Machine Learning Approaches To Classify Medications Based On Mechanisms

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Abstract: A crucial part of drug development is the mechanism of action. It can assist scientists in the drug discovery process. This research presents a machine learning approach for predicting a drug's mechanism of action. Binary Relevance K Nearest Neighbors (Type A and Type B), Multi-label K-Nearest Neighbors, and a proprietary neural network are the machine learning models employed in this paper. The mean column-wise log loss is used to evaluate these machine learning models. With a log loss of 0.01706, the custom neural network model had the best accuracy. The Flask framework is used to integrate this neural network model into a web application. A user can upload a custom testing features dataset that includes gene expression and cell viability. The top drug classes will be displayed on the online application, along with scatter plots for each medication.

Keywords BRkNN-a Model, BRkNN-b Model, Custom neural network model, Protein, Inhibitors

Introduction

The phrase "mechanism of action" (MoA) refers to how a drug or other chemical works in the body to produce an effect. For example, a drug's mode of action might be how it affects a specific target in a cell, such as an enzyme, or how it affects a cell function, like cell proliferation. The mechanism of action of a medicine can reveal information about its safety and how it affects the body [1].

The majority of drugs interact with proteins in the host or pathogen to operate. Drug targets comprise a wide range of proteins, with the term "receptor" applied only when the contact leads in a signal transmission cascade. An endogenous substance is identified and bound by a receptor, which is a molecular or polymeric structure on the outside of a cell or within a cell An agonist is a chemical that generates a demonstrable physiological or pharmacological response typical of the receptor. After attaching to a receptor site, certain drugs may be unable to begin any activity on their own, but they can block the action of other agonists. Antagonists are what they're called [2].

Understanding the mechanism of action of a biologically active molecule requires not only identi fying the target but also looking into the biological chemistry that occurs before or after target bi nding. Many genes have a role in the mechanism of action of a medicine, and hence have an infl uence on sensitivity.
The intracellular target(s) of a small molecule, as well as the actions that occur before and after t arget engagement, are all included in the mechanism of action [3]. Because the interactions between Tuberculosis medication and Mycobacterium tuberculosis are so complex, Tuberculosis therapy need a thorough understanding of MOA, which is crucial for the effective delivery of drug candidates. Several approaches for studying TB drug MoAs were given, as well as recommendations for future tuberculosis medication development. They assessed several platforms for their strengths and limitations in elucidating Tuberculosis medication MOAs in the context of Mycobacterium tuberculosis pathogenesis [4].

Bioinformatics is a discipline that aids in the study of Mechanisms of Action by combining several layers of information such as image-based data, pathways, and gene expression. Understanding MoA necessitates an examination of the complex reactions of the human biological system to pharmacological therapies. The importance of bioinformatics on drug discovery was reviewed, as well as many bioinformatic tools for understanding Mechanisms of Action [5].

The different machine learning models and their accuracies are discussed in this work. The Flask web framework is also used to create a web application. This web application was created using the most accurate machine learning model available. This online application may be beneficial to scientists working on medication development. The remainder of this work is arranged in the fol lowing manner.A literature review on mechanism of action is presented in Sect. 2. The approach is shown in Sect. 3. The pre-
processing of the dataset is discussed in Sect. 4. The assessment of the machine learning model is discussed in Sect. 5. Various machine learning models and their outcomes are described in Sect. 6. The architecture of the web application is described in Sect. 7. Exhibited. The screenshots of the running web application are shown in Sect. 8. Finally, Section 9 brings this paper to a close.

Literature survey

The mechanism of action of several medications is unknown. Meanwhile, the mechanisms of action of various medications have been revealed. Aspirin, for example, works by irreversibly inhibiting the enzyme cyclooxygenase, which decreases inflammation and discomfort by inhibiting the synthesis of thromboxanes and prostaglandins. Drugs can have a variety of mechanisms of action. Table 1 summarises a literature review of several medicines' mechanisms of action.

