Genetic Brain Disease Classification using Machine Learning And Deep Learning

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***Abstract*—This research brings out a new approach for the identification of genetic brain diseases in their early stages by employing DNA sequence embeddings. This dataset has employed the largest dataset used for brain disease classification till now. Our methoded maps raw DNA sequences into a structured vector representation, which includes important structural and functional genomic features. These embeddings are used as input to more sophisticated classifiers such as the proposed Stacking Classifier and basic deep learning classifiers such as the CNNs, to learn patterns that may point towards different brain diseases. From the results of our experiments, we can conclude that the proposed Stacking Classifier, trained according to the particularities of a specific domain, has an accuracy of 79 percent, which is nearly similar to the CNN model's performance. This equivalence in performance does not only establish the effectiveness of the proposed ensemble system design that incorporates multiple base learners in a coherent and synergistic manner but also points to the possibility of utilizing high-level features extracted from DNA embeddings to improve the diagnostic pipelines in genomic applications.**

***Index Terms*—Brain Diseases, DNA sequence, DNABert embeddings, deep learning, machine learning, bioinformatics**

I. Introduction

Genomic research in the context of the current and future development has brought more insights into the genetic factors that underlie complex diseases, especially those of neurological nature. This increase in knowledge is mainly due to the combination of high-throughput sequencing techniques with advanced computational approaches, which give the investigators a vast view of the molecular mechanisms of neurological diseases. However, these issues have not been resolved and the task of making sense of raw DNA sequences remains as difficult as ever, presenting a great opportunity for developing new approaches to unlock the potential of the vast amounts of genetic data available.

In response, our work proposes a novel framework that incorporates DNA sequence embeddings to help identify brain diseases at an early stage. These embeddings learn to map genomic DNA sequences into real-valued vectors while preserving relevant structural and functional characteristics. Our method utilizes the state-of-art deep learning architectures such as Convolutional and Artificial Neural Networks to extract the features from these embeddings. These features make them highly useful in diagnosing neurological disorders ranging from Alzheimer's, Parkinson's and various neurodevelopmental disorders.

The effectiveness of our method and its ability to generalize well across different datasets can be highlighted by the results of the experiments we conducted on multiple datasets, which not only significantly improves the interpretability of the genomic data, but also lays the foundation for future work in this area. These two accomplishments help to contribute to the development of genomic medicine to help identify possible treatments and strategies for early diagnosis and the ultimate goal of enhancing patient care through specific targeted therapies.

II. Literature Survey

The paper by Ramalakshmi et al. (2021)[1] presents a literature survey on the classification of DNA sequences using deep learning techniques such as CNNs, hybrid models combining CNNs with LSTM and bidirectional LSTM networks. The authors review various existing studies employing deep learning models for DNA sequence classification across different applications, including identifying pathogens, detecting virus effects, and drug design. They discuss the use of techniques like CNNs, DNNs, N-gram probabilistic models, extreme gradient boosting algorithms with hybrid features, feature selection and stacking methods, alignment-free models based on K-mer feature extraction, and linear classifiers. The survey also covers the application of deep learning for predicting specific viruses like SARS-CoV-2, improving code construction for DNA sequences, classifying complex sequences with ensemble decision tree approaches, and classifying DNA sequences for cancer patients.

The paper by A. Raza et al. (2022)[2] analyzes a dataset with 44 attributes, including patient information, family history, medical test results, and genetic information. The proposed ETRF feature engineering approach combines the ET and RF algorithms to extract features from the genomes dataset, which are then used as input for learning techniques to predict genetic disorders and their types. The study introduces the ETRF method for feature extraction, which is utilized to develop learning models that predict genetic disorders. The research by S. Victor[3] focuses on the importance of prediction in medical diagnosis in the field of bioinformatics, highlighting its role in improving healthcare efficiency and

reducing complexities in treatment. The use of DNA sequences and structure information is proposed as a means to get the accuracy and optimization of disease. The study by Ismaeel et al. (2013) proposes a novel method for predicting disease based on mutations in the gene sequence, specifically focusing on breast cancer mutations. The method utilizes bioinformatics techniques such as FASTA and CLUSTALW to detect malignant mutations that increase the probability of cancer, and the backpropagation algorithm is trained to classify whether a patient has the disease or not[3].

