

Repurposing Therapeutics for COVID-19: Rapid Prediction of Commercially available drugs through Machine Learning and Docking

Sovesh Mohapatra¹, Prathul Nath,¹ Manisha Chatterjee,^{3,*,+} Neeladrisingha Das,⁴ Deepjyoti Kalita,⁵ Partha Roy,⁴ Soumitra Satapathi^{1,2,*,+}

¹*Department of Physics, Indian Institute of Technology, Roorkee, Haridwar, 247667, Uttarakhand, India*

²*Centre of Nanotechnology, Indian Institute of Technology, Roorkee, Haridwar, 247667, Uttarakhand, India*

³*Department of Pharmacology, Subharti Medical College Meerut, Uttar Pradesh, 250002, India*

⁴*Department of Biotechnology, Indian Institute of Technology, Roorkee, Roorkee, 247667, Uttarakhand, India*

⁵*Department of Microbiology, All India Institute of Medical Science Rishikesh, 249203, Uttarakhand, India*

ABSTRACT

The outbreak of the novel coronavirus disease COVID-19, caused by the SARS-CoV-2 virus has spread rapidly around the globe during the past 3 months. As the virus infected cases and mortality rate of this disease is increasing exponentially, scientists and researchers all over the world are relentlessly working to understand this new virus along with possible treatment regimens by discovering active therapeutic agents and vaccines. So, there is an urgent requirement of new and effective medications that can treat the disease caused by SARS-CoV-2. The research includes the study of drugs that are already available in the market and being used for other diseases to accelerate clinical recovery, in other words repurposing of existing drugs. The vast complexity in drug design and protocols regarding clinical trials often prohibit developing various new drug combinations for this epidemic disease in a limited time. Recently, remarkable improvements in computational power coupled with advancements in Machine Learning (ML) technology have been utilized to revolutionize the drug development process. Consequently, a detailed study using ML for the repurposing of therapeutic agents is urgently required. Here, we report the ML model based on the Naïve Bayes algorithm, which has an accuracy of around 73% to predict the drugs that could be used for the treatment of COVID-19. Our study predicts around ten FDA approved commercial drugs that can be used for repurposing. Among all, we suggest that the antiretroviral drug Saquinavir (DrugBank ID – DB01232) would probably be one of the most effective drugs based on the selected criterions. Our study can help clinical scientists in being more selective in identifying and testing the therapeutic agents for COVID-19 treatment. The ML based approach for drug discovery as reported here can be a futuristic smart drug designing strategy for community applications.

Keywords: COVID-19, SARS-CoV-2, Machine Learning, Repurposing, Digital Medicine, Drug Discovery, Pharmaceutics

*Corresponding Author- ssphf.fph@iitr.ac.in; manishachaterjee1988@gmail.com

+ Joint Corresponding Author

Introduction

The recent outbreak of novel coronavirus disease (COVID-19) is now considered to be a pandemic threat to the global population¹⁻³. Coronaviruses belong to a family of viruses mainly found in animals but with the recent outbreak, they have transmitted to humans. The new coronavirus, 2019-nCoV is termed as severe acute respiratory syndrome-related coronavirus SARS-CoV-2⁴⁻⁹ which has now affected more than 200 countries with over 12,18,991 cases confirmed and 65,878 deaths reported all over the world [as on 05 April 2020]. This could potentially bring major challenges to global healthcare and disastrous effect on the global economy if the virus is not contained within a few months¹⁰. The common symptoms include cough, fever, shortness of breath, fatigue etc which makes it confusing for the patients to differentiate the symptoms with that of the typical cold and flu¹⁰⁻¹³. Reports suggest that the virus is transmitted through body fluids of the infected patients, especially when in contact and while sneezing even though exact reasons are not known. Unfortunately, no drugs have been approved by regulatory agencies to treat SARS-CoV-2 infection until now. Efforts are ongoing on war footing to find the effective drug and vaccine to treat this pandemic.