Title	Identified
Efficacy and Mechanism of Action of Marine Alkaloid 3,10-Dibromofascaplys in Drug-Resistant Prostate Cancer Cells [6]	The effectiveness and mechanism of action of the marine alkaloid 3,10-dibromofascaplysin were investigated in human prostate cancer cells with varied levels of treatment resistance. Anticancer activity was found in all of the cell lines examined.
The mechanism of action of aspirin [7]	Aspirin inhibits the enzyme cyclooxygenase. By inhibiting this stage in the Prostaglandin synthesis pathway, as pirin- like medicines hampered the development of physiologically impo rtant Prostaglandins. This provided a cohesive explanation for the therapeutic action of aspirin-like medications as well as their typical side effects.
Research on the Mechanism of Action of a Citrinin and Anti-Citrinin Antibody Based on Mimotope X27 [8]	A mimotope is a strong recognition receptor that may be used to study the processes of antigen and antibody activity. A binding model between citrinin and antibody was developed using the mimotope approach. They spoke about how to improve the sensitivity of citrinin detection in immunoassays.
The mechanism of action of ramoplanin and enduracidin [9]	They used inhibitory kinetics and binding experiments to see if ra moplanin and enduracidin exhibited an intrinsic preference for one step over the other. They observed that, as compared to the MurG stage, both ramopla nin and enduracidin inhibited the peptidoglycan transglycosylation process.
Mechanism of action of antipruritic drugs[10, 18]	Antipruritic medications have a calming effect in the brain, howev er H1 receptor antagonists only have a peripheral antipruritic effec t when itching is induced by histamine release.
Mechanism of Action of Atypical Antipsychotic Drugs in Mood Disorders [11, 19, 20]	This research explored the brain processes of existing atypical antipsychotics and potential antipsychotics, as well as how they relate to their efficacy in mood disorders including anxiety and depression.

Methodology

To prevent training the model with the training dataset every time a new testing dataset is sent to the web application, serialisation and de-serialization are utilised. The model is trained using the training dataset in the first stage, as illustrated in Fig. 1. This model is saved as a file in the HDF5 file format [12]. Hierarchical Data Format 5 is the abbreviation for Hierarchical Data Format 5. Serialization is the term for this procedure, which is carried out with the help of the keras built-in module "save." This serialised file contains the model's architecture, weights, training setup (loss and optimizer), and optimizer state.

This file is then de-serialized and sent to the Flask web application. De-serialization is the term for this procedure, which is carried out with the help of the keras built-in module "load model." In this method, training the model with the training dataset every time a new testing dataset is published in the web application may be avoided (the model utilises the serialised file to load the pre-trained model's configuration).

Data pre-processing

A prior study [13] gave a full examination of this dataset as well as the technique utilised. kaggle [14] provided the dataset. The provided dataset is first separated into the training dataset a nd the testing dataset, as illustrated in Fig. 2. In addition, the features dataset and the target datas et have been separated from the training and testing datasets.

There are 23,814 training samples in both the training features and training target datasets. In addition, there are 3982 testing samples in both the testing features and testing target datasets. The categorical values of the characteristics are translated into numerical values in the data pre-processing step, as illustrated in Table 2.