The paper by Ismaeel et al. (2013)[4] on a machine learning model is to predict the disease due to mutations in the gene sequence and the researchers have applied the model especially for the breast cancer mutations. The method utilizes bioinformatics techniques such as FASTA and CLUSTALW to detect malignant mutations that increase the probability of cancer. Cross entropy is trained with expected malignant mutations of particular genes like BRCA1, BRCA 2 genes in breast cancer and used for the prediction of whether the patient is affected or not. Cancer diagnosis is the crucial step of cancer treatment and the paper stresses on the significance of early and accurate diagnosis and opens the possibilities provided by computer-aided diagnosis. Further researches will be directed with the goal of creating a regional data base of genetic diseases and creating an integrated system of early diagnostic for patients with genetic diseases using the identified method. The paper also mentions the use of feedforward back-propagation neural networks for classifying malignant mutations for breast cancer.

Classification of skin disease based on color and texture feature is the main concern presented in the paper under consideration [5] by K. V. Swamy. It employs the hue, saturation and value color model to transform the RGB color space to other more comprehensible space and infer the current state of affairs regarding texture based feature extraction techniques for skin disease identification. The algorithm proposed in the paper is, DT and SVM, and the classification is based on entropy, variance, and maximum histogram value of the feature, namely, HSV, and the performance analysis was done based on accuracy.

This paper by Pandey(2023) et al introduces a solution for early disease identification by leveraging DNA sequence classification, particularly crucial in the context of fast-spreading viruses like COVID-19. Utilizing samples from NCBI's Genbank, the proposed framework matches patient DNA samples to identify diseases, aided by a new hot vector-based representation for feature extraction. Through extensive experimentation and comparison with traditional classifiers, including CNN, SVM, KNN, Decision Trees, and RNN, the proposed method achieves a high accuracy rate of 93.9 percent, demonstrating its potential in enhancing public health efforts through early disease prediction and management[6].The paper by Senol et al (2011) addresses the complexity of disease prediction by considering the interplay of multiple genomes and their impact on disease susceptibility. By leveraging DNA sequences and Bayesian network pathway analysis, the system aims to determine the probabilistic levels of disease occurrence based on mutations in causal and associated genes. Emphasizing the importance of genetic information in disease prediction, the paper discusses methodologies and architectures to effectively identify disease markers and pathways. Case studies on diseases like Type-1 Diabetes and Crohn's disease further validate the system's potential in enhancing disease prevention strategies.[7]

In this study, Wu et al. [8] selected six frequently occurring facial skin diseases which are acne, freckles, rosacea, senile spots, seborrheic keratosis, and skin prolapse, and they compared five different networks, ResNet-50, Inception-v3, DenseNet121, Xception, and Inception-ResNet-v2 using the largest clinical image dataset of skin diseases in China Alshahrani also emphasized that Inception-ResNet-v2 was the best one which downloaded to a definite understanding that deep learning was promising in medical images processing. In the same vein, Ahmad et al. [9] introduced a discriminative feature leaning approach to hyper fine-tune ResNet152 as well as InceptionResNet-V2 model using a triplet loss function that boosts the efficiency of skin disease image classification. One of the remarkable alternatives of theirs is based on deep CNNs to embed input images into Euclidean space and distinguishes the images employing L-2 distance among images learning discriminative features yielding a comparatively high accuracy compared to many advanced methods. This study utilized a dataset of human face skin disease images from a hospital in Wuhan, China, to show the applicability of the conceived framework in outcomping conventional methods.

Saied et al. [10] employed a new approach with the S-parameter of six antennas placed around the head to monitor the shifts in the dielectric properties of the brain that are characteristic of AD. In their study, they employed differing methodologies that assist with machine learning, such as Logistic Regression, demonstrated a 98. For example, in distinguishing between Alzheimer's disease (AD) stages, it achieved 97% accuracy, outperforming the traditional MRI and PET scans. Gunduz [11] developed two deep learning frameworks that were based on CNNs for classifying PD using several sets of vocal features. The source of data for the study was the UCI Machine Learning Repository, and the author found marked enhancement in classification accuracy and discriminative ability over conventional techniques. Nair et al. [12] developed another study in adopting an ensemble approach employed feature selection and classification method that employs SVM, KNN, and Decision Tree algorithm that improves performance by using a majority voting system. Veetil et al. [13] have reviewed five major architectures of deep learning and the authors showed while there exists overlap, VGG19 performs best at classifying the T2-Weighted MRI scans That are from PPMI dataset and reiterated the usefulness of transfer learning in medical image classification.

