7% higher AUC performance than the second-best method SANE and LASSO-DNN. The HGATMDA model shows the third highest performance with 88.95%
Fig. 4. The quantitative estimates of drug-virus interaction.

Fig. 5. The result of the MPNN model for the ROC curve.

Fig. 6. The accuracy performance of the MPNN model.
compared to other models. We can see from the table that the IMCMDA model shows the lowest performance. The reason why our proposed model is superior to other graph and computational basic methods is that we continuously express coded molecular information in multidimensional and train the neural network with thousands of molecular information. Representing molecules in a continuous format mathematically provides convenience in determining drug-virus interactions. In addition, the reason for the high performance of the MPNN model is that it models the bond structures to be formed according to chemical properties such as atomic number, valence electron number, hydrogen number of drugs, and virus molecules. In short, it reflects very well that it models the bond structures to be formed according to chemical properties.

Finally, our model allows us to more accurately capture semantic information between nodes and edges in the neural network, thus helping to improve the predictive ability of our model.

5. Conclusion

In this study, we aimed to propose an effective MPNN model for rapid identification of candidate drugs to fight against COVID-19 infections. Our model integrated the antiviral drug in SMILES format into message passing neural networks and fully connected layer to infer virus-drug associations are some of the limitations of the proposed MPNN model.

Table 2
The comparison of the proposed model with others.

| Model type          | Model name      | AUC  |
|---------------------|-----------------|------|
| Graph neural network| HGATDVA         | 0.8895 |
| Computational model | HMDAKATZ        | 0.7750 |
| Graph neural network| GCNMDA          | 0.8685 |
| Computational model | WMGHMDA         | 0.7337 |
| Graph neural network| WNN-GNP         | 0.8002 |
| Computational model | NTSHMDA         | 0.7680 |
| Graph neural network| GCMDR           | 0.8485 |
| Computational model | IMCMDA          | 0.6235 |
| Graph neural network| SANE            | 0.8961 |
| Geometric deep learning | LASSO-DNN     | 0.8900 |
| Geometric deep learning | MPNN           | 0.9731 |

Credit author statement

Bhuter Das: Conceptualization, Methodology, Writing- Original draft preparation, Validation, Mucahit Kutsal: Software, Data collection, Coding, Resul Das: Visualization, Investigation, Writing- Reviewing and Editing, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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