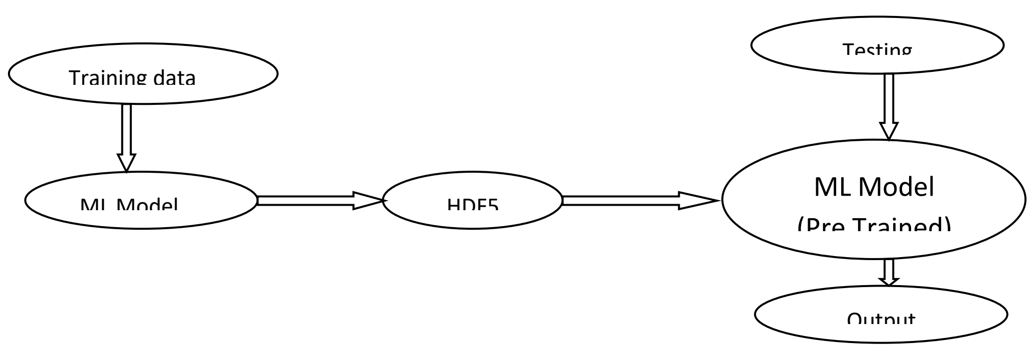

Fig: 1 Methodology of ML Model

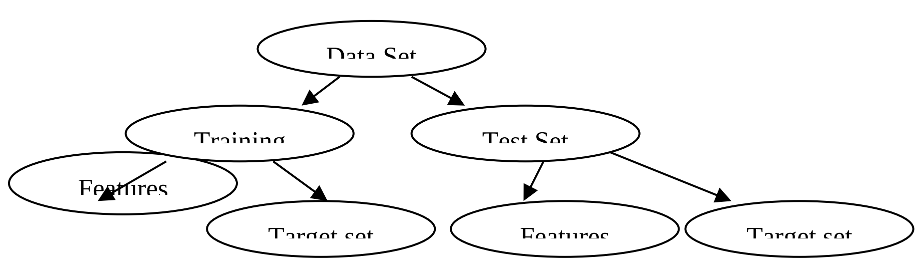

Fig: 2 Dataset Splitting

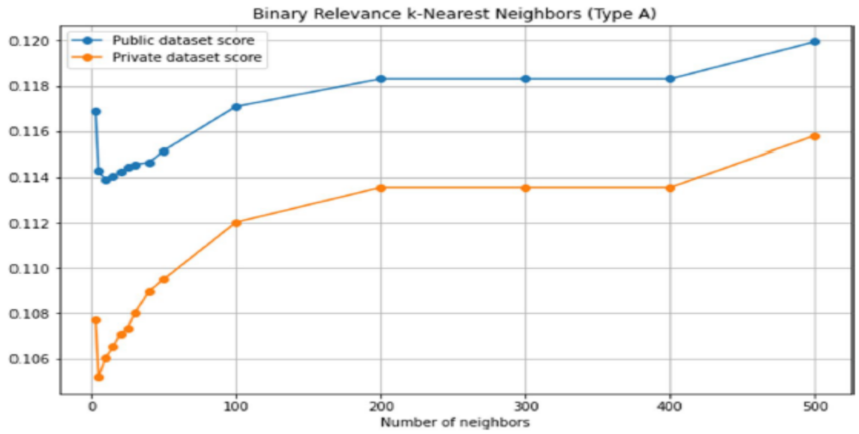

Fig: 3Accuracy of BRkNN-a Model

Evaluation of the machine learning model

For each drug-Mo A annotation pair, the machine learning model's accuracy is assessed using the log loss function. The model's evaluation is based on the mean column-wise log loss. For each Mo A target, the chance that the sample had a positive reaction must be forecasted for each sample id "sig id." A good answer indicates that a medicine belongs to a specific drug class (i.e. target). Better accuracy is indicated by a lower log loss (i.e. score). Eq. (1) [15] contains the formula for evaluating the machine learning model.

$$\text{score} = -\frac{1}{M}\sum_{m=1}^{M}\frac{1}{N}\sum_{i=1}^{N}\left[y_{i,m}\log\left(y_{i,m}\right) + \left(1 - y_{i,m}\right)\log\left(1 - y_{i,m}\right)\right], \tag{1}$$

The number of sig id observations in the test data is N I = 1,2,...,N). M represents the number of MoA objectives that have been scored (m = 1,2,...,M). For a sample id (sig id), yi,m is the expect ed probability of a positive MoA response. The ground truth is yi,m, which is 1 for a positive ans wer and 0 otherwise. The natural base e logarithm is represented by log().

Models and results

There might be many Mechanisms of Action (MoA) for each medication in the dataset. As a result, this machine learning task falls within the category of multi-label categorization. BRkNN (Binary Relevance K Nearest Neighbors), ML-KNN (Multi-label K-Nearest Neighbors), and a proprietary Neural Network are the machine models investigated in this article.

Table 2: Attribute values mapping

Attribute Name	Old value	New Values
Cp Type	Trt_cp	1

	Ctl_ Vehicle	0
Cp Time	24h	0
	48h	1
	72h	2
Cp Dose	D1	0
	D2	1

6.1 BRKNN (binary relevance K nearest neighbors)

BRkNN is a kNearest Neighbors (kNN) technique variation that effectively combines Binary Rel evance (BR) with the kNN algorithm. BRkNN is a kNN extension that makes separate prediction s for each label [16]. BRKNN is divided into two kinds based on the confidence score of each la bel: BRkNN-a and BRkNN-b.

