

Prediction of Drug Responses from Genomic and Drug Data Using Stacked Ensemble Model for Lung Cancer

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Abstract

Background. A large amount of research is being done on the subject of cancer, to improve cancer prediction and provide the best treatment. The prediction of drug responses by the analysis of multiple different structural types of genetic multi-omics and drug characteristics data at molecular level with the application of computational methods is essential for achieving precision medicine in oncology. Thus, cancer patients can do well out of such medical treatment by matching their tumour traits to the most effective drugs approved for the disease.

Objective. Since the research done so far are all mostly based on pan-cancer data, the accuracy to predict effective drugs specifically for lung cancer is not that efficient. With the amount of lung cancer cases on the rise and with the extensive discovery of new biomarkers and drugs, a model that suggests effective drugs by the prediction of drug responses specifically for lung cancer must be built that can prove to be of great help. To fulfill the goal of precision medicine, it is important to focus on improving efficacy of drug response to a biomarker. Given the recently developed extensive heterogeneous multi-faceted data from multiple sources, such data are to be integrated and robust models with high accuracy for drug response prediction must be developed.

Methods. In this work, Lung cancer datasets have been obtained from CCLE (Cancer Cell Line Encyclopedia) and drug details from PubChem and PRISM Drug Repurposing Database. The data is highly dimensional and hence its features are extracted using GCN, CNN, stacked AutoEncoder. The proposed system is a stacked ensemble model that consists of a set of hybrid Deep Learning models (CNN-LSTM, CNN-GRU, LSTM-GRU) constructed along with statistical models like BNN and Logistic Regression. The results of these base models are passed through a meta-learner and the final results are obtained. The work presents results that show us the drug response values for each lung cancer cell lines and drugs available for lung cancer.

Results. The hybrid deep learning models CNN-LSTM, CNN-GRU and LSTM-GRU part of the base learners of the stacked ensemble model posted an improvement of around 9%, 6%, 8% in R2 scores respectively, RMSE score reduced by around 8%, 7%, 7% respectively and the Pearson and Spearman coefficients have increased by 3% when compared to single models. The overall stacked ensemble model showed further improvement of 4% decrease in RMSE & MSE scores, and a 3% increase in Pearson & Spearman coefficients than the base learners, with a R2 score of 0.7377.

Keywords: CCLE, PRISM, Biomarkers, Precision Medicine, Drug Response Prediction, Deep Learning, Statistics, Hybrid Models, Stacked Ensemble.

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Introduction

Precision medicine is a treatment method designed to therapeutically benefit patients with diseases by using their gene-molecular profiles. It is an approach that uses the data information from their genetics to specifically diagnose, treat accurately or prevent the disease, and also in creating personalized drugs. In regard with cancer, precision medicine is being researched in depth and tested in clinical trials to

determine its effectiveness in patients. Precision medicine has become feasible because of the processing and analysis of biological big data and drug big data. Biological big data is termed as "multiomics data" which is the result of biological and molecular analysis of genome of cancer patients giving rise to information such as gene expressions and mutations, copy number variation, proteomics. CCLE (Broad

Institute Cancer Cell Line Encyclopedia) database contains comprehensive multi-omics data of over 1,000 cell lines that act as biomarkers of cancer in patients. PubChem is a repository of information about molecular formula, structure and other identifiers of drug chemicals. PRISM Drug Repurposing that contain results of viability screens of cancer-approved drugs against the cell lines. By integrating and processing such diverse data and finding potential associations between the biomarkers and drugs, we can understand the mechanism of the drugs and their response in the cancer patients. Owing to the huge size and high-dimensionality of this data and their availability as public repositories, there is a major interest in using computational and statistical tools to automate the processing of such datasets, thereby eliminating the need of conducting experiments by a skilled professional to assess the data. The tools can be helpful in predicting the potential response of a drug to a biomarker in an individual thus reducing the costs incurred in conducting experiments to select the personalized treatment for a patient. Although statistical and machine learning models have been used individually to determine the associations and predict drug response, no attempts have been made to explore the potentials of leveraging multiple models together at once to ascertain its capacity to predict accurately.

Cancer. A vast group of illnesses collectively referred to as cancer are characterised by the emergence of aberrant cells with the capacity to proliferate rapidly and gradually wreak havoc on healthy bodily components. Worldwide, cancer ranks as the second most common cause of death. Lung cancer incidences are increasing dramatically as a result of pollution levels. It is also one of the most malignant type of cancers with the greatest fatality rates. In 2020, it was estimated that there was more than 18.1 million new cases of cancer recorded globally.

Lung Cancer. When cancer cells are discovered in the lungs, it is called lung cancer. With a 12.2% contribution to all cancer cases, it is the second most prevalent cancer. Lung nodules, non-small cell lung cancer, small cell lung cancer, and mesothelioma are the most prevalent kinds of lung cancer. Biomarkers can be used to identify these early on. Biomarkers are biological molecules that are indicators of a healthy or unhealthy process, of a condition, or of a disease. They can provide information regarding how the body reacts to cancer therapies. In order to give patients the finest and most effective care possible, numerous health organisations are developing a variety of drugs for lung cancer by examining their properties and conducting tests on the biology of cancer cells. When testing drugs on biological molecules, the commonly

used measurement known as IC₅₀ (50% inhibitory concentration) is used to assess the drug reaction.

1.1. COMPUTATIONAL STATISTICAL METHODS

Computational Statistical Methods is a bond between statistics and computer science to transform raw data into knowledge. It majorly focuses on handling statistical problems with mathematical applications and the usage of computing devices to solve those problems.

Deep Learning. Deep Learning, modeled after the human brain, is a type of Machine Learning with neural networks that contain many layers to process, extract and learn from the data. It is based on the human principle, to "learn by example". It performs classification and regression tasks with great accuracy exceeding human-level performance.

Statistical Learning. Statistical methods mathematically help in the analysis of data to understand and interpret information more strategically. It allows to identify relationships between variables, quantify ideas and hypotheses, and make future predictions.