Coronaviruses are classified into four classes designated as alpha, beta, gamma, and delta¹⁴. The betacoronavirus class includes severe acute respiratory syndrome virus (SARS-CoV), Middle East respiratory syndrome virus (MERS-CoV), and the COVID-19 virus (SARS-CoV-2). Coronaviruses are found to be considerably large viruses with a single-stranded positive-sense RNA genome encapsulated inside a membrane envelope having proteins appearing like spikes protruding from their surface. These spikes adhere onto human cells, through certain receptors on target cells, after which undergoes a structural change that lets the viral membrane fuse with the cell membrane. The viral genes then enter the host cell, producing more viruses. Recent studies show that, like the virus responsible for 2002 SARS outbreak, SARS-CoV-2 spikes also bind to receptors on the human cell surface called angiotensin-converting enzyme 2 (ACE2)¹⁵. Like SARS-CoV and MERS-CoV, SARS-CoV-2 also attacks the lower respiratory system causing viral pneumonia. However, there are also reports that it could affect the gastrointestinal system, heart, kidney, liver, and central nervous system resulting in multiple organ failure¹⁶. Compiling the medical reports and data available from the patients, SARSCoV-2 is found to be more transmissible/contagious than SARS-CoV¹⁷.

Rapid development of computer aided technology like ML based on Artificial Intelligence (AI) can help accelerate the drug development process for different diseases¹⁸⁻²⁰. The advantage of AI approaches like ML is that they can be applied to learn from examples and build predictive models even when our understanding of the underlying biological processes is limited, or when computational simulations based on fundamental physical models are too expensive to be carried away. Another advantage of ML is to automatically learn to identify complex patterns that categorize sets from input

data and thereby make intelligent decisions based on independent datasets²¹. ML can accurately predict drug-target interactions as an enormous amount of complex information by studying hydrophobic interactions, ionic interactions, hydrogen bonding, van der Waals forces, etc. between molecules. Bioactivity datasets which are available from the numerous high throughput screens deliver useful means for machine learning classifiers as they contain binary information (active/inactive) as well as numerical values to classify different compounds under consideration^{22,23}. Such a huge number of datasets available on biological activities of molecules, derived from high throughput screens now allows to create predictive computational models.

In this study, we have applied a machine learning approach to predict several new potential drugs for the treatment of SARS-CoV-2 and validated the predicted drugs. Initially, we have trained our model with the inhibitors of the *SARS Coronavirus 3C-like Protease*. The FDA approved drugs are only taken from the Drug bank as a test model to predict the new drugs. These new drugs are again validated using a docking method to ensure that the drugs match with the same active site on the protein. A ranked list of drugs based on energy value is given that can be tested experimentally. Our study hypothesizes that the commercial FDA approved antiretroviral drug Saquinavir may be a potential candidate requiring to limit viral recognition of host cells or disrupt host-virus interactions thus requiring further clinical trial.

Results

Here, we have at first taken the inhibitors of SARS-CoV-2, which doesn't allow them to replicate in the host. These are screened and collected in the bioassay AID 1706 which were used as the main component for the modeling of the training model using ML. The 914 attributes were taken under consideration for more than 200,000 compounds. We have not used unsupervised learning to filter out the dataset, because it would have made the dataset much weaker. As mentioned in the method section, we have used a classifying algorithm to train the model and the best among them was further used for the testing and predicting the drugs from the Drug Bank. The schematic of the process is shown in Figure 1.

We have used the Naïve Bayes against the dataset. It has shown accuracy of approximately 72.999%. With this model, we have used the drugs from the Drug Bank to get predicted for the identification of the potential drugs which can be used for the treatment of disease caused by *SARS coronavirus*. Along with that the model has predicted 34754 True Positives and 3904 True Negatives.