BRkNN-a (type A):

If none of the labels occur in at least half of the k nearest neighbours, BRkNNdecides if BRkNN returns the empty set.If this requirement is fulfilled, the highest confidence label is outputted [16]. Figure 3 and Table 3 illustrate the graph and prediction scores for this model, respectively.

The Xaxis shows the number of neighbours, and the Yaxis represents the public and private data setcore in the graph shown in Fig. 3.From three to five neighbours, the private dataset score impr oves.The public dataset score improves as the number of neighbour's increases from three to ten. Following that, as the number of neighbours grows, both scores decrease.

BRkNN-b (type B):

After estimating the "s" (average size) of the label sets of the k nearest neighbours, BRkNN-b produces the integer that is closest to "s" labels and has the greatest confidence [16].Figure 4 and Table 4 illustrate the graph and prediction scores for this model, respectively.

The X-axis shows the number of neighbors, and the Y-axis represents the public and private dataset score in the graph shown in Fig.4.
From 3 neighbours to 2000 neighbours, both the private dataset score and the public dataset scor e improve.A score of 5000 neighbours results in a lower score.Following that, both scores remai n steady. which occurs when the number of neighbors is 30

Table 4 shows that the largest difference between the publicdataset scores and the private dataset score is 0.38482, which happens when the publicdataset score is higher than the private dataset s core.

6.2 ML-KNN (multi-label K-nearest neighbors)

The ML-KNN approach is based on the k-Nearest Neighbor (kNN) algorithm, which is well-known. For each test instance, the k closest neighbours in the training set are chosen first. The idea of maximum a posteriori (MAP) is then used.

Table 3: Prediction Scores of the BRkNN-a Model

No. Neighbors	Private Dataset Score	Public dataset Score
3	0.10773	0.11688
5	0.10518	0.11427
10	0.10605	0.11389
15	0.10651	0.11406
20	0.10709	0.11423
25	0.10733	0.11444
30	0.10801	0.11456
40	0.10898	0.11465
50	0.1095	0.11515
100	0.11202	0.11709
200	0.11356	0.11831
300	0.11356	0.11831
400	0.11356	0.11831
500	0.11581	0.11995

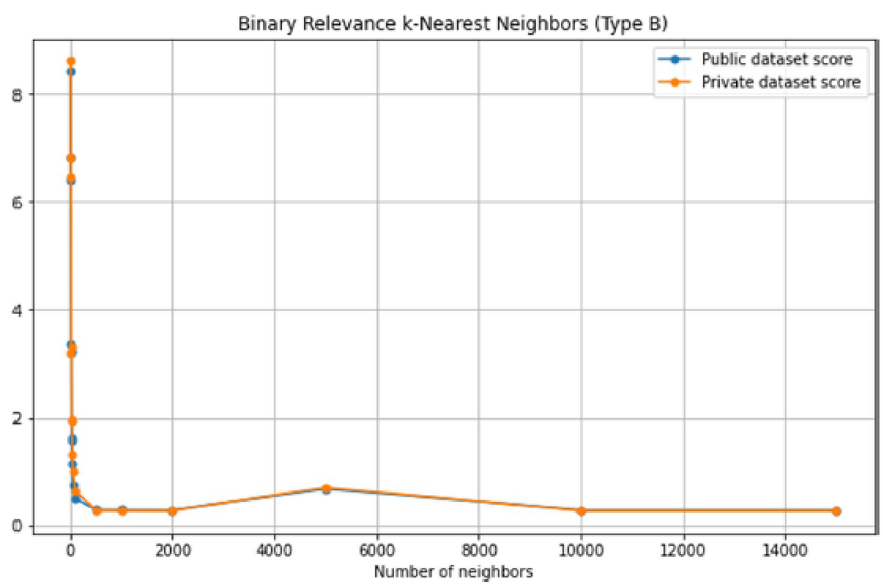

Fig: 3 Accuracy of BRkNN-b Model

Table 4: Prediction Scores of the BRkNN-b Model

No. neighbors	Private DatA set Score	Public Data set Score	Diff. of Private and public Data set Score
3	8.61531	8.44115	0.17416
5	6.82411	6.83867	−0.01456
10	6.46235	6.41718	0.04517
15	3.21137	3.36569	−0.15432
20	3.30373	3.2381	0.06563
25	1.92898	1.63633	0.29265
30	1.96073	1.57591	0.38482
40	1.30347	1.15522	0.14825
50	0.99511	0.76119	0.23392
100	0.6386	0.49542	0.14318
500	0.27721	0.28901	−0.0118
1000	0.27465	0.28606	−0.01141
2000	0.27254	0.28282	−0.01028
5000	0.70056	0.67626	0.0243
10,000	0.27254	0.28282	−0.01028
15,000	0.27254	0.28282	−0.01028