1. Related Work

Growing biological sequencing techniques, drug therapeutics development and advancement in pharmacology resulted in large volumes of multi-omics and drug characteristics data. Several public repositories with such data like GDSC (Genomics of Drug Sensitivity in Cancer) [1], CCLE (Cancer Cell Line Encyclopedia) [2], NCI60 (US National Cancer Institute 60 human tumor cell line anticancer drug screen) [3] were open to aid in the study of precision medicine. As GDSC and NCI60 were being widely used in the research, they posed a constraint of having tested limited number of cell lines with larger number of drugs or the vice versa. A balanced data must be involved in viability screening to represent the diverse associations between the cell line and drug interactions. PRISM addressed and validated this problem by profiling the drug responses to a relatively balanced number of cell line and drug candidates. Drug responses of biomarkers are key to suggest drug treatment and development in supporting data-driven precision medicine [4]. Several methods prior to the use of digital technologies were mostly based on statistical approaches, that studied on this area. In the work by Azuaje [5], the preprocessing of data, as well as the models used were statistical methods like elastic net, ridge regression, etc. But with the choice of uneven data and only establishing linear relations, these methods were not effective in cleaning the data before model training thereby resulting in a poor accuracy. To avoid these shortcomings, Tan [6] tested a kernelized multi-task learning to capture the non-linear relations, but the datasets used here deemed it difficult to capture the same as described by the

significant loss in the work. In Ahmadi Moughari & Eslahchi's work [7], it combined the previous methods with normalized laplacian to establish similarity matrices before training the data with classification methods. However, the performance did not sustain when scaling down the data to individual cancer types. In the review work done by Simon [8], it was stated that the use of statistical methods alone in this study needed re-evaluation before clinical trials because of its changing paradigms. The shift to the use of computational methods in the following studies improved the performances. Li et al. [9] used KNN for classification as sensitive or resistant drugs, and GA for regression prediction. Though they posted comparatively better results, both the methods showed issues of inefficient performance when using external data and predicted values being pulled from extremes because of averaging, respectively. In the work of Paltun et al. [10], the comparison proved that network-based approaches fared better. But the reduced accuracy in predicting unseen data due to lack of comprehensive data was evident. The review work of Kong et al. [11] indicated that deep learning methods had good performance than machine learning and non-ML methods. The use of extensive data and data integration techniques in Cheng et al.'s work [12] gave commendable results, but the focus was not given to exploring other models. All the above mentioned study were not done for lung cancer specifically. Existing works for lung cancer as in the works of Qureshi et al. [13] and Coker et al. [14] were with simple machine learning algorithms and unbalanced data. The downside of these existing works with unbalanced data was the "curse of dimensionality" that arose because of training with fewer features but huge observations, that hindered its ability to scale to the latest extensive diverse data. Hence this research work pivots to the usage of the aforementioned data, and explores the usage of a stacked ensemble approach that utilized both computational and statistical methods.

2. Materials and Method

The data materials used and the methods applied on them for the implementation of this work is described as below.

3.1. Data Extraction

The data to be obtained is quite complex and heterogeneous. The datasets used are extracted from 3 major pharmacogenomic databases Cancer Cell Line Encyclopedia (CCLE) [2], PubChem [15] and PRISM Drug Repurposing Database [16]. From CCLE, cell lines were extracted exclusively for Lung Cancer, miRNA expressions (posttranscriptional regulators of biomarkers at RNA level) and DNA Copy numbers (number of occurrences of the biomarker in the genome of the cancer patient, expressing the biomarker characteristics at gene level) of the cell lines were also

obtained. From PubChem, the extracted data contains drugs. The physicochemical features of the drugs were also obtained, along with their corresponding molecular fingerprints. Also, the 3-dimensional molecular structures of the drugs - SMILES were obtained. From PRISM Drug repurposing database, the data extracted contained the drugs, cell lines, IC50 values and other corresponding parameters (as shown in Figure 1).

DATASET	DATASET SIZE
Cell lines	73
DNA Copynumber	93 with 16383 dimensional vectors
MiRNA	92 with 734 dimensional vectors
Drug physiochemical properties	1448 with 269 dimensions
Drug SMILES	1448
Drug Fingerprint	1448 with 881 dimensions
Drug response data	41193

Cancer Cell-Line Encyclopedia
 PubChem
 Prism Drug Repurposing Database

Figure 1: Dataset Distribution

3.2 Conceptual Framework

Figure 2 gives an overview of the Conceptual Framework. It outlines the various modules such as Data Extraction, Data Preprocessing, Feature Extraction followed by application of Hybrid models and Meta learner, their evaluation and comparison.

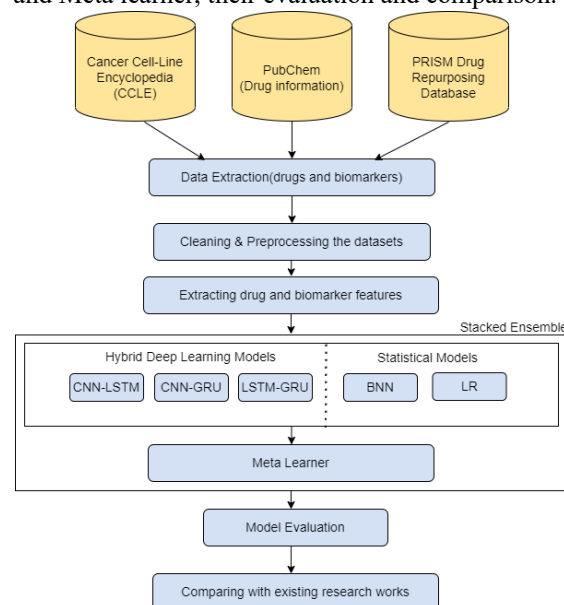


Figure 2: Conceptual Framework

3.3. Data Preprocessing

DNA copy number and miRNA expression data have different distributions, hence to avoid skewness in model training, they are normalized before feature extraction. For the drug SMILES, the strings are converted into molecular graphs using RDKit tool from its 3D chemical structure for better

understanding and molecular fingerprint (binary vector) was not processed before its extraction because of the peculiarity of its structure.

The IC₅₀ values are too broad in range. Hence, raw data is logarithmically processed while checking if the initial IC₅₀ values can be restored again. The outliers were identified using box plot. The upper quartile Q3 and lower quartile Q1 of all drug response data were taken. The interquartile range is calculated. IC₅₀ values that are less than $Q1 - 1.5 * IQR$ and greater than $Q3 + 1.5 * IQR$ were regarded as outliers[12]. Specifically, the data used contained 1448 drugs and 73 cell lines. Initially, the data contained 41,193 labels. Out of which 1779 labels were found to be outliers. After removing data ended up containing 39,414 labels.

After feature extraction is done, the features are then loaded along with IC₅₀ values. The DNA copy number data and miRNA expression data are normalized so that it is brought to a lower range. Then the loaded features are mapped to the corresponding labels. Finally, this data is splitted into training set, testing set and validation set in the ratio 8:1:1 (as shown in Figure 3).