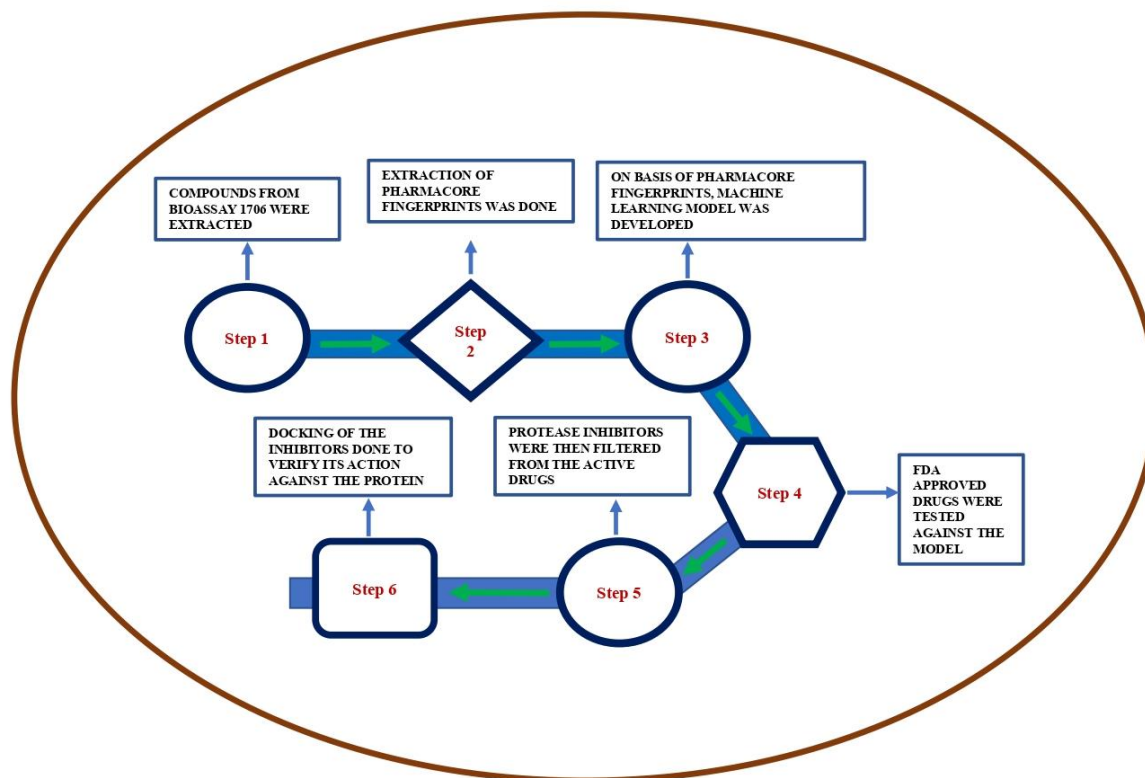


Figure 1: Flowchart of the process

The Naive Bayes has 0.194 MCC and BCR i.e., 76.69%. As per the independent validation, the algorithm with the lowest possible False Positives and highest possible True Positives can be considered to be the most effective model for the prediction of the drugs from the Drug Bank. In all the cases, the compounds for the False Positives were set to 23%. The comparison of the False Positive Rate and True Positive Rate for all algorithms used in the case of preparation of ML models are shown in Figure 2. When these results are compared with the rest of the dataset, it is found to be way better because it has satisfied both criteria and the rest of the algorithms has not reached the mark that has been achieved by Naive Bayes.

The model created with Naive Bayes algorithm predicted around 471 drugs out of all the 2388 approved drugs. These 471 drugs contain all the drugs which may be for the treatment of disease caused by *SARS coronavirus-19*. Here, we have predicted several drugs and out of which, we have docked and suggested the top 10 of them keeping align both the ML accuracy and the docking result. The docking results have been used for binding energy prediction and its effectiveness to bind with the compound. The results are shown in Table 1.