relies on statistical information acquired from the label sets of neighbouring cases [17] to identif y the label set for the test instance The graph and prediction scores for this model are shown in Fi g. 5 and Table 5. The X-axis shows the number of neighbours, and the Y-axis represents the public and private dataset score in the graph shown in Fig. 5. From 3 neighbo urs to 20 neighbours, both the private dataset score and the public dataset score improve. Followi ng that, as the number of neighbours grows, both scores decrease.

6.3 Custom neural network

Keras [18–20] is used to design a neural network. Keras is a TensorFlow-based deep learning API written in Python. The input layer units are 875 since there are 875 input features in the dataset. Likewise, there are 206 outputs.

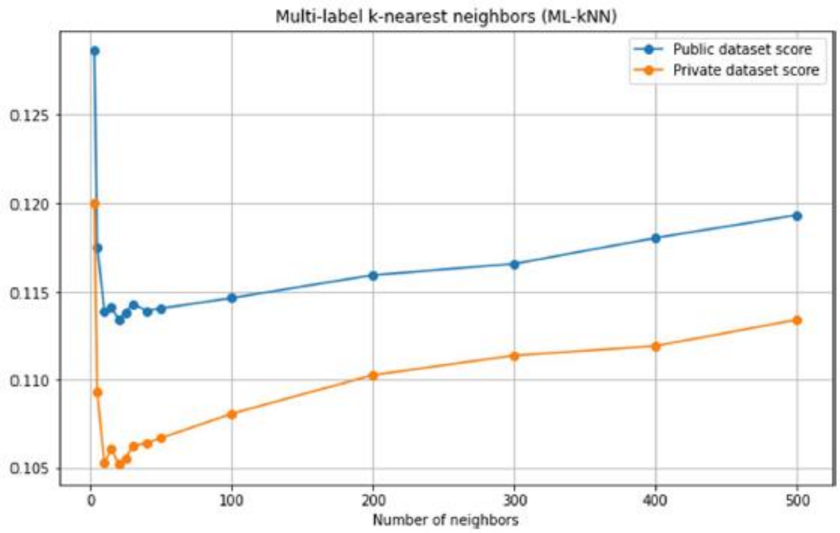

Fig 5: Accuracy of ML-KNN Model

Table 5: Prediction Scores of ML-KNN Model

No. Neighbors	Private Dataset Score	Public dataset Score
3	0.12005	0.12859
5	0.10933	0.11755
10	0.10528	0.11393
15	0.10609	0.11414
20	0.10523	0.11343
25	0.10552	0.11385
30	0.10625	0.11431
40	0.10643	0.11393
50	0.10670	0.11406
100	0.10808	0.11465
200	0.11028	0.11595
300	0.11139	0.11659
400	0.11193	0.11806
500	0.11342	0.11936

The output layer units for targets are 206. The dropout rate for both dropout layer 1 and dropout layer 2 is 0.5. The binary cross-entropy loss function is used to build the model. Adam is the optimizer that was utilised. The code for implementing neural networks may be accessible on Github [21]. The layers of the neural network are depicted in Figure 6.The descriptions of each of the layers employed are listed in Ta

ble 6. The activation functions for the dense layers and the output layer are shown in Table 7. Th e graphs for the sigmoid and RELU activation functions are shown in Figures 7 and 8, respective ly. The accuracy graph is shown in Figure 9.
The prediction scores for this model are shown in Table 8.

The epochs are shown on the Xaxis, and the public and private dataset scores are represented on t he Yaxis in the graph displayed in Fig. 9. From 15 epochs to 75 epochs, the private dataset score and the public dataset score both improve.Following that, as the number of epochs grows, both s cores decrease.