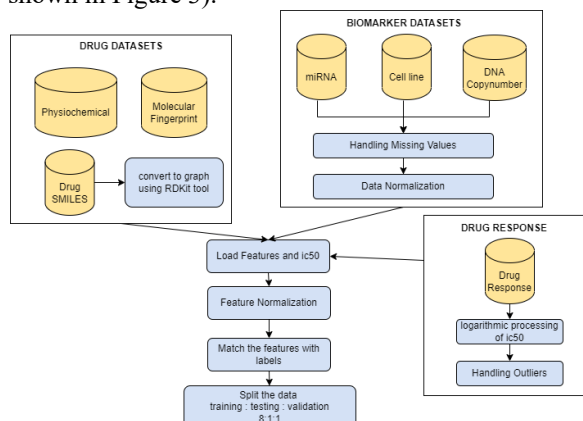


Figure 3: Data Preprocessing

3.4. Feature Extraction

Feature extraction refers to the process of transforming raw data into numerical features that can be processed while preserving the information in the original data set. It helps to reduce the amount of data. This reduction of data helps to build the model with less machine effort and also increases the speed of learning. It yields better results than applying the model to the raw data. Here, a total of 4 feature extractions is done. 2 features for Drug (SMILES and Molecular fingerprints) and 2 features for Biomarker (DNA Copy number and miRNA expression) which will be input to the model (as depicted in Figure 4). From SMILES, the drug sequence is transformed into a molecular graph and needs to be stored in a matrix. In order to extract this feature, Graph Convolution Network (GCN) is used.

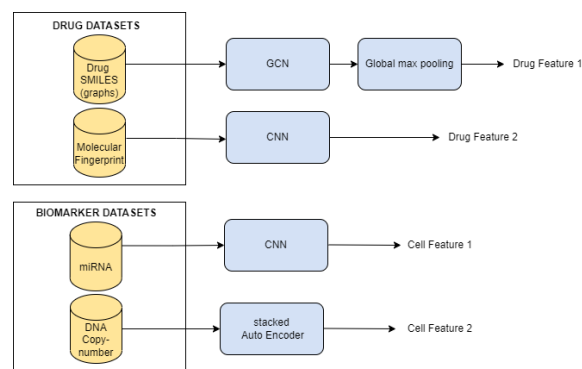


Figure 4: Feature Extraction

Then, global max pooling is performed so that the matrix can be converted into a vector form, which will be the drug feature 1. In case of molecular fingerprints, the data is already in vector format, hence it is passed through a Convolutional Neural Network(CNN) to extract its features. This is done by scanning the data regularly, conducting matrix element multiplication and summation to obtain a single vector feature which is the drug feature 2.

2 features for biomarkers are also extracted. From the miRNA expression data, since its dimensions are similar to the molecular fingerprint data, it is similarly passed through a Convolutional Neural Network (CNN) and the feature is extracted i.e., cell feature 1. DNA copy number data is a huge data with very high dimensions. Hence to reduce the dimensionality, a stacked Auto Encoder is used for extracting cell feature 2 [12].

3. The Proposed Stacked Ensemble Model

The proposed system is a Stacked Ensemble model to predict the IC₅₀ drug response values for biomarker-drug pairs. This system helps to combine different techniques of all the models used to leverage the unique capabilities of each of them. The proposed system works on the principle of Stacked Generalization, where a meta-learner trains on the predictions made by the base learners. The system involves multiple hybrid computational deep learning models (CNNLSTM, CNN-GRU, LSTM-GRU) and statistical models (BNN, LR) that act as the base learners of the system. The proposed stacked ensemble model undergoes k-fold cross-validation, where the data set is separated into k-folds. Each of the base learners make predictions, which are concatenated to form the ensemble input data to the meta learner. The meta-learner acts on this ensemble input data as input to make the final prediction of output IC₅₀ drug response values. (as illustrated in Figure 5).

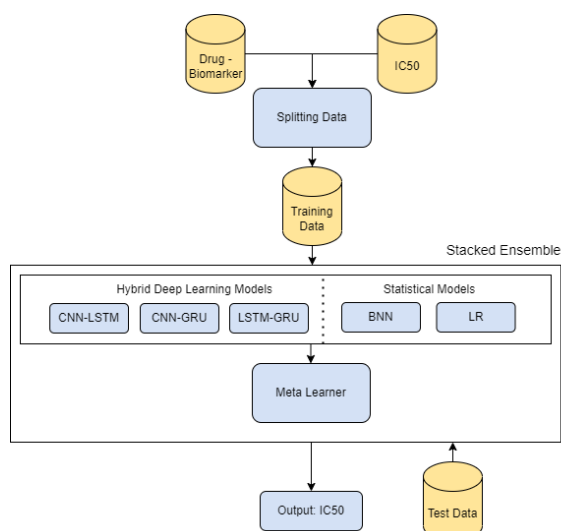


Figure 5: The Proposed Stacked Ensemble Model

Convolutional Neural Networks (CNN). are called regularized multilayer perceptrons as they prevent over-fitting. CNN has three types of layers namely convolution layers, pooling layers and fully connected layers. CNNs integrate concepts such as shared weights, local receptive fields and take advantage of parallel and cascading convolutional filters to solve high dimensional problems such as regression. By sharing weights in each layer and processing limited dimensions, CNN requires lesser parameters than a standard neural network which makes it much easier to train.

Long Short-Term Memory (LSTM). is a variety of Recurrent Neural Networks (RNN). The main feature of LSTM are memory cells that can ‘memorize’ parts of the input and use them in making predictions. Adding and removing information from these memory cells is regulated by gates, assisted by pointwise multiplication operation and a sigmoid neural net layer that assist the mechanism. LSTMs are advantageous in solving the vanishing gradient problem, thus, are capable to process longer sequences unlike RNN which make predictions only based on the most recent information in the sequence.

Gated Recurrent Units (GRU). are a kind of RNN and a variant of LSTM by having a forget gate but not a output gate. Since it has fewer gates than LSTM, it makes it comparatively faster to train. With its two gates: reset gate and update gate, these vectors can help the model to determine how much long term memory it needs to make predictions. Thus, GRUs also overcome the vanishing gradient problem.

4.1. BASE MODELS

4.1.1. Hybrid Deep Learning Models

CNN-LSTM. The first base learner is a hybrid heterogeneous architecture which combines CNN with LSTM . The proposed base learner is optimised, thus comprising of a two CNN layers (each with a

convolutional layer, an activation layer and a max-pooling layer) followed consequently by a LSTM layer, a flatten layer and a dense layer. The activation layer commonly used in CNN is ReLU which transforms negative inputs and makes all outputs of the neurons in the postive range, also helping in improving the computing power and lessen overfitting. The hidden dimension and number of hidden layers for LSTM is defined as 10 and 3. The flatten layer is used to reshape the output of LSTM to better fit the dense layer which makes the output predictions (as shown in Figure 6).