The paper by Sarada Jayan et al. (2022)[16] compares different machine learning techniques for cancer classification by employing RNA-seq data, considering 5 types of cancerous tumors are breast carcinoma, KIRC refers to kidney renal carcinoma, and LUAD is an acronym for lung adenocarcinoma

as does PRAD for prostate adenocarcinoma while the last is COAD for colon adenocarcinoma. Carried out using exploratory analysis, PCA is subsequently used for data feature reduction; the paper examines six algorithms: Naïve Bayes, knn , logistic regression, decision tree, random forest, and svm. The overall working and performance analysis indicates that out of all the algorithms, SVM and random forest have surpassed all with accuracy, SVM has achieved an optimum accuracy of 100% and its time complexity is lesser than that of Random Forest, AUC-ROC, and class separability is as well higher in SVM that in Random Forest. A recent paper by Kiran Kumar et al. (2019)[17] offer a review of the various machine learning techniques utilized in early cancer predicting and prognosis models for the various types of cancer such as breast, oral, skin, colon, and lung cancer among others. Regarding computational methods and methodologies of the past and present for machine learning in cancer prediction and diagnosis, it describes the advantages, disadvantages, and critical points related to existing methodologies with which one may need help developing new machine learning methodologies for greater disease-specific prediction and diagnosis.

P. Jyothi et al. [20] put forward an approach using the Support Vector Machine (SVM) in connection with DNAPred to predict hereditary diseases by analyzing the DNAs sequences inherited from parents to children. The base of the methodology is to improve the accuracy of the forecasts using the neural networks, and to emphasize that the selected method – SVM – showed the best result among all the classifiers that were tested. Many studies have used human genome data with an attempt to diagnose severe dengue prognoses using various machine learning techniques; the C. Davi et al. [18] study used SNP selection support vector machine and an artificial neural network for classification. A traditional strategy they used bearing evidence of high accuracy, sensitivity, and specificity was pointing towards the fact that the genetic context offers the possibility of defining the phenotype in dengue. Dolci et al. [19] suggest a deep MMG architecture incorporating f/ sMRI & retiring/learnable genomes for AD. functional MRI, structural MRI, retiring genomes, learnable genomes In an attempt to fill this gap, their model leverages knowledge transferred from generative adversarial networks in an effort to perform better in predicting admittance to the Alzheimer's even when presented with incompletely acquired data.

III. Methodology

In this section, we detail the development and implementation of our dataset,Machine Learning & deep Learning Algorithms and our custom stacking classifier model. This section outlines the systematic approach taken to evaluate and integrate multiple predictive algorithms into a cohesive and optimized framework, ensuring both high accuracy and robust performance in our predictive tasks.

A. Data Collection

The methodology for retrieving data from the NCBI Nucleotide database uses a focused web scraping approach with the BioPython library Entrez module, which allows programmatic access to biological data. Specific queries are formulated for diseases such as Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Down Syndrome, Epilepsy, and Parkinson's Disease, using the format "[Disease Name][Title] AND Homo sapiens[Organism]" to ensure searches are confined to human-related studies and exclude non-human data. The Entrez.esearch function conducts searches within the 'nucleotide' database, retrieving a predefined number of entries (typically 100) that match the disease-specific criteria, producing a list of sequence identifiers. These identifiers are then used with the Entrez.efetch function to download the sequence data in FASTA format. Sequences are processed using SeqIO.parse for parsing and extracting both the sequence IDs and their corresponding sequences, facilitating systematic data extraction and subsequent analysis tailored to specific research needs.

B. BERT Embeddings

We utilized the 'bert-base-uncased' BERT model to create embeddings from nucleotide sequences associated with various genetic brain diseases. This model is adept at capturing deep contextual relationships within data, which is crucial for understanding complex biological sequences. We transformed these sequences into 6-mer tokens to align with BERT's input requirements, ensuring that each token adequately represents the genetic information. After tokenizing, these sequences were fed into the BERT model, and we extracted embeddings by averaging the outputs of the last hidden state, resulting in a 768-dimensional vector for each sequence. The final dataset, structured into a DataFrame, includes columns for the sequence ID, its associated disease label, and the 768 embedding dimensions.