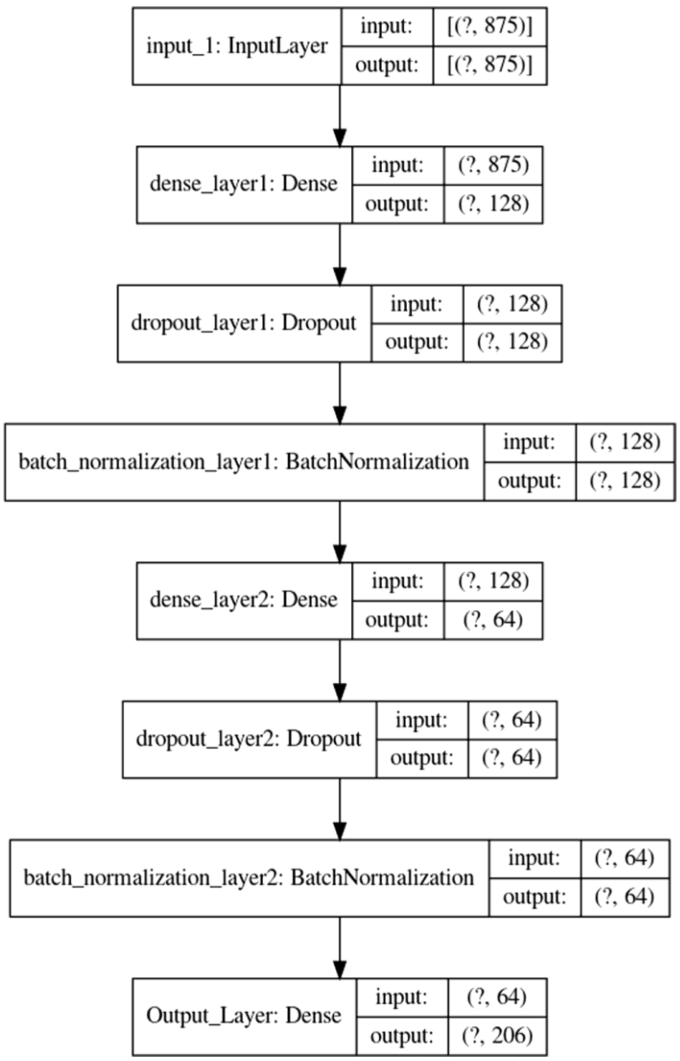

Fig 6: Custom Neural network Layers

Table 6: Custom neural network layers Description

Layers	o/p shapes	No. parameters

Input layer	(None, 875)	0
Dense layer 1	(None, 128)	112,128
Dropout layer 1	(None, 128)	0
Batch normalization layer 1	(None, 128)	512
Dense layer 2	(None, 64)	8256
Dropout layer 2	(None, 64)	0
Batch normalization layer 2	(None, 64)	256
Output layer	(None, 206)	13,390

Table 7: Custom neural Network Activated function

Layer	Function Activation
Dense layer 1	RELU
Dense layer 2	RELU
Output layer	Sigmoid