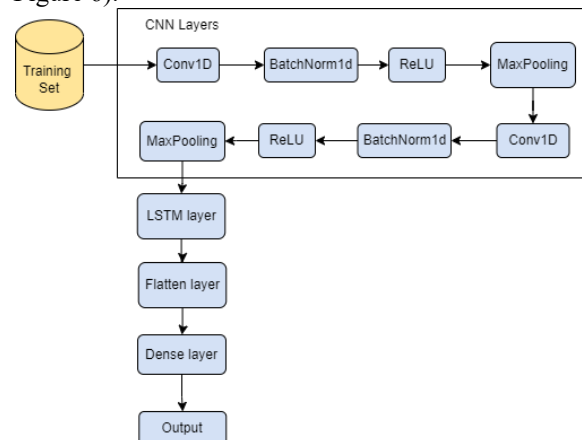


Figure 6: CNN-LSTM architecture

CNN-GRU. The second base learner is a hybrid heterogeneous architecture which combines CNN with GRU . The proposed base learner is optimised, thus comprising of two CNN layers (each with a convolutional layer, an activation layer and a max-pooling layer) followed consequently by a GRU layer, a flatten layer and a dense layer. ReLU activation layer is also used here. The hidden dimension and number of hidden layers is defined as 10 and 3 for GRU, which has no cell state. The flatten layer is used to reshape the output of the GRU layer to better fit the dense layer which makes the output predictions (as shown in Figure 7).

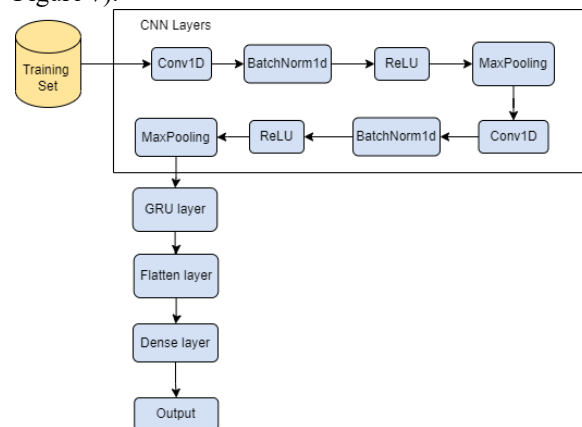


Figure 7: CNN-GRU architecture

LSTM-GRU. The third base learner is hybrid heterogeneous architecture which combines LSTM with GRU. This model is optimised by defining the number of hidden dimensions for LSTM and GRU as 240 and 10 respectively with 3 hidden layers. A subsequent flatten layer is used to reshape the output of the GRU layer to better fit the dense layer which makes the output predictions (as shown in Figure 8).

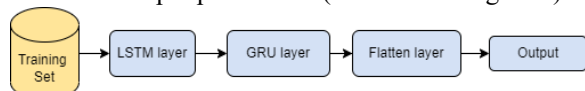


Figure 8: LSTM-GRU architecture

4.1.2. Statistical Models

Bayesian Neural Network (BNN). Standard Neural Networks are powerful because of their flexibility of having many model parameters that are learned by optimisation. But because of this powerful flexibility, they are prone to overfitting. Bayesian Neural Networks (BNNs) are an extension of Standard Neural Networks as they learn model parameters by marginalization - a process of attaching probability distributions to the model parameters (weights and biases). This makes the model robust and helps it to generalize better without overfitting. In addition to finding the distributions of model parameters, it finds the conditional distribution of them by the property of Bayesian inference to compute the posterior probability as the output. Thus, this model is also beneficial in quantifying uncertainties which play a pivotal role in reducing effects of uncertainties in learning. Our fourth base learner is optimised and comprises of three layers of BNN and a ReLU activation which on processing through a sigmoid function provides the predictive output (as shown in Figure 9).

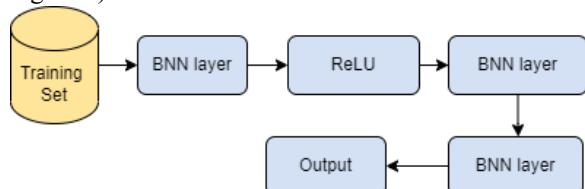


Figure 9: BNN architecture

Logistic Regression (LR). Logistic Regression is a probabilistic predictive technique that finds a link between characteristics of the data and the likelihood of a specific outcome. Our fifth base learner comprises an optimised order of two sets of a Linear layer, a ReLU activation and a 0.5 Dropout rate, which is followed by a dense layer that yields the prediction (as shown in Figure 10).

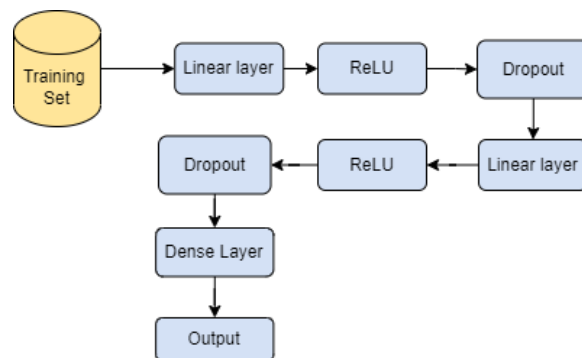


Figure 10: LR architecture

4.2. META LEARNER

The output of the base learners serve as the input to the meta learner, which is a dense layer with 5 neurons corresponding to the predictions from the 5 base learners. The final layer is the sigmoid function that tallies all the output values between 0 and 1. The proposed system uses ‘Adam’ optimizer (an adaptive moment estimation algorithm) which is a commonly used default optimizer known for its quick computation and requirement of fewer parameters for optimization. MSE (Mean of Squared Errors) loss function, which finds the average of the squared differences between the actual and predicted values, is used for back-propagation of the network.

Results

The results obtained after training, validating and testing the models corresponding with the evaluation metrics chosen are discussed in detail below.

5.1. Performance Metrics

In order to get the most approximate results, the proposed system’s performance is evaluated using four metrics. Mean Squared Error (MSE) and Root Mean Squared Error (RMSE) helps to understand the losses incurred during prediction. To determine the strength and direction of relationships between the variables, Pearson and Spearman Correlation Coefficients are calculated. R2 score helps to assess how well the model performs, with a good baseline score (generally ≥ 0.5) fixed to compare.

