iJRASET
International Journal For Research in
Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 9 **Issue:** VI **Month of publication:** June 2021

DOI: https://doi.org/10.22214/ijraset.2021.36170

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.429
Volume 9 Issue VI June 2021- Available at www.ijraset.com

Machine Learning Approach for Automatic Detection of Alzheimers Disease using Resting State fMRI

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Abstract: Alzheimer's Disease (AD) is a neurological disease that affects memory and the livelihood of the people that are diagnosed with it. Efficient automated techniques for early diagnosis of AD is very important because early diagnosis is used to prevent a patient from death. In this work, we present a novel computer-aided diagnosis (CAD) techniques using machine learning algorithms for the early diagnosis of AD. The input resting state fMRI(rsfMRI) images are taken from Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The input image is pre-processed using Discrete Wavelet Transform(DWT). Automated thresholding algorithm is used to segment the image. Then, the segmented resting state fMRI images are used to extract useful and informative features. The best features are selected by Fisher's code feature selection algorithm. Finally, an automated Image classification step is performed using machine learning algorithms Support Vector Machine(SVM), Decision Tree , Random Forest and Multi-Layer Perceptron algorithms to distinguish between normal patients and AD patients.
Keywords: Mild Cognitive Impairment (MCI), resting state functional Magnetic Resonance Imaging (rs-fMRI), Discrete Wavelet Transform(DWT), Support Vector Machine(SVM), Multi-Layer Perceptron(MLP), Decision Tree(DT), Random Forest(RF)

I. INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disease in people older than 65 years of age. Memory loss is the earliest sign of cognitive impairment followed by behavioral disturbances. These symptoms are associated with a rigorous neuronal decline and the appearance of two brain lesions, senile plaques and neurofibrillary tangles, which are mainly composed of Aβ and hyper phosphorylated tau protein, respectively. According to World Alzheimer Report (2018) [24], 50 million people around the world were affected by this disease in 2018, which is estimated that it will increase triple times by 2050.Usually, the symptoms of Alzheimer's are visible in people above 60 years of age [23]. However, some forms of AD develop very early (30-50 years) for individuals having gene mutation [22].

India is home to more than 70 million people older than 60 years as per the 2001 Census [1]. The numbers of persons with Alzheimer's double every 5 years and so India will have one of the largest numbers of elders with this problem. There is a growing realization that the care of older people with disabilities makes enormous demands on their careers. The Alzheimer's and Related Disorders Society of India (ARDSI) introduced attentiveness programmes in 1993 to speak this rising problem in India. In affiliation with the Alzheimer's disease International (ADI), many organisation has been working to increase the awareness of Alzheimer's and dementia for the persons with dementia and their families. Still, dementia and Alzheimer's are the hidden problems in India because people are poor and illiterate in many parts of India.

According to the Alzheimer's Association there are 3 phases of AD: preclinical, mild cognitive impairment(MCI) and dementia due to AD. The MCI phase includes "mild variations in memory and thinking capabilities that are evident-enough to be noticed and measured but are not accompanied by deficiency that compromises daily activities and functioning". Dementia due to AD involves "mental and behavioural signs that are present and are of sufficient severity to impair the patient's daily life activities". The symptoms of AD will vary between patients and also vary based on the phase of the disease that they are in. However, some common symptoms occur in in all AD patients such as, memory loss, changes in personality, vision impairment and behavioural disturbances. These symptoms will be likely to progress as the disease progresses. They will finally die because their body becomes unable to fight infections or regulate ordinary functions. Thus, accurate detection of AD in its early stage also known as mild cognitive impairment (MCI), is very important. Researchers believe that early detection will be essential to prevent, reduce the Alzheimer's disease. In the last 10 years, we have seen a tremendous growth in research on early detection of AD.

II. LITERATURE REVIEW

Brain imaging techniques plays a vital role to provide informative biomarker even before clinical symptoms have appeared. Many researchers used functional MRI(fMRI) to detect brain activity, variation in blood oxygenation and flow which arise due to hemodynamics. Usually, more oxygen is consumed by the active area of the brain which increases blood demand. activation maps that is produced by fMRI are represented in different color codes. It shows the strength and involvement of specific brain region in a specific mental activity. The reason why many researchers used fMRI is that it does not use any radiation just like CT and PET [17]. The authors were used an approach to extract shape texture features of the Hippocampus region from the MRI images and a Neural Network Classifiers for detection of several phases of Alzheimer's Disease.

