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AN AUTOMATED TB DRUG RESISTANCE PREDICTION USING CT AND DEEP LEARNING

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Abstract:

Tuberculosis (TB) is an infectious disease primarily caused by Mycobacterium tuberculosis, mainly affecting the lungs but potentially spreading to other organs like the brain, kidneys, or spine. It spreads through microscopic droplets released when an infected person coughs, sneezes, or talks. In 2021, the World Health Organization estimated that 10.6 million people worldwide were affected by TB, with 1.6 million deaths. Notably, TB cases increased by 3.6% between 2020 and 2021. When TB bacteria enter the respiratory system, immune cells called macrophages attempt to engulf them, but the bacteria c an survive and form granulomas—dense clusters of immune cells and bacteria. Early detection, prognosis, and identification of resistant TB cases are crucial.The objective of this work is to use deep learning Convolutional Neural Network (CNN) to predict drug resistance and drug sensitivity in tuberculosis based on the genomic data. The existing techniques for determining drug resistance in tuberculosis strains are laborious and include growing bacteria in the presence of drugs. Getting the outcomes of this can take a long time. These techniques can also produce false positives or false negatives and are not always accurate. The proposed work intends to address these shortcomings by offering a quicker and more precise way to determine drug resistance in strains of tuberculosis. In terms of prediction performance, the proposed approach attained 97.27% accuracy. This model may be applied in clinical applications to diagnose tuberculosis drug resistance more quickly and accurately, improving patient outcomes after treatment.

Keywords: Drug resistance, Drug sensitivity, TB drugs, Prognosis, Diagnosis, Macrophages, Genomic data, Deep CNN, CT images

INTRODUCTION

A bacterial infection that mostly affects the lungs but can potentially spread to other parts of the body is tuberculosis. Mycobacterium tuberculosis is the bacteria that causes it. When an infected person coughs, sneezes or talks, they release microscopic respiratory droplets that contain the bacteria that cause tuberculosis. Although Mycobacterium tuberculosis is the main and best-known cause of tuberculosis, other related mycobacteria can also cause diseases that are similar to tuberculosis. The World Health Organization (WHO) estimates that 10.6 million individuals worldwide are afflicted with tuberculosis in 2021, and 1.6 million of those cases resulted in fatalities. Additionally, the incidence rate of tuberculosis increased significantly between 2020 and 2021 by 3.6%. While the lungs are the primary organ affected by tuberculosis, it can also damage the brain, kidneys, or spine. The primary problem that needs to be addressed is the need for early detection, prognosis, and identification of resistant tuberculosis occurrences.Lung infections can occur when Mycobacterium tuberculosis germs get into a person's respiratory system. After then, immune cells known as macrophages absorb the bacteria, and these cells allow the germs to live and

proliferate. Granulomas, which are microscopic, dense aggregates containing bacteria and immune cells, may result from this. Since ancient times, tuberculosis has been a serious threat to world health and remains so today, particularly in areas with poor access to public health resources and medical care. Vaccination, early detection, efficient treatment, contact tracking, and public health initiatives to lower transmission are all part of the fight against tuberculosis.Concepts such as drug sensitivity and resistance are crucial for treating tuberculosis. These words describe the reactions of the Mycobacterium tuberculosis bacteria to the medications used in tuberculosis treatment.

LITERATURE SURVEY

Acharya, B., Acharya, A., Gautam, S., Ghimire, S.P., Mishra, G., Para- juli, N. and Sapkota, B., 2020. Advances in diagnosis of Tuberculosis: an update into molecular diagnosis of Mycobacterium tuberculosis. Molecular biology reports, 47, pp.4065-4075.Tuberculosis (TB) is a major cause of deaths by a single infectious agent and has now been a global public health problem due to increasing numbers of drug-resistant cases. Early and effective treatment is crucial to prevent the emergence of drug-resistance strains. This demands the availability of fast and reliable point-of-care (POC) diagnostic methods for effective case management. Commonly used methods to screen and diagnose TB are clinical, immunological, microscopy, radiography, and bacterial culture. In addition, recent advances in molecular diagnostic methods including MTBDRplus, loop-mediated isothermal amplification (LAMP), line probe assay (LPA), GeneXpert, and whole genome sequencing (WGS) have been employed to diagnose and characterize TB. These methods can simultaneously identify Mycobacterium tuberculosis (MTB) and mutation(s) associated with routinely used anti-TB drugs. Here, we review the use of currently available diagnostic

methods and strategies including conventional to recently implemented next-generation sequencing (NGS) methods used to detect MTB in clinical perspective.