Pearson’s Correlation Coefficient. is used to measure the relationship between 2 variables. Usually ranging between -1 to +1, it gives an insight on the magnitude or association between the variables.

$$r = \frac{\sum (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum (x_i - \bar{x})^2 \sum (y_i - \bar{y})^2}}$$

Where,

r = Pearson's Correlation Coefficient

x_i = x variable samples

y_i = y variable samples

$\bar{x}$ = Mean of x variable samples

$\bar{y}$ = Mean of y variable samples

R-Square. score indicates how much of a variation of a dependent variable is seen by the independent variable.

$$R^2 = 1 - \left\{ \frac{\text{sum squared regression (SSR)}}{\text{total sum of squares (SST)}} \right\}$$

$$= 1 - \frac{\sum (y_i - \hat{y}_i)^2}{\sum (y_i - \bar{y})^2}$$

Where,

y_i = Actual y values

$\hat{y}$ = Predicted y values

$\bar{y}$ = Mean of the y values

Spearman's Rank Correlation Coefficient. It is a non-parametric version of Pearson. It tells the monotonic relationships of the variables and the dependence of the ranking between them, instead of using the actual observations

$$\rho = 1 - \frac{6 \sum d_i^2}{n(n^2 - 1)}$$

Where,

ρ = Spearman Correlation Coefficient

d_i = Difference between the two ranks of each observation

n = Number of observations

Root Mean Squared Error (RMSE). measures the average difference between values predicted by a model and the actual values. It gives out an estimation of how well the model is able to predict the target value (accuracy).

$$RMSE = \sqrt{\frac{\sum_{i=1}^n (\hat{y}_i - y_i)^2}{n}}$$

Where,

$\hat{y}$ = Predicted y values

y_i = Actual y values

n = Number of observations

Mean Squared Error (MSE). tells us how much the predicted value differs from the actual value. It shows the error (deviation) is seen in the prediction.

$$MSE = \frac{1}{n} \left\{ \sum_{i=1}^n (y_i - \hat{y}_i)^2 \right\}$$

Where,

$\hat{y}$ = Predicted y values

y_i = Actual y values

n = Number of observations

5.2. Performance Results

5.2.1. Evaluation of Single, Hybrid and Base Models

The results of the single models, base learners, and the proposed stacked ensemble model are as follows. The models undergo 5-fold cross-validation, where the data set is separated into 5-folds. Of each fold, one part is set as validation set, another as test set, while the eight other parts are the training set. The training set is utilized in training the system and by using the validation set, the most optimal result is acquired. The final results after the training phase of 100 epochs are collected with the help of the test set.

Results of the single models (as shown in Tables 1 - 3), the base learners consisting of the hybrid models (as shown in Tables 4 - 6) and the statistical models (as shown in Tables 7 - 8) over 5 folds are tabulated and their averages are calculated. Similarly, the results of the overall proposed stacked ensemble model over 5 folds are tabulated and averages are calculated (as shown in Table 9).

Table 1: Results of CNN model(100 epochs)

Fold	RMS E	MSE	Pearson s's coeffici ent	Spearm an coeffici ent	R ² score
Fold 0	0.13 47	0.01 82	0.8265	0.8142	0.66 4
Fold 1	0.12 78	0.01 63	0.8435	0.8201	0.70 54
Fold 2	0.12 7	0.01 61	0.8396	0.8128	0.70 06
Fold 3	0.13 75	0.01 89	0.8061	0.8032	0.64 56
Fold 4	0.13	0.01	0.8172	0.8201	0.65

	78	9			37
Average	0.133	0.0177	0.8266	0.8141	0.6739

Table 2: Results of LSTM model(100 epochs)

Fold	RMS E	MSE	Pearson's coefficient	Spearman coefficient	R ² score
Fold 0	0.1393	0.0194	0.8063	0.7299	0.646
Fold 1	0.1356	0.0184	0.8185	0.7725	0.6564
Fold 2	0.1321	0.0175	0.8206	0.7564	0.6647
Fold 3	0.1387	0.0192	0.8145	0.7556	0.6538
Fold 4	0.1335	0.0178	0.8255	0.7671	0.6708
Average	0.1358	0.0185	0.8171	0.7563	0.6583

Table 3: Results of GRU model(100 epochs)

Fold	RMS E	MSE	Pearson's coefficient	Spearman coefficient	R ² score
Fold 0	0.1304	0.017	0.839	0.7864	0.7021
Fold 1	0.1337	0.0179	0.8236	0.776	0.6757
Fold 2	0.1247	0.0155	0.8335	0.7699	0.6922
Fold 3	0.1283	0.0165	0.8367	0.7889	0.6994
Fold 4	0.1274	0.0162	0.8392	0.7955	0.7038
Average	0.1289	0.0166	0.8344	0.7833	0.6947

Hybrid models CNN-LSTM, CNN-GRU, LSTM-GRU are built using the mentioned single models. It is observed that the hybrids models showed an

improvement of around 9%, 6%, 8% in R2 scores respectively, RMSE score reduced by around 8%, 7%, 7% respectively and the Pearson and Spearman coefficients have increased by 3% when compared to single models.

Table 4: Results of CNN-LSTM model(100 epochs)

Fold	RMS E	MSE	Pearson's coefficient	Spearman coefficient	R ² score
Fold 0	0.1261	0.0159	0.8608	0.8252	0.7358
Fold 1	0.1196	0.0143	0.8454	0.8141	0.7123
Fold 2	0.1225	0.015	0.8616	0.8187	0.7423
Fold 3	0.1198	0.0144	0.8583	0.8264	0.7342
Fold 4	0.1245	0.0155	0.8511	0.8194	0.7241
Average	0.1225	0.015	0.8554	0.8207	0.7297

Table 5: Results of CNN-GRU model(100 epochs)

Fold	RMS E	MSE	Pearson's coefficient	Spearman coefficient	R ² score
Fold 0	0.1222	0.0149	0.8534	0.8103	0.7042
Fold 1	0.1228	0.0151	0.8532	0.8175	0.7248
Fold 2	0.1173	0.0138	0.8544	0.8178	0.7275
Fold 3	0.1213	0.0147	0.8435	0.8115	0.7096
Fold 4	0.1251	0.0156	0.854	0.811	0.7281
Average	0.1217	0.0148	0.8517	0.8136	0.7188

Table 6: Results of LSTM-GRU model(100 epochs)