Recently, resting-state functional magnetic resonance imaging (rs-fMRI) is widely used for the detection of AD and its progression. rs-fMRI is noninvasive and has shown how AD spreads in the living brain. Various researchers have tested the accuracy of AD-related fMRI measurements and found positive prediction related to cognitive degeneration [13, 14]. Many researchers have applied the computer-aided AD classification from rs-fMRI images. In [19,20], the authors have applied the statistical based techniques such as the General Linear Model (GLM) for fMRI analysis. In this method, correlation between the template model and fMRI time sequences are calculated to detect activated brain regions. In[19,21, It has been shown that the graph theory concepts were combined with machine learning approaches to classify patients with MCI, patients with AD, and normal control(NC) in rs-fMRI images..

Jie B etal have used manifold regularized multi-task feature learning and multi-kernel learning techniques by integrating both temporal and spatial properties of DCNs for automatic brain disease diagnosis [2]. DCNs were constructed from the rs-fMRI time series at continuous non-overlapping time windows. The correlation of functional sequences associated with this region was computed to characterize the spatial variability of a specific brain region and then both temporal and spatial properties of DCNs was integrated to improve classification accuracy. The experimental results on 149 subjects with baseline rs-fMRI data from ADNI suggest that this technique can *not only* improve the performance but *also* provide insights into the spatio-temporal interaction patterns of brain activity and their variations in brain disorders.

Visibility Graph (VG) were used to construct the time-dependent brain networks as well as functional connectivity network to examine the changes of AD brain using fMRI [3]. In this, VG method was used to map the time series of single brain region into networks. Then topological features were extracted and the most significant features were selected as discriminant features for SVM classification for SVM classification. The functional connectivity in the brain regions was calculated based on the correlation of regional degree sequences. They found some abnormal brain regions, including left insular, right posterior cingulate gyrus and other cortical regions.

In [4], the authors have addressed the neuroanatomical correlates of apathy in the early stage of AD using task-free fMRI. Patients from the Neurology and Psychiatry Departments of İstanbul University, İstanbul School of Medicine were analyzed. In the study, patients with clinical dementia rating 0.5 and 1 were included. The patient group was divided into two subgroups as apathetic and non-apathetic AD according to their psychiatric examination and assessment scores. A healthy control group was also included in this study. For all subjects, the resting-state condition was recorded eyes open for 5 minutes.

Tejeswine etal. have compared the performance of various data mining techniques in neuro-degenerative data[5]. They were implemented decremental Feature Selection Method to yield best feature subset that produces high prediction accuracy. More investigation of several computational methods will aid in recognizing the genetic cause of these diseases and design suitable medicines to target the gene property.

In [7], the authors have focused on detecting the changes in brain networks in patients by using a graph theoretical approach and advanced machine learning methods. The various directed graph measures were calculated on rs-fMRI data using multivariate granger causality analysis . The graph measures were used as the original feature set. From these, the best features were selected by using Filter and wrapper feature selection methods.

Zhang T etal have utilized the functional brain network and graph theory [6] to examine the effectiveness of a classification framework to differentiate early mild cognitive impairment (EMCI) from late mild cognitive impairment (LMCI). The algorithms namely minimal redundancy maximal relevance (mRMR), sparse linear regression feature selection algorithm based on stationary selection (SS-LR), and Fisher Score (FS) were applied to select the features of network attributes, separately. Then, SVM was used with nested cross validation to classify the samples into two categories to obtain best results. The classification results showed that the features selected by the mRMR algorithm produced better performance than those selected by the SS-LR and FS algorithms. This approach was used to help diagnose MCI disease in clinic and predict its conversion to Alzheimer's disease at an early stage.

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In [8], the authors have proposed multi model classification measures from functional MRI, diffusion weighted MRI and rsfMRI.Measures from multiple modalities improves the classification performance over unimodal classification performance for mild AD as well as moderate AD. This optimal combination of various measures consisted of grey matter density, white matter density, mean diffusivity, fractional anisotropy and sparse partial correlations between functional networks.

de Vos F etal extracted eight measures namely functional connectivity (FC) dynamics, FC metric, FC states, graph properties, FC for each voxel, FC for each hippocampus and low-frequency fluctuation, eigenvector centrality, and the combination of all these networks to detect the resting-state abnormality in MCI and HC. They were conducted experiments on few images which is one of the limitations of this study [11].