Ranjitha, J., Rajan, A. and Shankar, V., 2020. Features of the bio- chemistry of Mycobacterium smegmatis, as a possible model for Mycobacterium tuberculosis. Journal of infection and public health, 13(9), pp.1255-1264.Objective Actinomycetes have been known to be the great natural sources to explore antibiotics for the treatment of tuberculosis (TB). The isolation of actinomycetes from the samples in Vietnam followed by the screening of their antimycobacterial activity was performed in this study. The metabolites isolated from the most active strain were further evaluated for their antimycobacterial, antimicrobial and cytotoxic activity. Methods Actinomycetes were growth in culture media, isolated and identified by colony, spore chain morphology and 16S rRNA gene sequencing. Agar diffusion assay was used for the screening of the isolated strains against Mycobacterium smegmatis, a safety surrogate for Mycobacterium tuberculosis. The metabolites produced from the most active strain were investigated by actinomycete fermentation, extraction and isolation from biomass and cultures. The structures of the isolated compound were elucidated by spectral data and comparison with the reported literatures. Results 181 strains were isolated from nine regions along the north to central Vietnam. The five most active strains against Mycobacterium smegmatis were detected. Following the bioassay-guided result, the strain A121 (Streptomyces alboniger) was selected for further isolation of the bioactive metabolites.

Ernest, J.P., Strydom, N., Wang, Q., Zhang, N., Nuermberger, E., Dar- tois, V. and Savic, R.M., 2021. Development of new tuberculosis drugs: translation to regimen composition for drug-sensitive and multidrug- resistant tuberculosis. Annual review of pharmacology and toxicology, 61, pp.495-516.Tuberculosis (TB) kills more people than any other infectious disease. Challenges for developing better treatments include the complex pathology due to within-host immune dynamics, interpatient variability in disease severity and drug pharmacokinetics-pharmacodynamics (PK-PD), and the growing emergence of resistance. Model-informed drug development using quantitative and translational pharmacology has become increasingly recognized as a method capable of drug prioritization and regimen optimization to efficiently progress compounds through TB drug development phases. In this review, we examine translational models and tools, including plasma PK scaling, site-of-disease lesion PK, host-immune and bacteria interplay, combination PK-PD models of multidrug regimens, resistance formation, and integration of data across nonclinical and clinical phases.We propose a workflow that integrates these tools with computational platforms to identify drug combinations that have the potential to accelerate sterilization, reduce relapse rates, and limit the emergence of resistance.

Singh, V. and Chibale, K., 2021. Strategies to combat multi-drug resis- tance in tuberculosis. Accounts of chemical research, 54(10), pp.2361-2376.Drug resistance is an unavoidable consequence of the use of drugs; however, the emergence of multi-drug resistance can be managed by accurate diagnosis and tailor-made regimens."Antimicrobial resistance (AMR), is one of the most paramount health perils that has emerged in the 21st century. The global increase in drug-resistant strains of various bacterial pathogens prompted the World Health Organization (WHO) to develop a priority list of AMR pathogens. Mycobacterium tuberculosis (Mtb), an acid-fast bacillus that causes tuberculosis (TB), merits being one of the highest priority pathogens on this list since drug-resistant TB (DR-TB) accounts for ~29% of deaths attributable to AMR. In recent years, funded collaborative efforts of researchers from academia, not-for-profit virtual R&D organizations and industry have resulted in the continuous growth of the TB drug discovery and development pipeline. This has so far led to the accelerated regulatory approval of bedaquiline and delamanid for the treatment of DR-TB.