Fold	RMS	MSE	Pearson	Spearman	R ²
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	E		s's coeffici ent	an coeffici ent	score
Fold 0	0.12 34	0.01 56	0.8527	0.811	0.72 6
Fold 1	0.12 39	0.01 53	0.8491	0.8095	0.71 24
Fold 2	0.11 98	0.01 43	0.8486	0.8018	0.71 6
Fold 3	0.12 32	0.01 52	0.8505	0.8144	0.72 27
Fold 4	0.12 34	0.01 52	0.847	0.8041	0.70 31
Avera ge	0.12 27	0.01 51	0.8496	0.8082	0.71 57

Table 7: Results of BNN model(100 epochs)

Fold	RMS E	MSE	Pearson s's coeffici ent	Spearm an coeffici ent	R ² score
Fold 0	0.13 88	0.01 93	0.8043	0.7778	0.63 89
Fold 1	0.14 28	0.02 04	0.8253	0.774	0.61 42
Fold 2	0.13 87	0.01 92	0.8245	0.7859	0.64 11
Fold 3	0.14 09	0.01 98	0.7983	0.7602	0.62 56
Fold 4	0.13 92	0.01 94	0.8079	0.7832	0.65 23
Avera ge	0.14 01	0.01 96	0.812	0.7762	0.63 44

Table 8: Results of LR model(100 epochs)

Fold	RMS E	MSE	Pearson s's coeffici ent	Spearm an coeffici ent	R ² score
Fold 0	0.11 92	0.01 42	0.8606	0.8263	0.74 07

Fold 1	0.12 05	0.01 45	0.8587	0.8248	0.73 47
Fold 2	0.12 17	0.01 48	0.8567	0.819	0.74 19
Fold 3	0.12 35	0.01 53	0.8517	0.8187	0.81 87
Fold 4	0.12 22	0.01 49	0.8604	0.8173	0.73 83
Avera ge	0.12 14	0.01 47	0.8576	0.8212	0.75 49

Table 9: Results of Hybrid Stacked Ensemble model(100 epochs)

Fold	RMS E	MSE	Pearson s's coeffici ent	Spearm an coeffici ent	R ² score
Fold 0	0.11 9	0.01 42	0.8589	0.8316	0.73 71
Fold 1	0.12 2	0.01 49	0.8554	0.8222	0.72 99
Fold 2	0.12 32	0.01 52	0.856	0.8222	0.73 25
Fold 3	0.12 3	0.01 51	0.8527	0.8226	0.72 63
Fold 4	0.11 33	0.01 28	0.8732	0.8214	0.76 25
Avera ge	0.12 01	0.01 44	0.8593	0.824	0.73 77

5.2.2. Results of the Proposed System with Meta Learner

The averages of the results of the single models, the base learners and the proposed stacked ensemble model with meta-learner form the overall performances to be compared (as shown in Table 10). A good performing predictive model must have comparatively lower loss scores (RMSE & MSE) than existing ones, and higher correlation coefficients (Pearson and Spearman coefficients). Usually, a larger R2 score (≥ 0.7) describes a good model that fits a set of observations well.

Table 10: Comparison of overall results of single models, base learners and the proposed system

Model	RMSE	MSE	Pearson's coefficient	Spearman coefficient	R ² score
CNN	0.133	0.0177	0.8266	0.8141	0.6739
LSTM	0.1358	0.0185	0.8171	0.7563	0.6583
GRU	0.1289	0.0166	0.8344	0.7833	0.6947
CNN-LSTM	0.1225	0.015	0.8554	0.8207	0.7297
CNN-GRU	0.1217	0.0148	0.8517	0.8136	0.7188
LSTM-GRU	0.1227	0.0151	0.8496	0.8082	0.7157
BNN	0.1401	0.0196	0.812	0.7762	0.6344
Logistic Regression	0.1214	0.0147	0.8576	0.8212	0.7549
Stacked Ensemble	0.1201	0.0144	0.8593	0.824	0.7377

5.2.3. Comparison of Models across all the Performance Metrics

The proposed system involves hybrid deep learning models alongside statistical models as base learners. The following graphs indicate the advantages of using hybrid models instead of single models in terms of the performance metrics (as shown in Figures 11 - 15). The hybrid models showed improved results in RMSE scores, with around 7% decrease from those of single models. The stacked ensemble model showed further improvement in RMSE and MSE scores by reducing them to around 4% more than the other models. Hybrid models showed an improvement in correlation coefficients by around 3% than those of single models. The stacked ensemble model showed a further noticeable improvement of around 2% than the other compared models. Hybrids models showed an increase of around 7% in R2 scores compared to the scores of single models. The stacked ensemble model's R2 is a commendable score ($R^2 \geq 0.7$ is a good score) but fared second best after logistic regression, which can

be attributed to its complex model structure. This can be subject to improvement in future studies.

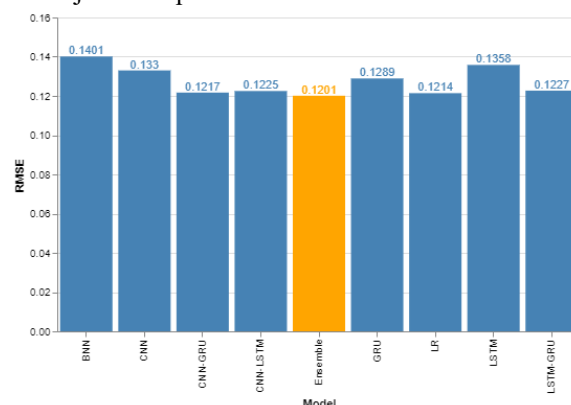


Figure 11: Root mean square error (RMSE)

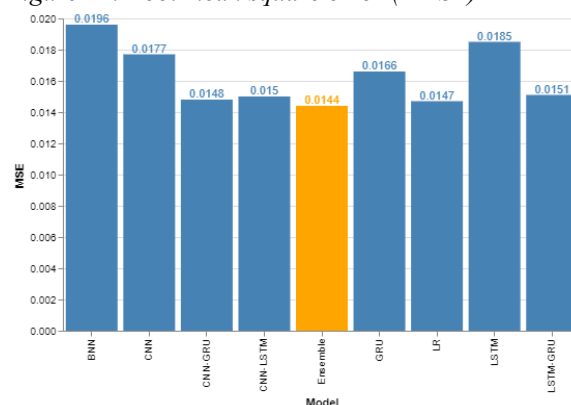


Figure 12: Mean square error (MSE)