C. Pseudocode:

Approach taken for generating the sequence embeddings from NCBI is described in Algorithm I

D. Dataset Details

In our study, we have compiled a dataset comprising 5,000 genetic sequences sourced from the NCBI database. To maintain class balance, we included 1000 sequences from each of five different diseases: Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Down Syndrome, Epilepsy, and Parkinson's Disease. Each genomic sequence was transformed into embeddings using DNA BERT, resulting in 768-dimensional vectors that encapsulate the features of the sequences. Consequently, our final dataset dimensions are 1000 rows, each corresponding to a sequence, and 768 columns, representing the feature vectors derived from DNA BERT embeddings.

Algorithm 1 Generate Sequence Embeddings from NCBI Database

Require: BERT tokenizer and model initialized
Ensure: Sequence embeddings are generated and saved

Input: disease_name
Initiate search for nucleotide data associated with the disease
Retrieve sequence IDs from NCBI database
if sequence IDs are found **then**
    Fetch sequences using sequence IDs
    if sequences are successfully retrieved **then**
        Generate embeddings using BERT model
        Prepare a data structure to store sequence IDs, embeddings, and disease name
        Save the data structure to an Excel file
        Print confirmation of saved embeddings
    else
        Print error message: No sequences retrieved
    end if
else
    Print error message: No sequences found
end if

E. Data Quality Enhancements

To ensure the integrity and non-redundancy of our dataset, we implemented a rigorous two-fold verification system. This approach was necessitated by the conversion of all sequences into embedding vectors, allowing for more nuanced similarity analyses.

1) Cosine Similarity Analysis: We used cosine similarity to compare the embedding vectors of our 5000 sequences, resulting in 12,497,500 pairwise comparisons. Our analysis revealed:

- 20% of comparisons resulted in 100% similarity
- 60% of comparisons showed similarity above 95%

These findings indicated significant potential redundancy within our dataset, necessitating further investigation and refinement.

2) Needleman-Wunsch Algorithm for Secondary Verification: To address sequences with high similarity ($\geq$95% but $<$100%), we implemented a secondary verification using the Needleman-Wunsch algorithm. We randomly selected 100 sequence pairs from those with $\geq$95% cosine similarity for this analysis.

Our two-fold verification system allowed us to

- Remove truly redundant data with high confidence
- Retain sequences that represented unique biological entities despite high embedding similarity

3) Dataset Refinement: Following these analyses, we refined our dataset by removing 100% similar sequences, eliminating near-identical sequences confirmed by Needleman-Wunsch alignment, and flagging ambiguous cases for expert review. The resulting refined dataset served as the basis for our subsequent analyses, with a portion reserved for testing purposes.

This comprehensive approach to dataset curation combined efficient computational methods with intensive biological sequence analysis, balancing computational efficiency with biological relevance. The result was a dataset of significantly improved quality and reliability for our genetic disease classification of brain disorders.

F. Model Training

1) Machine Learning& Deep Learning Models: : As part of our work, we used different machine learning techniques, such as Random Forest, XGBoost, K-NN, SVM, CatBoost, AdaBoost, Decision Tree, Naive Bayes, Convolutional Neural Network (CNN), and Multi-Layer Perceptron (MLP). All these algorithms have been selected for their ability to address different aspects of the genetic data that goes into the classification of diseases.

TABLE I
HYPERPARAMETER TABLE

Algorithm	Final Hyperparameter Values
Random Forest	n_estimators: 100 criterion: 'gini' max_features: 'auto' max_depth: 30 min_samples_split: 2 min_samples_leaf: 1 bootstrap: True
XGBoost	n_estimators: 100 max_depth: 6 learning_rate: 0.1 subsample: 0.9 colsample_bytree: 0.9
K-Nearest Neighbors	n_neighbors: 5 weights: 'uniform' p: 2 leaf_size: 10
Support Vector Machine	C: 1 kernel: 'rbf' gamma: 'scale'
CatBoost	depth: 6 learning_rate: 0.01 iterations: 100
AdaBoost	n_estimators: 100 learning_rate: 0.1
Decision Tree	max_depth: 20 min_samples_split: 2 min_samples_leaf: 1
Naive Bayes	No hyperparameters to tune
Convolutional Neural Network	filters: 64 kernel_size: 3 Dense: 128 Dropout: 0.5
Multi-Layer Perceptron	hidden_layer_sizes: (100,) alpha: 0.0001 solver: 'adam'