Jamal, S., Khubaib, M., Gangwar, R., Grover, S., Grover, A. and Hasnain, S.E., 2020. Artificial Intelligence and Machine learning based prediction of resistant and susceptible mutations in Mycobacterium tuberculosis. Scientific reports, 10(1), p.5487.Tuberculosis (TB), an infectious disease caused by Mycobacterium tuberculosis (M.tb), causes highest number of deaths globally for any bacterial disease necessitating novel diagnosis and treatment strategies. High-throughput sequencing methods generate a large amount of data which could be exploited in determining multi-drug resistant (MDR-TB) associated mutations. The present work is a computational framework that uses artificial intelligence (AI) based machine learning (ML) approaches for predicting resistance in the genes rpoB, inhA, katG, pncA, gyrA and gyrB for the drugs rifampicin, isoniazid, pyrazinamide and fluoroquinolones. The single nucleotide variations were represented by several sequence and structural features that indicate the influence of mutations on the target protein coded by each gene. We used ML algorithms - naïve bayes, k nearest neighbor, support vector machine, and artificial neural network, to build the prediction models. The classification models had an average accuracy of 85% across all examined genes and were evaluated on an external unseen dataset to demonstrate their application. Further, molecular docking and molecular dynamics simulations were performed for wild type and predicted resistance causing mutant protein and anti-TB drug complexes to study their impact on the conformation of proteins to confirm the observed phenotype.

PROPOSED METHODOLOGY

The project "Automated TB Drug Resistance Prediction using CT and Deep Learning" is implemented entirely using Python. The interface for this project is created using Python's Tkinter library. The prediction system utilizes Convolutional Neural Networks (CNN) and Gradient Boosted Trees (GBT) algorithms. In this project, the user needs to upload a CT scan image and provide some basic details like age, gender, and medical history. After uploading the image and entering the details, the user can click the predict button to predict TB drug resistance based on the provided inputs. The system offers an accuracy score between 0 and 1, indicating the reliability of the prediction.

Data pre-processing is a process of preparing the raw data and making it suitable for a machine learning model. It is the first and crucial step while creating a machine learning model. When creating a machine learning project, it is not always a case that we come across the clean and formatted data. And while doing any operation with data, it is mandatory to clean it and put in a formatted way. So, for this, we use data pre-processing task. A real-world data generally contains noises, missing values, and maybe in an unusable format which cannot be directly used for machine learning models.

Data pre-processing is required tasks for cleaning the data and making it suitable for a machine learning model which also increases the accuracy and efficiency of a machine learning model.Once the model has been trained, it must be evaluated on a separate test dataset to measure its performance. This phase tests the model's ability to generalize to new, unseen data. Performance metrics like accuracy, precision, recall, and F1 score are often used to evaluate how well the model is detecting spam while minimizing false positives and false negatives. The test set acts as a proxy for how the model will behave in real-world applications.A real-world data generally contains noises, missing values, and maybe in an unusable format which cannot be directly used for machine learning models.

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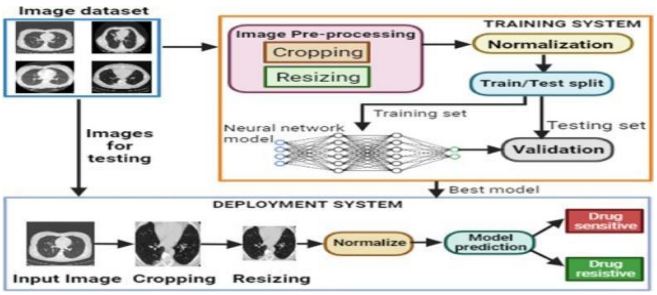

Figure 1: Proposed System Architecture

Data Split :Once a dataset has been collected, it is typically divided into three subsets: training, testing, and validation (or hold-out) data. The training data is used to train the machine learning model, allowing the system to learn patterns and relationships within the data. The testing data is used to evaluate the model's performance on previously unseen examples, providing an estimate of how well the model will perform in the real world. The hold-out set or validation set is used for hyperparameter tuning or to check the model's performance periodically during the training phase. A common split is 70% for training, 15% for testing, and 15% for validation.

Pre-processing :Before feeding the data into a machine learning model, pre-processing is essential to clean and prepare the data. This may involve steps such as removing irrelevant information (e.g., special characters, stopwords), converting text to lowercase, normalizing text (e.g., stemming or lemmatization), and handling missing values. Pre- processing also includes handling outliers or noisy data that could disrupt the model's learning process. The goal is to ensure that the data is in a clean and usable format, optimizing the learning process.