Khazaee etal. make use of the local and global graph measure features with SVM and naïve Bayes classifier [9]. feature selection was performed by Fisher algorithm followed by forward-sequential feature selection and the results are validated using tenfold cross validation. Among the two classifiers, Bayes classifier performed well and achieved higher AUC in HC vs AD classification.

In another study, [10] They focused on graph measures Global and local graph measures were calculated by separation and integration using graph theory which ended with 913 features. sequential feature collection was used to find the best features. SVM was used for classification and leave one out cross-validation was used for validate the results.

In [1], The authors make use of the graph theoretical approach and the pattern recognition method on rs-fMRI images for classifying patients with AD from the Normal Control. Informative graph measures were related to the brain cortical regions are used to improve the prediction accuracy. However, additional investigations are required for validation in larger datasets.

III. PROPOSED WORK

The detailed block diagram of the proposed work is shown in Fig.1. In this, the resting state fMRI images are utilized for early diagnosis of AD. Initially, the input rs fMRI images taken from ADNI database are pre-processed using Discrete Wavelet Transform(DWT). After pre-processing, Adaptive thresholding is applied to segment the images for the ventricle segmentation. From the segmented rs-fMRI images, the following features are extracted Nodal Degree(ND), Betweenness Connectivity(BC)and Nodal path Length(NL). After that Fisher's code feature selection algorithm is applied to select k best features. Subsequently, the best k features are given to the following four machine learning algorithms namely SVM, decision tree (c4.5), Random Forest and MLP for classification to detect AD patients and Normal Control(NC). To find the better accuracy,70/30 cross validation method is applied for cross validating the results.

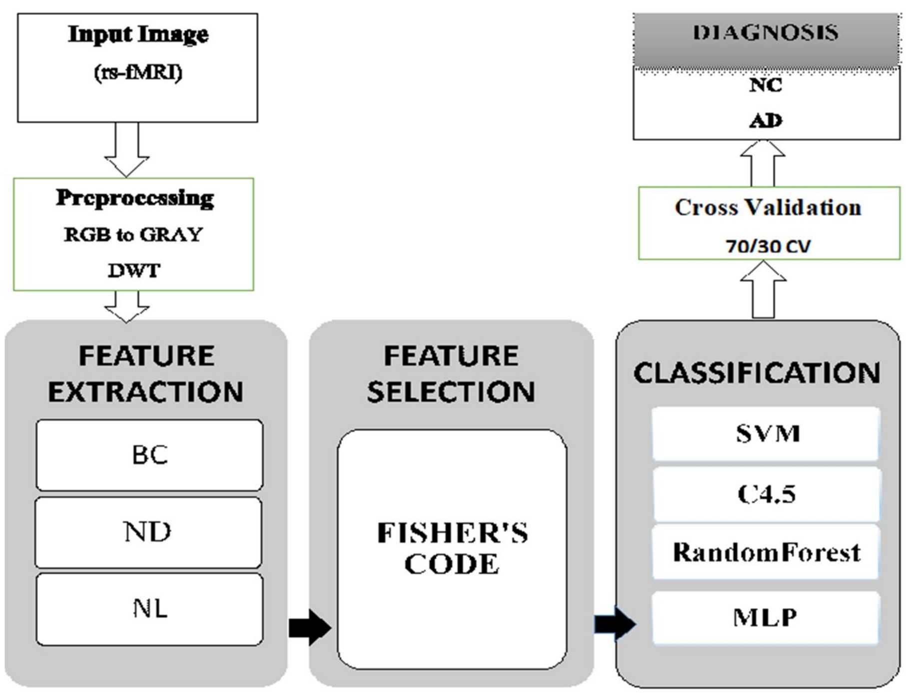

Fig.1 Block diagram for automatic diagnosis using machine learning Approach

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A. Data Set Collection and Preprocessing

The rs-fMRI dataset is taken from ADNI database http://adni.loni.usc.edu. The data set comprised of 6720 DICOM images. Since the rs-fMRI images contains less signal-to-noise ratio(SNR) the collected data are pre-processed to reduce the impact of noise. Initially, the RGB image is converted into grayscale image. Then Discrete Wavelet Transform (DWT) is applied to pre-process the mage.