2) Hyper-parameter Tuning: To find the best set of hyperparameters for different machine learning models that will enhance the predictive accuracy of disease classification from genetic data, we used the Grid Search technique. Grid Search is an iterative process that consists of comparing several combinations of hyperparameters which have been predetermined and then using cross-validation to check their performance. Because of this, we can seamlessly cover all possible combinations of the parameters and determine the best values for each

model. The values from the grid search which are seen in the reference table, Table I include parameters such as the number of estimators, depth of the trees, learning rates and other model specific parameters for models like Random Forest, XGBoost, SVM and many more. These values reflect the settings we used in this study that yielded the highest-performing models on our data,.

3) Custom Model: Building on the foundational research of previous studies, we have developed a novel custom stacking classifier model, the mechanics of which are detailed in the flow chart below (see Fig1). This model operates by initially evaluating a range of algorithms to identify those that deliver the most accurate predictions. The selected algorithms are then utilized as base models, with the highest performing algorithm serving as the meta-model. This strategic configuration results in a custom model that is uniquely tailored to optimize performance. The primary advantage of our custom stacking classifier is its enhanced predictive accuracy and robustness, achieved by effectively combining the strengths of individual models into a cohesive system. This approach, which represents a novel contribution to the field, ensures that our model not only advances theoretical understanding but also enhances practical applications in predictive analytics.

As shown in the pseudo code below we have taken

Algorithm 2 Stacking Classifier Approach

Require: Dataset D, base models set M
Ensure: Trained stacking classifier
Split D into D_{train} and D_{test}
for each model $m_i \in M$ **do**
    Evaluate m_i on D_{train} via cross-validation
    if performance of $m_i > threshold$ **then**
        Add m_i to selected models S
    end if
end for
Train each model in S on D_{train}
Generate predictions P from S on D_{train}
Train meta-model M_{meta} on P
Generate final predictions using S and M_{meta} on D_{test}
return Trained stacking classifier

IV. Results & Discussion

This section presents a comparative analysis of the different machine learning, deep learning and Custom Models applied to BERT embeddings, focusing on their performance across three crucial metrics: Accuracy, Precision, Recall, and F1 Score.

The comparative study of several machine learning techniques presented in Table II reveals diversified results depending on the algo- rithms used, suggesting that Random Forest and XGBoost are very close performers, thus confirming that ensemble methods yield the best performance with the feature set extracted from BERT. These findings are also quite accurate, further suggesting that even simple classification techniques like KNN and SVM can harness the power of the rich feature maps to solve classification problems.

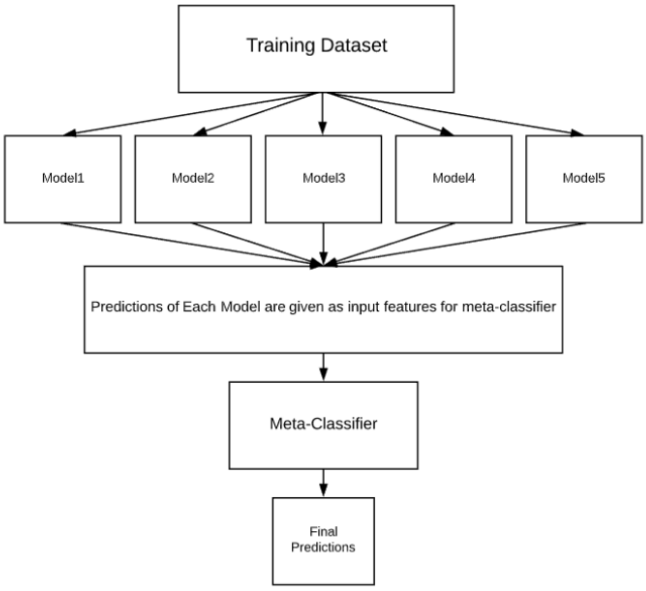


Fig. 1. Flow Diagram of Stacking/Blending Classifier

TABLE II
Model Performance on BERT- Embeddings

Algorithm	Accuracy
Random Forest	0.7437
XGBoost	0.7425
KNN	0.7312
SVM	0.7587
CatBoost	0.7400
AdaBoost	0.4862
Decision Tree	0.6125
Naive Bayes	0.6200
CNN	0.7900
MLP	0.7400
Stacking Classifier	0.7900
Voting Classifier	0.7850