Train : The training phase involves using the labeled dataset to train a machine learning model. The algorithm learns from the data by adjusting its internal parameters to minimize error. During training, the system is exposed to a large number of examples (both spam and legitimate messages) to help it distinguish between the two. This phase is crucial because the quality of training directly impacts the performance of the model. If the model is trained on a representative dataset, it is more likely to perform well on unseen data.

Test :Once the model has been trained, it must be evaluated on a separate test dataset to measure its performance. This phase tests the model's ability to generalize to new, unseen data. Performance metrics like accuracy, precision, recall, and F1 score are often used to evaluate how well the model is detecting spam while minimizing false positives and false negatives. The test set acts as a proxy for how the model will behave in real-world applications.

Hold-out :The hold-out set is used to ensure that the model's performance is evaluated on data that was not used during training. The hold-out set is typically kept aside during the training process, and once the model is trained and fine-tuned, the hold-out data is used for final evaluation. This step helps to prevent overfitting, where the model becomes too tailored to the training data and fails to generalize well to new data.

Applications :

Early Detection of Drug Resistance: Deep learning models can analyze CT scans to predict drug resistance in TB patients, enabling timely intervention and personalized treatment plans.Treatment Outcome Prediction: By analyzing longitudinal CT scans, these systems can predict treatment outcomes, helping clinicians adjust therapies to improve patient recovery rates.Reduction in Diagnostic Time: Automated systems can significantly reduce the time required for diagnosing drug-resistant TB compared to traditional culture-based methods.Resource Optimization: In resource-limited settings, these tools can provide cost-effective and efficient diagnostic support, reducing the burden on healthcare systems.

Enhanced Accuracy: Deep learning models can improve diagnostic accuracy by identifying subtle patterns in CT scans that may be missed by human radiologists.Support for Clinical Decision-Making: These systems can assist clinicians in making informed decisions about drug regimens and treatment strategies.Public Health Monitoring: Automated tools can contribute to large-scale monitoring and surveillance of drug-resistant TB, aiding in public health planning and policy-making.Research and Development: These technologies can be used in research to study the progression of TB and the effectiveness of new drugs or treatment protocols.

Advantages :

Improved Diagnostic Speed: The system can rapidly analyze CT images and predict drug resistance, significantly reducing the time compared to traditional methods like culture tests.High Accuracy: Deep learning algorithms can detect subtle patterns in CT images that may be overlooked by human experts, leading to more accurate predictions.

Personalized Treatment Plans: By identifying drug resistance profiles early, the project allows for tailored treatment strategies, improving patient outcomes.Cost-Effective Solution: Once developed, the system can provide diagnostics at a lower cost, making advanced care accessible, especially in resource-limited settings.

Scalability: The system can handle large volumes of data, enabling widespread screening in high TB-burden areas.Non-Invasive Diagnosis: Unlike certain laboratory tests, CT-based prediction is a non-invasive approach, enhancing patient comfort.

Enhanced Resource Allocation: Faster and more accurate predictions allow healthcare systems to better allocate resources, focusing efforts where they are most needed.Aid to Radiologists: The system can serve as a decision-support tool, assisting radiologists in diagnosing complex cases with greater confidence.

Reduction in Multidrug-Resistance Spread: Early identification of drug resistance helps curb the spread by ensuring timely and appropriate treatments.Research Contributions: The project can contribute valuable data and insights to the field, driving further advancements in TB diagnosis and treatment.

EXPERIMENTAL ANALYSIS

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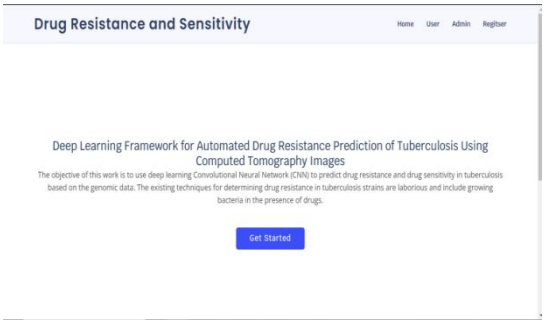