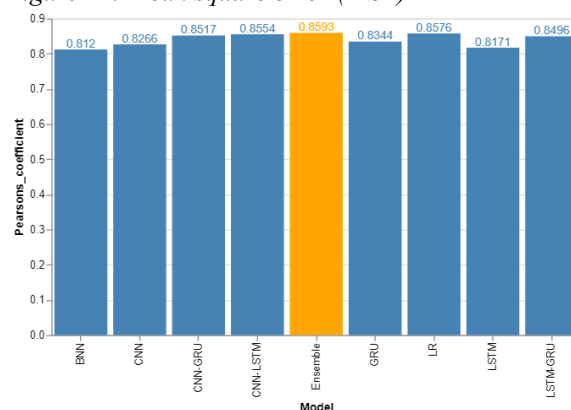


Figure 13: Pearson correlation coefficient

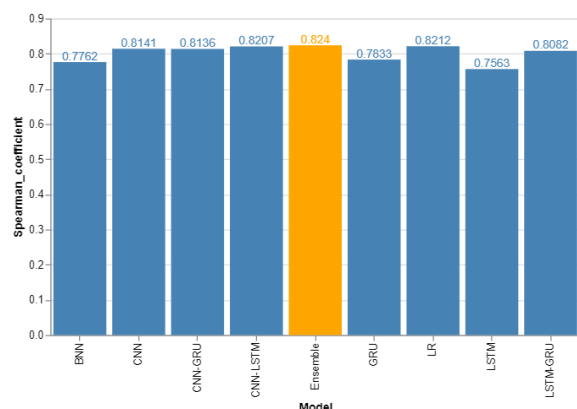


Figure 14: Spearman's coefficient

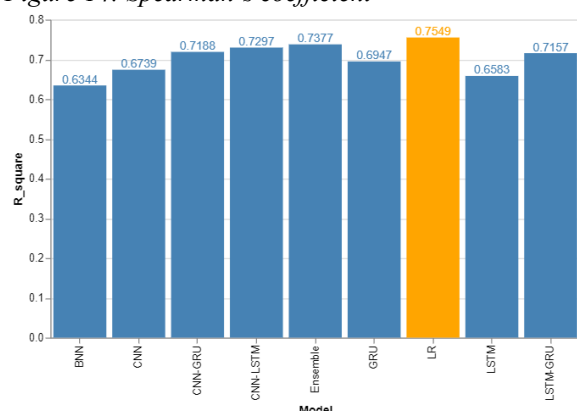


Figure 15: R-square

5.2.4. Assessment of Drug-Response Values

The lower values of IC50 suggest that the drug is effective in smaller concentrations and so may show less toxicity in the patients to whom it is administered to. For example, in (as shown in Table 11), for A549 LUNG biomarker, among the group of drugs, Carboxyamidotriazole is the most effective drug as it requires the lowest concentration of drug needed to be given to the patient to inhibit the growth of that biomarker. Drug AZ960 will be needed in comparatively higher concentration amounts to inhibit that biomarker. Thus, this system will be valuable in helping medical professionals determine the drug to administer, lowering the cost of experimentation like side effects, uncertainty of drug effectiveness and facilitates quicker treatment. It will also be beneficial to pharmaceutical companies to know the drug effectiveness, thereby in identifying potent drugs and creating personalized treatment.

Table 11: Drug-Response Values

ccl_name	pubchem_cid	drug_name	label_ic50	pred_ic50
A549_LUNG	108144	carboxyamidotriazole	0.636113684	0.65524286
A549_LUNG	121926	ZK-93423	0.821813671	0.65667886
A549_LUNG	216345	nutlin-3	0.812020714	0.65676796
A549_LUNG	1549000	levocetirizine	0.834251164	0.66175777
A549_LUNG	9799509	ER-27319	0.755840472	0.66340894
A549_LUNG	2802	clonazepam	0.538081743	0.66456234
A549_LUNG	5284616	sirolimus	0.823603832	0.6702838
A549_LUNG	25254071	GDC-0980	0.766966977	0.67129654
A549_LUNG	151194	vatalanib	0.870017719	0.67129874
A549_LUNG	25099184	AZ960	0.640776624	0.6747414



5.2.5. Comparison of Results With Existing Work

The datasets used make the data integration and preprocessing methods performed in this work unique to them and confines the comparison to be done with existing similar works. In the work done by Cheng et al. [12], they used a pan-cancer dataset which includes more than one cancer types - with biomarker data obtained from CCLE, drug data from PubChem and drug response data from PRISM Repurposing repositories and used a fully connected layer to predict the drug responses. The metrics used to analyse the performance are RMSE and MSE scores, Pearson and Spearman coefficients, R2 score. Firstly, the existing model of fully connected layer in [12] is run with the lung cancer dataset and the results are tabulated (as shown in Table 12). The performances of the proposed system and the fully connected layer [12] with the lung cancer dataset are compared in the Table 13.

Table 12: Results of existing model (fully connected layer) [12] with lung cancer dataset

Fold	RMS E	MSE	Pearson s's coefficient	Spearman coefficient	R ² score
Fold 0	0.1212	0.0147	0.8494	0.8308	0.7556
Fold 1	0.1209	0.0146	0.8544	0.804	0.7284
Fold 2	0.1223	0.015	0.8579	0.8236	0.7527
Fold 3	0.1231	0.0151	0.8568	0.825	0.7325
Fold 4	0.1201	0.0144	0.8605	0.8202	0.7387
Average	0.1215	0.0148	0.8558	0.8207	0.7416

Table 13: Comparison of performance metrics of existing model (fully connected layer) [12] and the proposed system (Stacked Ensemble) with the lung cancer dataset

Model	RMSE	MSE	Pearson's coefficient	Spearman coefficient	R ² score
Fully Connected Layer	0.1215	0.0148	0.8558	0.8207	0.7416
Stacked Ensemble	0.1201	0.0144	0.8593	0.824	0.7377

It can be observed that, with the lung cancer dataset, the proposed stacked ensemble model fared well than the fully connected layer [12]. Comparing their evaluation metrics, the stacked ensemble's RMSE & MSE scores were a 2% decrease, Pearson and Spearman Coefficients were an 0.4% increase than the fully connected layer [12] and R2 score was still > 0.7, registering as 0.7377. Thus, the proposed system has good performance with improvement in the performance metrics over the baseline. Following this, with the external pan-cancer dataset, the results of the fully connected layer in [12] are tabulated as in Table 15, and the results of the proposed stacked ensemble with the external pan-cancer dataset are tabulated as in Table 14. The proposed system performs similarly to the existing work [12] with the external pan-cancer dataset (as shown in Table 16).