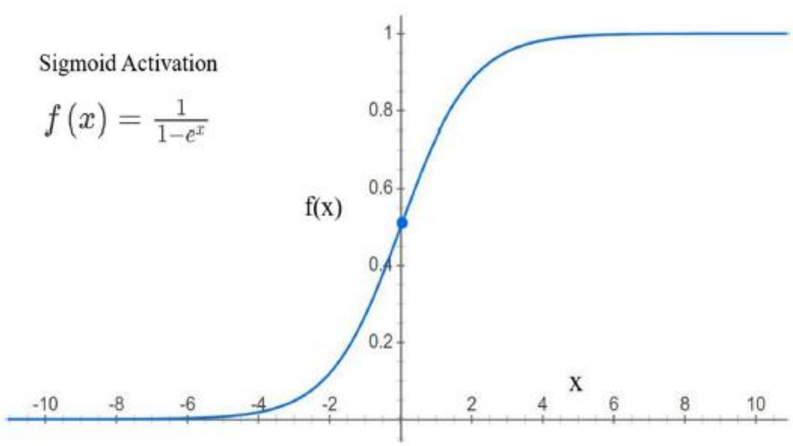

Fig 7: Activation function graph for sigmoid

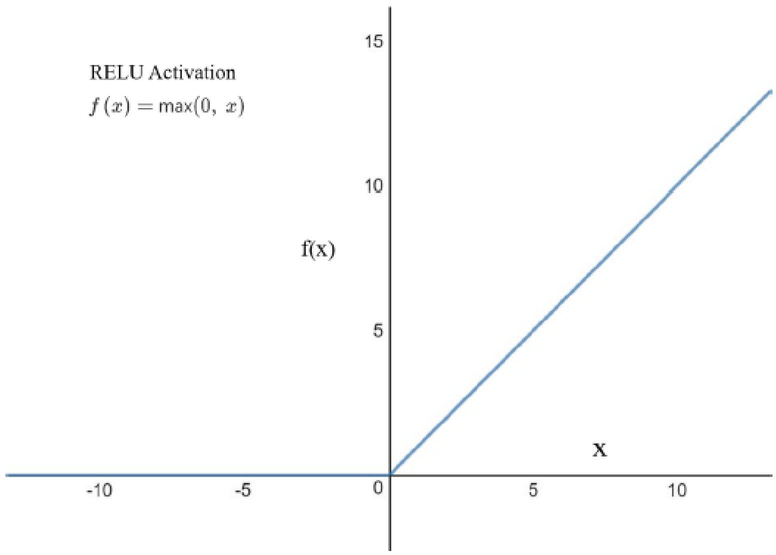

Fig 7: Activation function graph for RELU

Because the best score for the private dataset acquired with each of the models is used to score the final leader board, the best score for the private dataset achieved with each of the models is used. Table 9 shows a summary of the best accuracy for each of the models. The custom neural network with 75 epochs and 100 batch size performs the best, as shown in Table 9.

7 Architecture of the web application

The Mechanism of Action of each medicine is visualised using a web application. This web application's source code is available on Github [21]. The Flask framework [22] was used to create this web application. The Jinga Templating Engine [23] is also used.

The web application's architecture is depicted in Figure 10. Each drug's gene expression and cell viability results are contained in a CSV file. The result is the top drug classifications (with the highest probability). The variable NUMBER OF TOP MOA can be used to specify the number of top MoAs to be presented in the output.

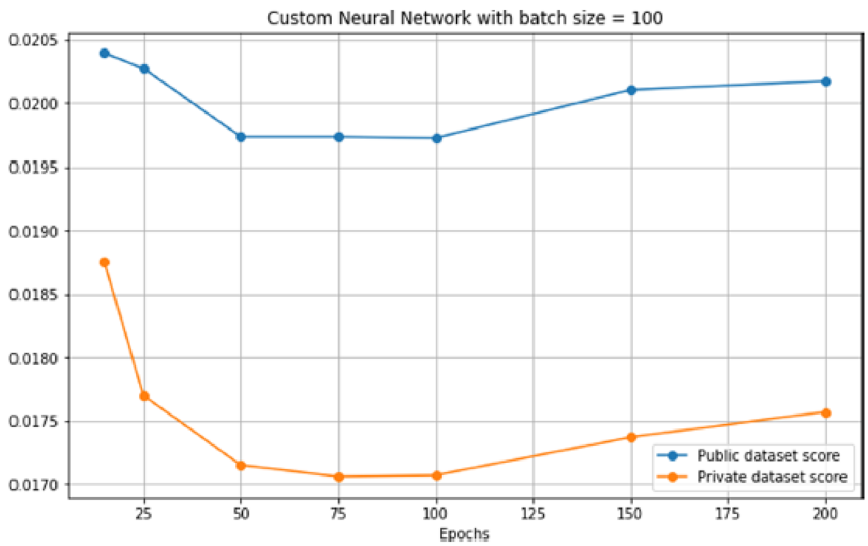

Fig 8: Accuracy of Custom Neural Network

Table 8: Custom Neural Network Prediction Scores

Epochs	Private dataset score	Public dataset score
15	0.01875	0.02039
25	0.0177	0.02027
50	0.01715	0.01973
75	0.01706	0.01973
100	0.01707	0.01972
150	0.01737	0.0201
200	0.01757	0.02017