Figure 2: Home Page

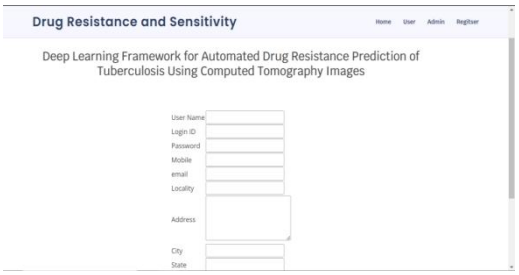

Figure 3: Registration Page

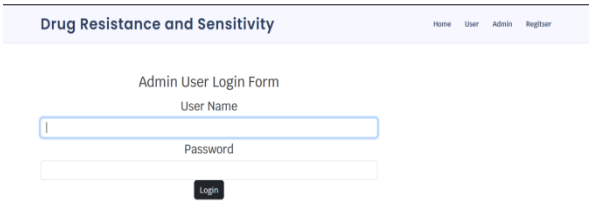

Figure 4: Admin Page

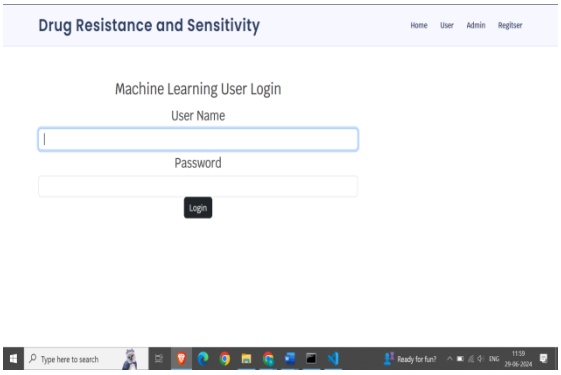

Fig 5 : User Login Page

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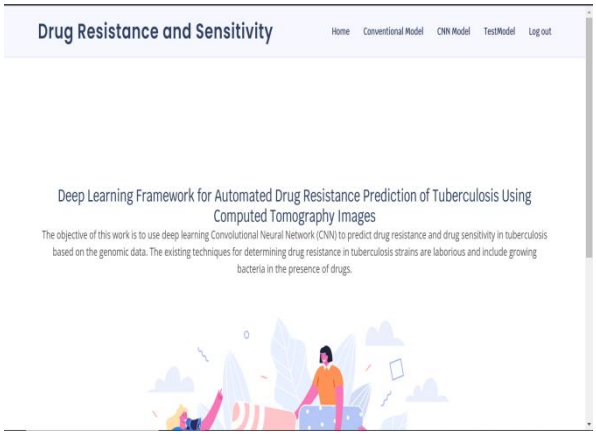

Figure 6: User Home Page

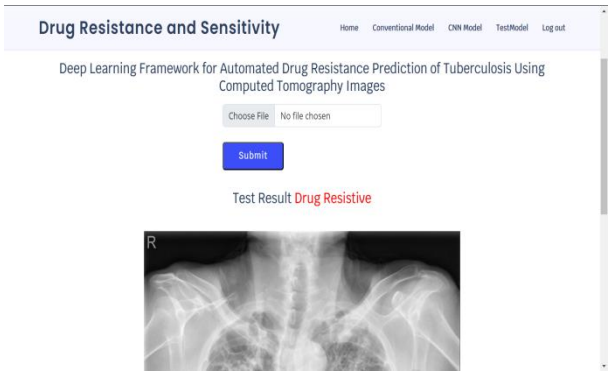

Figure 7: Final Prediction Page

CONCLUSION

In the proposed work, we have developed a deep learning model for the classification of tuberculosis drug response using CT images. The prediction is made using a deep learning CNN model. This study demonstrates the effectiveness of deep learning techniques, with the proposed CNN-based model achieving a 97.27% classification accuracy. CNN can increase precision and speed up the diagnosis and treatment of tuber- culosis, enabling more rapid evaluations of drug sensitivity and resistance. This can therefore result in more specialized and successful treatment plans. The proposed model does not exhibit overfitting and yielded good results in the testing set. Additionally, the creation and implementation of the user interface helps radiologists diagnose tuberculosis in real-time. Overall, the proposed approach can greatly support radiolo- gists in making more informed medical judgments when it comes to determining the treatment response of samples of tuberculosis. It is important to understand that using CNNs to predict drug resistance is just one factor in the process; other factors that must be considered in order to provide reliable predictions include choosing the right model architecture and having a high-quality dataset. It is imperative to collaborate with domain experts and physicians to ensure that the model's predictions align with clinical practice and decision-making.