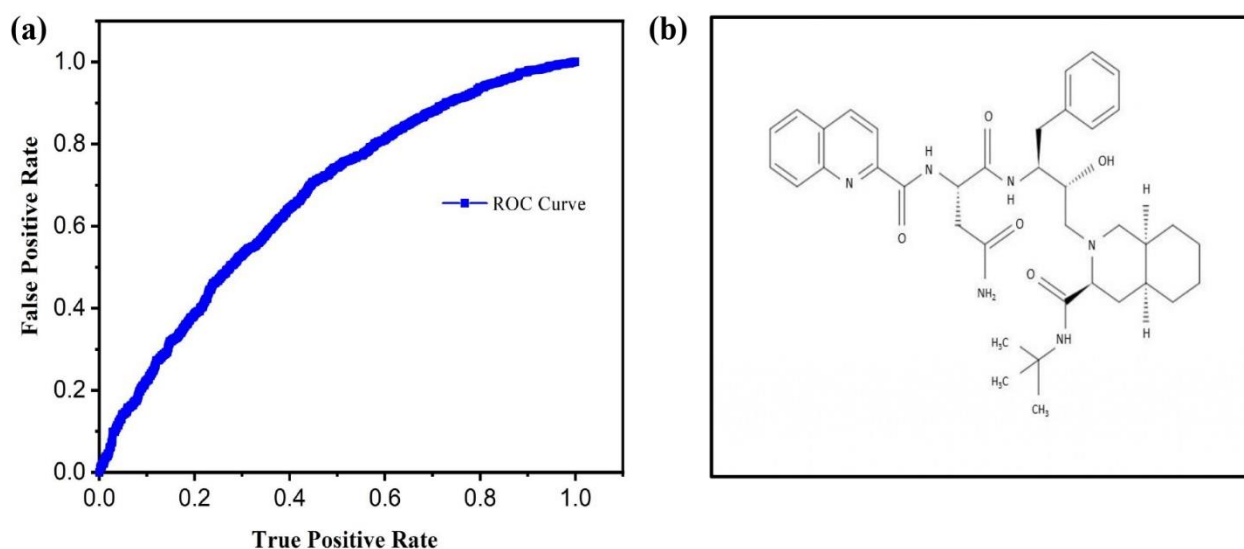


Figure 2: (a) The comparison of the False Positive Rate and True Positive Rate for all Algorithms used in case of preparation of Machine Learning models (b) Chemical Structure of the drug

Based on the docking study, we identified 10 possible drugs namely Saquinavir (Drug Bank ID: DB01232), Atazanavir (Drug Bank ID: DB01232), Indinavir (Drug Bank ID: DB01232), Lopinavir (Drug Bank ID: DB01232), Tipranavir (Drug Bank ID: DB01232), Amprenavir (Drug Bank ID: DB01232), Fosamprenavir (Drug Bank ID: DB01232), Ritonavir (Drug Bank ID: DB01232), Darunavir (Drug Bank ID: DB01232) and Paritaprevir (Drug Bank ID: DB01232) for the treatment of novel SARS Coronavirus.