In comparison, it was observed that AdaBoost performed substantially worse, which may be attributed to noise and outliers present in high-dimensional data which is a common feature of the BERT-developed datasets. The Decision Tree algorithm had a lower performance which might have been caused by generalization problems, particularly when dealing with more comprehensive data structures. Naive Bayes performed the worst, which highlighted the inefficiency of applying probabilistic techniques to address the context of the embeddings in a high-dimensional environment. The CNN and MLP models, trained over 20 epochs, demonstrated varying degrees of success with the BERT embeddings. The highest accuracy achieved by these models was 0.79, indicating a strong capacity to effectively capture and utilize complex patterns from the embeddings.

In Fig 3.Each curve represents the model's ability to distinguish between one specific disease and all other classes, with the area under the curve (AUC) providing a measure of the model's overall performance. High AUC values, ranging from 0.91 for Epilepsy to 0.97 for ALS, indicate that the

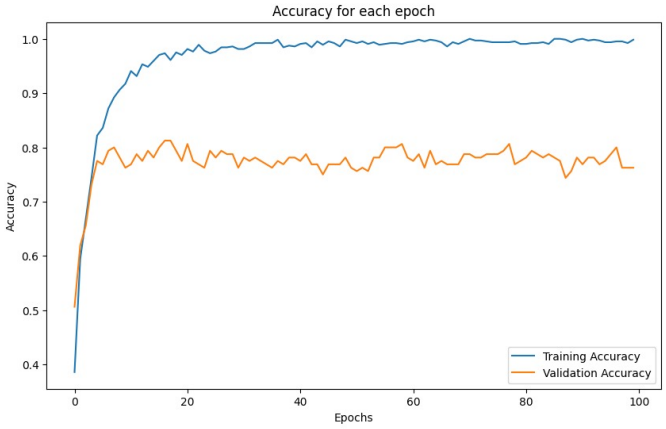


Fig. 2. Accuracy Vs Epochs Graph Of CNN

model effectively discriminates between classes with a low rate of false positives. The closeness of these curves towards the upper left corner reflects high true positive rates and low false positive rates, showcasing the model's accuracy and reliability in disease prediction across multiple conditions.

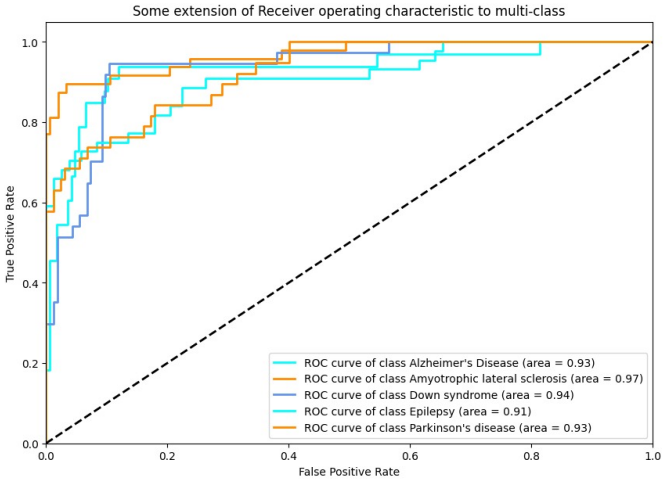
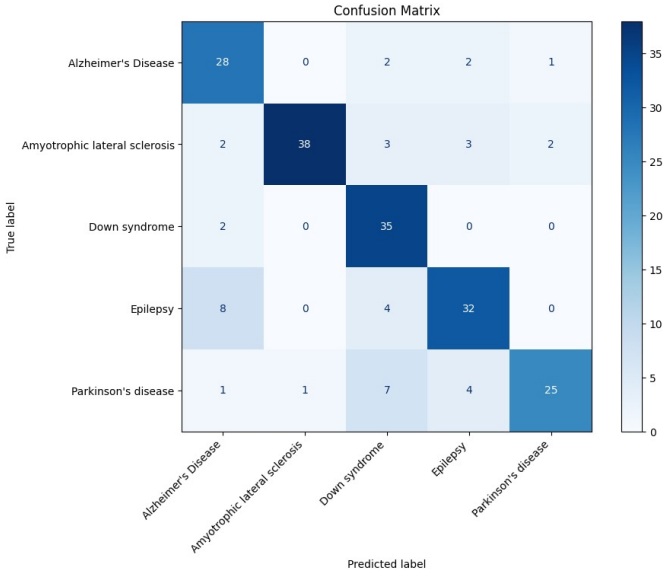