CNN MODEL

Input Data Preparation: Collect CT scan images of patients' lungs, which will serve as the input data for the CNN model. Ensure that the images are in a consistent format and resolution.Labeling Data: Annotate the images with labels indicating whether the TB strain is drug-resistant or drug-sensitive. These labels are essential for supervised learning.

Normalization: Normalize the pixel values of the CT scan images to a range (e.g., 0 to 1) to ensure consistent input for the CNN.Augmentation: Apply data augmentation techniques such as rotation, flipping, and scaling to increase the diversity of the training dataset and improve the model's robustness.

Convolutional Layers: The core components of the CNN are the convolutional layers, which apply convolutional filters to the input images to extract features.Filters/Kernels: Small matrices that scan over the input image, detecting patterns such as edges, textures, and shapes.Stride and Padding: Parameters that control how the filters move over the image and how the image boundaries are handled.

Activation Function: Apply a non-linear activation function, typically the Rectified Linear Unit (ReLU), to introduce non-linearity into the model.

ReLU Activation: f(x)=max⁡(0,x)f(x) = \max(0, x)

Pooling Layers: Reduce the spatial dimensions of the feature maps, retaining the most important information and reducing computational complexity.Max Pooling: Takes the maximum value from each patch of the feature map.

Fully Connected Layers: After several convolutional and pooling layers, flatten the feature maps and pass them through fully connected layers to perform classification.Dense Layers: Connect every neuron in one layer to every neuron in the next layer.

Loss Function: Choose a suitable loss function to measure the difference between the predicted and actual labels. For binary classification, the binary cross-entropy loss is commonly used.

Optimizer: Select an optimizer to update the model's weights based on the loss gradients. Common choices include Adam, SGD, and

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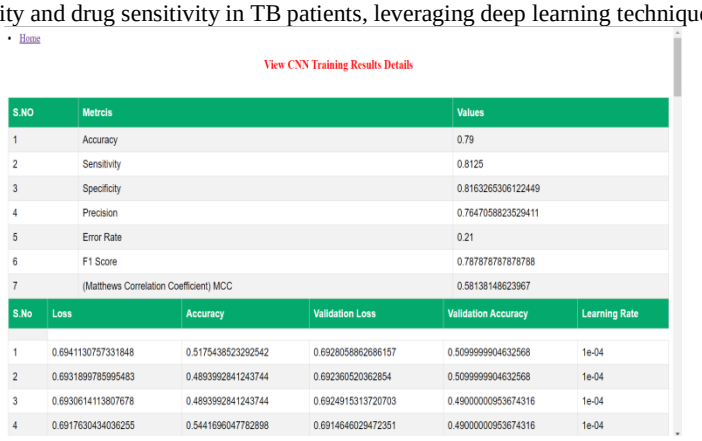
RMSprop.Adam Optimizer: An adaptive learning rate optimizer that combines the advantages of both SGD and RMSprop.Training Data: Feed the preprocessed CT scan images and corresponding labels into the CNN model. Batch Size: The number of training samples processed before the model's weights are updated.
Backpropagation: Calculate the gradients of the loss function with respect to the model's weights and update the weights to minimize the loss.Validation: Use a portion of the data as a validation set to monitor the model's performance and prevent overfitting.
Classification Report: Generate a detailed classification report including metrics such as precision, recall, F1-score, and support for each class.Test Data: Input new CT scan images into the trained CNN model to predict drug resistivity or drug sensitivity.
Output: The model outputs the predicted class label (e.g., drug-resistant, drug-sensitive) along with a confidence score indicating the probability of the prediction.This step-by-step explanation outlines how the CNN algorithm processes CT scan images to predict drug resistivity and drug sensitivity in TB patients, leveraging deep learning techniques to achieve accurate and efficient predictions.