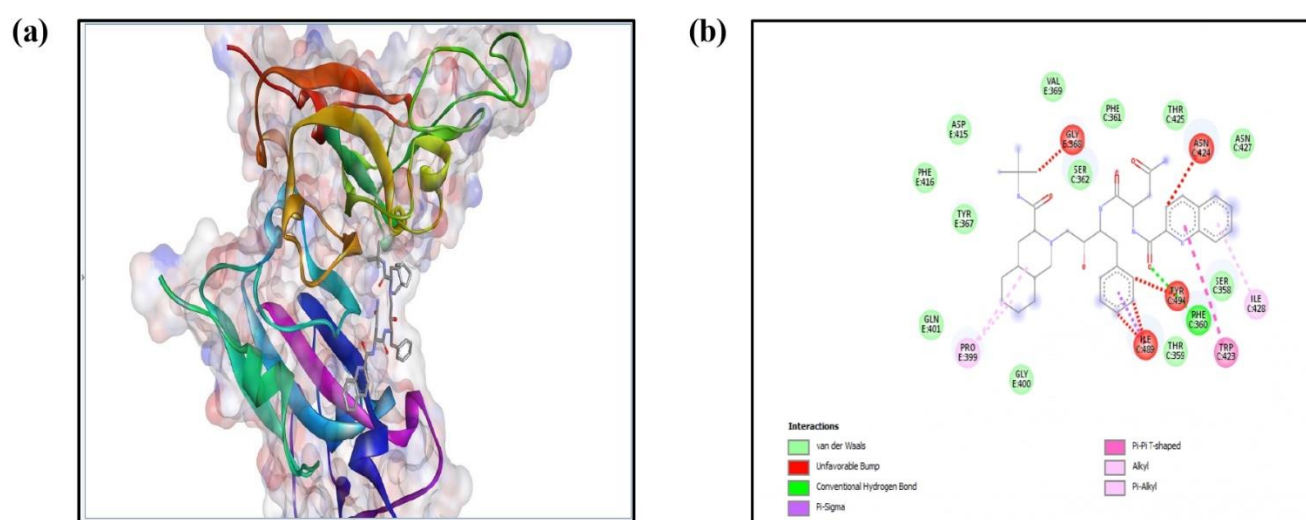


Figure 3: (a) Solution model showing Protein-ligand docking, (b) ligplot analysis showing possible bonds between protein and ligand.

The PDB structure of SARS spike protein receptor binding domain was retrieved from Protein data bank (PDB ID: 2GHV). The docking experiment was done with the patchdock server (<https://bioinfo3d.cs.tau.ac.il/PatchDock/>). The results refinement and energy calculation was performed as per the algorithm used in the Firedock server. The result having minimum global energy was taken into consideration. Out of all 10 drugs predicted, Saquinavir (DrugBank ID – DB01232)(Figure 3a) has shown the minimum global energy. Figure 3b shows the ligplot analysis having conventional H-bonding between ligand and TYR-C-494.

Discussion:

In our study, we have taken those drugs for docking purpose which show protease inhibition activity. The docking of SARS protein with the approved drug Saquinavir (DrugBank ID – DB01232), has a global energy of around -53.62eV which confirms that it had numerous steric clashes with the adjoining strands and thus highlight its potential to inhibit novel SARS coronavirus. Saquinavir is a small molecule antiretroviral drug (Figure 2b), usually sold under the brand names Invirase and Fortovase, used together with other medications to treat or prevent HIV/AIDS. It is an HIV protease inhibitor which acts as an analog of an HIV protease cleavage site. It is a highly specific inhibitor of HIV-1 and HIV-2 proteases.

Table 1: Global energy value for predicted drugs

Drug Bank ID	Name of Drugs	Global Energy	Attractive VdW	Repulsive VdW	ACE
DB01232	Saquinavir	-53.62	-21.90	8.32	-18.08
DB01072	Atazanavir	-41.82	-18.85	2.66	-12.25
DB00224	Indinavir	-39.59	-26.31	11.95	-9.05
DB01601	Lopinavir	-37.30	-24.24	11.90	-9.59
DB00932	Tipranavir	-35.42	-22.45	26.60	-16.42
DB00701	Amprenavir	-34.18	-21.97	14.11	-10.58
DB01319	Fosamprenavir	-33.76	-25.28	15.45	-8.01

DB00503	Ritonavir	-31.53	-22.56	19.15	-12.28
DB01264	Darunavir	-27.59	-12.86	2.16	-8.51
DB09297	Paritaprevir	-19.49	-12.33	2.35	-6.40

In addition to the docking of the above drug, we have also docked several other approved drugs available in the Drug Bank, which are predicted by our ML model with a confidence level of above 95% and also shows the activity of protease inhibition. With reference to that, we have found that the other drugs predicted by the model with the inclusion of all the parameters taken under consideration can also be quite effective.

The rapid identification of active therapeutic agents against SARS-CoV-2 is a major challenge. Analyzing the available knowledge on their safety profiles, and in some cases, efficacy against other coronaviruses and repurposing existing antiviral drugs is a potentially crucial short-term strategy to tackle COVID-19.

Under the current scenario, it takes more than 15 years to bring a drug from the investigational stages to market availability. It is because of the trial and error process or the so-called Edisonian Approach, where one keeps on analyzing several compounds to find the best possible one. These days with the inclusion of digital medicine, this time span has been reduced to a great extent and people are able to approach in a rational manner for the drug discovery process. Here, we have targeted for the repurposed drugs towards the development of effective treatment of COVID-19 to speed up clinical trial. We have found that ML model created on the basis of the Naive Bayes algorithm is the most effective one with the accuracy of almost equal to 73%. The drugs predicted by this model is further verified by the docking process. ~~So, We speculate can expect~~ that our predicted the drugs show immense potential for treatment of the COVID-19.