Table 14: Performance of the proposed stacked ensemble model on pan-cancer dataset

Fold	RMSE	MSE	Pearson's coefficient	Spearman coefficient	R ² score
Fold 0	0.0901	0.0081	0.858	0.8313	0.7357
Fold 1	0.0897	0.008	0.8604	0.8309	0.7398
Fold 2	0.0909	0.0083	0.8564	0.8304	0.7332
Fold 3	0.0912	0.0083	0.8547	0.8286	0.7302

Fold 4	0.0902	0.0081	0.8594	0.8338	0.7379
Average	0.0904	0.0082	0.8578	0.831	0.7354

Table 15: Performance of existing model (fully connected layer) [12] with the pan-cancer dataset

Fold	RMSE	MSE	Pearson's coefficient	Spearman coefficient	R ² score
Fold 0	0.0896	0.008	0.8656	0.8326	0.7325
Fold 1	0.0905	0.0082	0.8651	0.8312	0.732
Fold 2	0.894	0.008	0.8698	0.8211	0.7436
Fold 3	0.0895	0.008	0.8602	0.8301	0.7396
Fold 4	0.09	0.0081	0.8562	0.8312	0.7337
Average	0.0898	0.0081	0.8634	0.8292	0.7363

Table 16: Comparison of performance metrics of existing model (fully connected layer) [12] and proposed system (Stacked Ensemble) with pan-cancer dataset

Model	RMSE	MSE	Pearson's coefficient	Spearman coefficient	R ² score
Fully Connected Layer	0.0898	0.0081	0.8634	0.8292	0.7363
Stacked Ensemble	0.0904	0.0082	0.8578	0.831	0.7354

The reason for this can be attributed to the effect of the weaker base model BNN. This is evidently understood from the previous section elaborating our base model performances against the ensemble technique where BNN posted the weakest results across all metrics. BNN's performances decreases further as the size of

the dataset increases, as its capability of specifying distributions over the model parameters works well in quantifying uncertainty when the data and features are scarce. When size increases, the distributions sharpen giving no uncertainty (variance) to the parameters, thus the solutions start to resemble standard neural networks which result in overfitting.

4. Discussion

The implementation of the proposed work is done by integrating and preprocessing the data, constructing the base learners and meta learner for the proposed system's Stacked Ensemble model, training and evaluating the system's performances. The proposed system predicts the drug-response values for the corresponding biomarker-drug pairs after preprocessing the data and extracting the various features. The drug-responses are IC50 values (50% inhibitory concentration) which is a conventionally used measure to determine the effects of the drug while testing on biological molecules. It indicates the amount of drug that can be administered to the patient to inhibit a biological process (such as cancer metastasis) in them by 50%, by which it can be ascertained whether the patient is sensitive or resistant to the drug. Drugs that have lower drug-response scores, in general sense, are chosen as the treatment for the particular biomarker. On comparing the overall performances, it is analysed that the stacked ensemble model has improved RMSE & MSE scores by reducing them to around 4% from the base learners and Pearson & Spearman coefficients are also increased by nearly around 2% than the base learners. Lower loss scores show that the actual and predicted values are close to each other indicating better accuracy. The improved correlation coefficients can be attributed to the low loss scores, showing a close relationship and exactness between the actual and predicted values. However the stacked ensemble's R2 score is not as good as when compared to that of Logistic regression. This maybe because of LR model's simple structure which defines a marginally better estimate of relationship between the dependent and independent variables than our proposed system's complex structure. But the marginal difference observed does not affect the goodness of-fit of the stacked ensemble model much, although it can be improved. The proposed stacked ensemble performs similarly well as the existing fully connected layer [12] despite BNN's weak performance as the other base models leverage their better results in improving the metrics. This exhibits the benefits of proposed system's stacked ensemble model. Modifying the stacked ensemble model by replacing BNN with another strong model will most likely increase the current performance significantly, as well as refinements by trying with another set of base models and meta learner may see possible improvements.

5. Conclusion

In this work, the prediction of drug responses from multi-faceted omics and drug data using a stacked ensemble model for lung cancer is attempted. Study of literatures pointed at multiple problems. Firstly, the lack of use of diverse and latest data in this area of study was identified. To counter this, the recently created PRISM Repurposing dataset is made used and CCLE's cell line dataset with miRNA expression and DNA copy number features is utilized. Drug physiochemical data and features like SMILES and molecular fingerprints were obtained. Additionally, to fulfill the need of integrating and processing these structurally different datasets, appropriate preprocessing to normalize, remove outliers were done and their features were extracted by various methods like GCN, CNN, RDKit tool. This solves another limitation seen in previous works which is 'curse of dimensionality', suffered by existing models which were trained with fewer features but huge data. This feature extraction done here enables such large diverse information to be ready for feeding into the trainable model. The proposed stacked ensemble model is designed to harness all the benefits of multiple models when used at once. The meta learner results of the stacked ensemble produced a more robust performance than the base models used. The advantage by using hybrid deep learning models CNN-LSTM, CNN-GRU and LSTM-GRU in the stacked ensemble is noticed as they posted an improvement of around 9%, 6%, 8% in R2 scores respectively, RMSE score reduced by around 8%, 7%, 7% respectively and the Pearson's and Spearman coefficients have increased by 3% than the single models. The proposed stacked ensemble showed further improvement of 4% decrease in RMSE & MSE scores and 3% increase in Pearson & Spearman coefficients than the base learners, and a R2 score of 0.7377. Thus, the stacked ensemble approach proves its capacity to provide a boosted performance by combining multiple models in the same problem. The limitation of this work was the similar performance seen, as the existing work [12], while scaling the observations. It is understood that the functions of the base models must be kept in mind when selecting them to utilize in the stacked ensemble, when the incoming data is huge in size. As mentioned in the performance analysis, this is achievable, as stacked ensemble approach opens room for any type and number of base models to be used. Hence, future studies may be done with this in mind and test various combinations of models with the aim of improving performance. Further, the proposed system can be coupled with pathway analysis of the drug's behaviour in the body while suggesting for treatment. This would be beneficial while using in clinical trials to deploy the

proposed system into actual practice for physicians. Also, suggesting a combination of multiple drugs for treatment is a possible scope as more data on the effects of such therapies become available to avoid any toxic side effects.

Compliance with Ethical Standards

Competing Interests: All Authors and co-authors declare that they have no conflict of interest.

Ethical Approval: This article does not contain any studies of human participants or animals performed by any of the authors. The manuscript is not submitted to more than one journal for simultaneous consideration.

Consent to Participate: Informed consent is not necessary as this article does not involve human or animal participants.

Consent to Publish: All the authors agree to publish the manuscript in the journal without any conflict.

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