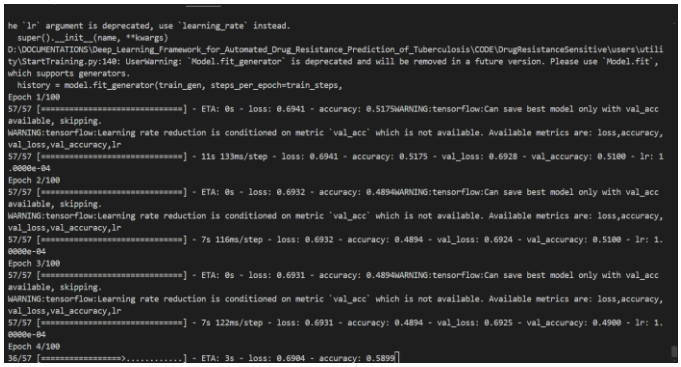
Home

View CNN Training Results Details

S.NO	Metrcis	Values
1	Accuracy	0.79
2	Sensitivity	0.8125
3	Specificity	0.8163265306122449
4	Precision	0.7647058823529411
5	Error Rate	0.21
6	F1 Score	0.787878787878788
7	(Matthews Correlation Coefficient) MCC	0.5813148623967

S.No	Loss	Accuracy	Validation Loss	Validation Accuracy	Learning Rate
1	0.6941130757331848	0.5175438523292542	0.6928058862686157	0.5099999904632568	1e-04
2	0.6931899785995483	0.4893992841243744	0.692360520362854	0.5099999904632568	1e-04
3	0.6930614113807678	0.4893992841243744	0.6924915313720703	0.49000000953674316	1e-04
4	0.6917630434036255	0.5441696047782898	0.6914646029472351	0.49000000953674316	1e-04

Figure 8: CNN Model results



```
he `lr` argument is deprecated, use `learning_rate` instead.
  super().__init__(name, **kwargs)
D:\DOCUMENTATIONS\Deep_Learning_Framework_for_Automated_Drug_Resistance_Prediction_of_Tuberculosis\CODE\DrugResistanceSensitive\users\utili
ty\StartTraining.py:140: UserWarning: `Model.fit_generator` is deprecated and will be removed in a future version. Please use `Model.fit`,
which supports generators.
  history = model.fit_generator(train_gen, steps_per_epoch=train_steps,
Epoch 1/100
57/57 [==============================] - ETA: 0s - loss: 0.6941 - accuracy: 0.5175WARNING:tensorflow:Can save best model only with val_acc
available, skipping.
WARNING:tensorflow:Learning rate reduction is conditioned on metric `val_acc` which is not available. Available metrics are: loss,accuracy,
val_loss,val_accuracy,lr
57/57 [==============================] - 11s 133ms/step - loss: 0.6941 - accuracy: 0.5175 - val_loss: 0.6928 - val_accuracy: 0.5100 - lr: 1
.0000e-04
Epoch 2/100
57/57 [==============================] - ETA: 0s - loss: 0.6932 - accuracy: 0.4894WARNING:tensorflow:Can save best model only with val_acc
available, skipping.
WARNING:tensorflow:Learning rate reduction is conditioned on metric `val_acc` which is not available. Available metrics are: loss,accuracy,
val_loss,val_accuracy,lr
57/57 [==============================] - 7s 116ms/step - loss: 0.6932 - accuracy: 0.4894 - val_loss: 0.6924 - val_accuracy: 0.5100 - lr: 1.
0000e-04
Epoch 3/100
57/57 [==============================] - ETA: 0s - loss: 0.6931 - accuracy: 0.4894WARNING:tensorflow:Can save best model only with val_acc
available, skipping.
WARNING:tensorflow:Learning rate reduction is conditioned on metric `val_acc` which is not available. Available metrics are: loss,accuracy,
val_loss,val_accuracy,lr
57/57 [==============================] - 7s 122ms/step - loss: 0.6931 - accuracy: 0.4894 - val_loss: 0.6925 - val_accuracy: 0.4900 - lr: 1.
0000e-04
Epoch 4/100
36/57 [===============>.............] - ETA: 3s - loss: 0.6904 - accuracy: 0.5899
```

Figure 9: CNN Model training phase

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