Table 9: summarization of best prediction score for each model

Name of the Model	Private data score	Configaration
BRkNN-a	0.10518	5 Neighbors
BRkNN-b	0.27254	2000 Neighbors
ML-KNN	0.10523	20 Neighbors
Custom neural network	0.01706	75 Epochs, 100 Batch size

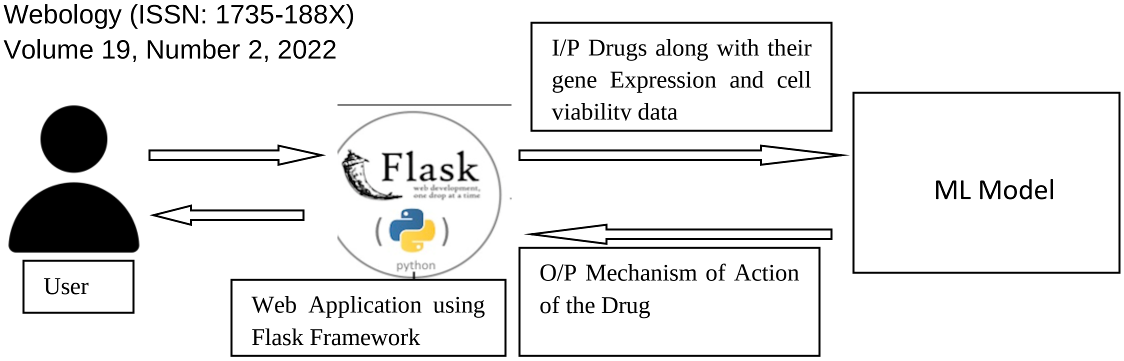

Fig 9: Architecture of web Application

8 Running the web application

Table 10 shows the testing dataset (testing dataset.csv) that must be uploaded to the web applicat ion. The top MoAs for each of the drugs in the testing dataset are displayed for each of the drugs. A scatter plot is also given for each of the drugs. Each medication class is assigned an ID in orde r to see the scatter plot. ID 1 is assigned to the first class of medicine (i.e. 5alpha reductase inhibi tor), ID 2 to the second class (i.e. 11-beta hsd1 inhibitor), and so on. A python list is used to hold this set of IDs (present in the flask applic ation). The ID of the drug class is represented on the X-axis of the scatter plot.

The Yaxis reflects the likelihood that the drug belongs to that class of drugs, and the Xaxis repres ents the chance that the drug belongs to that class of drugs. Figure 11 depicts the web application 's home page. Figures 12 and 13 depict the major drug classes. Figures 14 and 15 show the scatte r plot.

9 Conclusions

The mechanism of a medicine can aid scientists in their drug discovery efforts. This research examined several machine learning methods for predicting a drug’s mechanism of action. A user may also enter a custom testing features dataset encompassing gene expression and cell visibility levels using flask web application. The top drug classes, as wel as their scatter plot, are the output. This can assist scientist in predicting the mechanism of action and in the development of novel medications. The log loss of all machine Learning models employed in this work is summarizes in the fig 10 and table 10. The custom neural network model outperformed all of the others machine learning models.

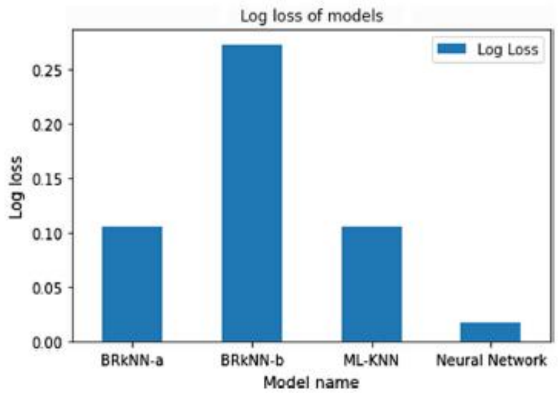

Fig 10: Bar chart for Log loss of all machine Learning Models

Table 9: summarization of log loss of all machine learning models

Name of the Model	Log Loss
BRkNN-a	0.10518
BRkNN-b	0.27254
ML-KNN	0.10523
Custom Neural Network	0.01706

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