Considering the ongoing efforts to prevent the spread of COVID-19 all over the world, we are optimistic that the outbreak may subside in a few months like SARS and MERS. However, the outbreak has stressed the urgent need for renewed efforts towards the development of broad-spectrum therapeutic agents to combat coronaviruses which are repeatedly found to be a realistic threat of this century till now. Our this finding will provide a base for further enhanced drug discovery programs.

Methods

Preparation of Dataset

In the present study, the compounds of the dataset are tested in the cell based system using plate readers and then their results are stored as Bioassay Dataset in the Pub chem. This dataset of PubChem Bioassay assigned AID 1706 contains around 290893 compounds as one activity set and they are the inhibitors of *SARS coronavirus 3C-like Protease* in the cells. This dataset is stored in the section Bioassay of PubChem database of National Centre for Biotechnology Information (NCBI), and they have the identification AID number as AID 1706²³. This corresponding bioassay belongs to the Scripps Research Institute Molecular Screening Center of replication in *SARS coronavirus 3C-like Protease* in the cells. The compounds are classified under three distinct categories as actives, inactives and inconclusive. Compounds that inhibit luminescence activity may kill *SARS coronavirus*, inhibit *SARS coronavirus* invasion or inhibit development of the parasite within the host cell and hence these are classified under the active section and the compounds which do not show effectiveness are classified under inactive section. These complete datasets were downloaded in the form of SDF (Structure Data File) from the PubChem Database.

The Drug Bank is an online database which contains detailed data about various medications²⁴. Today, it is being widely used to facilitate in silico drug target discovery, drug design, drug docking or screening, drug metabolism prediction, drug interaction prediction and for general pharmaceutical education. This database of more than 4900 Drugs is categorized into many different types as Trial stages Drugs, Approved Drugs and Withdrawn Drugs. In this database, more than 45% of drugs are approved for various medication purposes²⁴. In this research, we have focused only on the FDA approved drugs for repurposing purpose which are around 2388 with the intention that it will minimize clinical trial in the present situation. These drugs were downloaded in the form of SDFs and after processing, the descriptions generated were taken as the test model for developing the train model which was made on the basis of a database containing the inhibitors of the *SARS coronavirus*. The developed model has predicted few of the potential drugs.

The NCBI Protein Database was used in the process of getting the FASTA sequence of the desired protein (*SARS coronavirus*). Further, the FASTA sequence is used for the modeling of the three-dimensional protein structure and on the basis of this structure the docking of the known and predicted drugs have been carried out²⁵.

Processing Dataset

Since the datasets are present in the form of SDFs, we have generated the attributes present in the SDFs. First, the information present in the SDFs are generated as CSV files which are used as the training dataset and test dataset for preparing the ML models. These CSV files containing both the actives and inactive points are split into 80% as training

dataset and 20% as test dataset. This entire splitting process was random. This process is done by self-written python code to split as per the conditions.

Classification Algorithm

We have used Machine learning (ML) model to the selected dataset from the PubChem which was considered as inhibitors and tested against the drugs from the Drug Bank to find more suitable drugs for the CoronaVirus-19²⁶. Using ML, we have implemented the classification algorithms as described below.

The classification is a type of supervised learning in which the computer system can learn from the dataset which contains the detail and practical results. The algorithmic procedure of the classification is to assign an input value according to the description in the datasets²⁷. So, for this, it requires a mathematical classifier that can assign specific class (active and inactive) labels to instances defined by the attributes. In this process, the training model is made to learn using dataset where the classification is already assigned and on the basis of which it is able to run on different datasets to classify them according to the present instances. In this study, we have compared the results from the classifier that is Naïve Bayes classification algorithm.

Naive Bayesian classification algorithm is a simple and elegant approach by assuming that its classification attributes are independent and they don't have any correlation with each other²⁸. It is a type of classifier that depends on Bayes' hypothesis. Naive Bayes does work best in two cases: complete independent feature (as expected) and functionally dependent features (as expected) and is a widely tested method for probabilistic induction. This classifier functions well and has advantages over many other induction algorithms. It has no entangled iterative parameter that makes it work for vast data sets.