Fig. 3. AUROC Curve

Regarding our ensemble approach, the Stacking Classifier emerged as the top-performing model with an accuracy of 0.79, matching the highest scores seen in our experiments with CNN and MLP models. This ensemble method effectively combines multiple learning algorithms to benefit from their distinct and complementary strengths. In our specific configuration of the Stacking Classifier, we utilized Random Forest, XGBoost, and SVM as the base models due to their strong individual performances and robustness in handling complex features like those of BERT embeddings. We chose Logistic Regression as the meta-model, which efficiently integrated the predictions from the base models, providing a final decision that leveraged the nuanced insights of each underlying classifier. This resulted in us getting the accuracy similar to that of a Deep Learning Model, CNN.



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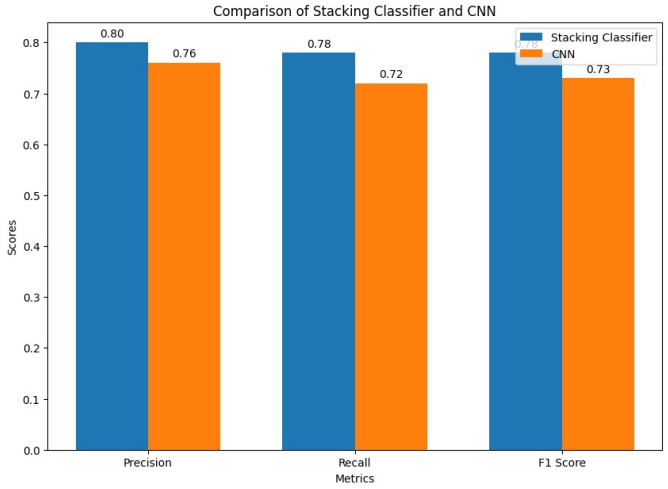

Fig. 5. Evaluation Metrics

The bar chart in Fig 4 compares the performance of the Stacking Classifier and the CNN model across three key metrics: Precision, Recall, and F1 Score. The Stacking Classifier outperforms the CNN in both Precision and F1 Score, registering values of 0.80 and 0.78 respectively, against the CNN's 0.76 and 0.73. This indicates that the Stacking Classifier not only predicts more relevant results (as reflected in the higher Precision) but also maintains a better balance between Precision and Recall, as evidenced by the superior F1 Score.

However, CNN achieves a slightly higher recall of 0.72 compared to the stacking classifier, 0.70, suggesting that CNN is marginally better at identifying all relevant cases within the dataset. The enhanced performance of the Stacking Classifier in the other two metrics can be attributed to its combination of multiple base models, which allows it to capture more diverse

patterns within the data, ultimately resulting in a more robust and accurate prediction model overall.

V. Conclusion

The outcome of our Stacking Classifier model is quite impressive; it has achieved an accuracy of 0. 79 per cent, which is in parity with the advanced CNN model which also achieved an average of 0.79 percent. This parity in performance demonstrates the utility of the Stacking Classifier's ensemble learning methodology, which integrates the features of many base models to achieve the same levels of efficiency in addressing the BERT embedding as the deep learning CNN model. Therefore, given the fact that the Stacking Classifier has been developed to the level of achieving high results comparable to CNN models, it can be stated that it is quite viable to use it for similar tasks in natural language processing.

VI. Future Enhancements

As the next steps, there are some possibilities to refine the models in the future. First, trying out other possibilities of base models to be stacked in the Stacking Classifier could reveal other combinations that can improve the performance of the algorithm. Further, using more data or using data augmentation techniques could help the models in having a wider range of examples to understand better. Finally, the future work could include the application of enhanced regularization approaches and the investigation of more recent architectures for CNN, which could further enhance the model's generalization ability and yield better performance in future applications.

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