This algorithm is more useful than any other induction algorithms because of its computation speed and reliability. It can be useful for both the binary classification as well as multi-classification²⁹.

Training Model

The training model is prepared by 80% of the original dataset. The dataset is completely classified from where the computer learns and finds the relations among various attributes. The cross-validation is used along with the algorithm to train the model. In this case, the cross-validation is n set with n-folds dataset. Then it is supposed to divide the training dataset into n parts, and the n-1 parts will be used as training data and the other one will be used to validate the rest. This process of iteration goes on for n iteration times. Here, we have used 10-fold and it is chosen as per the size of the dataset^{30,31}.

Generally, the datasets containing binary classification based on several attributes are imbalanced. We observe the similar trend here. These imbalanced datasets are not possible to be handled by the normal classifiers since they give importance to each of the attributes equally which could lead to misclassification errors. This can decrease the accuracy of the dataset for the trained model^{32,33}. Therefore, we have used the misclassification cost where the trained model becomes cost sensitive and able to find the lowest expected cost. This approach is actually much randomized because it neither depends upon the number of attributes nor on the minority class ratio; rather it depends on the base classifier^{34,35}. Here, we had two methods to introduce the misclassification cost with the imbalance dataset. The first method is to classify the algorithm into the cost-sensitive one and proceed with the rest settings³⁶. The other is the use of a wrapper, which helps in the base classifiers into cost sensitive ones.

We have used Naïve Bayes classifier which uses the cost insensitive algorithm to predict the probability estimations of the test instances and then using this it predicts class labels for the examples of the test dataset. In our report, we have classified our datasets into two classes i.e. active and inactive. So, we used the 2X2 matrix which is generally used for the binary classification. In the matrix sections are True Positives (active classified as active), False Positives (Inactive classified as active), False Negatives (active classified as inactive) and True Negatives (inactive classified as inactive). In this case, the percent of False Negatives are more important than the percent of False Positives and the upper limit for False Positives were set to 20%^{32,36}. In this process, we increase the misclassification up to the set percent which also helps in the increasing of the True Positives.

Since, the actives are very less in number, we have replicated them to around 100-110 times to match it with the inactives and make the model less biased.

Independent Validation

There are various methods for the validation of the binary classifiers. The True Positive Rate is the ratio of the actual actives to the predicted positives and this can be obtained as $(TP/TP+FN)$. The False Positive Rate is the ratio of the predicted false actives to actual inactives and this can be obtained as $(FP/TN+FP)$. Accuracy shows the model's performance relative to the real values and this can be calculated as $(TN+TP/TN+TP+FP+FN)$. The Sensitivity shows the model's ability to identify the positive results and this is calculated as $(TP/FN+TP)$ and the Specificity shows the model's ability to identify the negative results and this is calculated as $(TN/TN+FP)$. A model with high specificity and sensitivity has a low error rate. The Balanced Classification Rate (BCR) is the mean of the sensitivity and specificity, which provides the accuracy of the model applied on the imbalanced dataset. This BCR can be calculated as $0.5*(specificity+sensitivity)$.

Apart from the BCR, the Mathews Correlation Coefficient (MCC) is also used whose range varies from -1 to 1. The Receiver Operating Characteristic (ROC) curve is the visualization of the ratio of FPR to TPR. In this case, the FPR and TPR are placed on the x- and y-axis respectively. The Area under curve shows the probability prediction of the classifier and its ability to classify the randomly chosen instance into the correct class.

Docking of the Predicted Drugs

Around 178 drugs were predicted by our ML model which can be effective for the treatment of diseases caused by SARS-Cov-2. There are no available drugs as of now, since the epidemic has just recently accelerated to over 12,18,991 cases [As of 5th April, 2020].

The predicted compounds with above 95% of confidence were docked using Firedock server.

ACKNOWLEDGEMENTS: SS acknowledge Young Faculty Research Grant from Ministry of Information Science and Technology, Government of India.

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