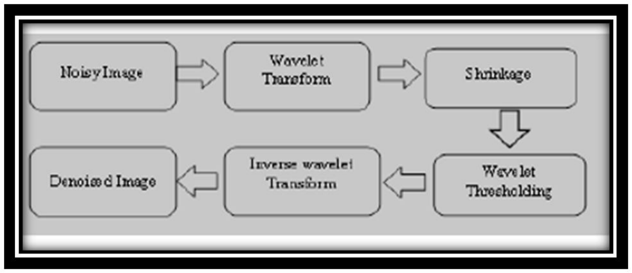

Fig.2 Discrete Wavelet Transform for de noising the image

Fig. 2 shows discrete wavelet transform for de-noising the image used in [16,18]. DWT can be viewed as a sum of wavelet functions with different locations and scales. When an image is decomposed into wavelets, a pair of waveforms are generated namely the high frequency(HF) and low frequency(LF). The HF parts correspond to the detailed part of the image whereas the LF part corresponds to the smooth parts of the image The LF part is split again into high and low frequency parts, while the HF part contains information about the edge components.

B. Segmentation

Adaptive thresholding(AT) is used for segmentation. AT divides foreground image from the background image based on pixel intensity differences of each region. Thresholding value is calculated for an image whose intensity histogram doesn't contain unique peaks to segment the desired part.

$$\left.\begin{array}{l} H(x,y) = 1,\ \text{if } H(x,y) > T \\ H(x,y) = 0,\ \text{if } H(x,y) <= T \end{array}\right\} \text{……….(1)}$$

Where T- adaptive threshold

C. Feature Extraction

Feature extraction is a special form of dimensionality reduction. When the input data to an algorithm is too large and it is redundant then the input data will be transformed into a reduced form. After that, the features are extracted from the input data instead of the full size input data. In image processing feature extraction algorithms are widely used to detect and separate various desired features of a digitized image or a video stream.

In this, the following nodal features such as betweenness centrality (BC), nodal degree (ND), and nodal path length (NL) are extracted. For a given node *i* , BC, ND and NL were expressed as follows:

$$B_i = \sum_{i \neq j \neq m \in V} \frac{S_{jm}(i)}{S_{jm}} \quad \text{………. (2)}$$

$$K_i = \sum_{j \in V} b_{ij} \quad \text{………. (3)}$$

$$L_i = \frac{\sum_{j \neq i \in V} L_{ij}}{(V-1)} \quad \text{………. (4)}$$

where L_{ij} represents the minimum number of edges between node *i* and *j*, *V* is the size of a graph, b_{ij} is the connection status between the node *i* and *j*, S_{jm}, represents the number of shortest path lengths between node *m* and *j*, and $S_{jm}(i)$ represents the number of shortest paths through the node *i* between node *m* and *j*. Naturally, path length L_i measures the speed of the message that passes through a given node, and the degree of an individual node K_i is equal to the number of links connected to that node, and if th value of B_i is greater, then the node *i* is the more important in the information communication in the network, thus reflecting the level of interaction in the network.

D. Feature Selection

Feature selection module can be used for dimensionality reduction on sample sets, either to improve accuracy or to boost the performance on high dimensional datasets. The goal of feature selection in machine learning is to find the best set of features that allows one to build useful models of studied phenomena. Feature selection algorithms roughly divide into two categories: filter and wrapper methods. The filter methods select a subset of features according to the general characteristics of data, independently of chosen classifier. However, the predetermined classifier is used in wrapper methods and features are evaluated according to their performances in perception of classes.

The widely used supervised feature selection method is Fisher score. However, it selects each feature independently based on their scores under the Fisher criterion, which leads to a suboptimal subset of features. This algorithm will return the ranks of the variables according to the fisher's score in descending order. We can then select the variables as per the case.

$$f_j = \frac{(\mu_{j(+)} - \mu_{j(-)})^2}{(\sigma_{j(+)})^2 + (\sigma_{j(-)})^2} \quad \text{......... (5)}$$

Where, $\mu(+)$: the mean of the feature values for positive
$\mu(-)$: the mean of the feature values for negative
$\sigma(+)$: standard deviations
$\sigma(-)$: standard deviations
This algorithm has following Steps:
In each case, the algorithms are evaluated for different numbers of features d

1) The range d = 1, …, 40
 -Choose a small number of features in order to render interpretability of the function
 -It is anticipated that a large number of features are noisy and should not be selected

2) The task may not simply be just to identify relevant characteristics via feature selection but also to provide a prediction system.

E. Classification

Here, the number of rather more sophisticated machine learning algorithm for classification namely Support vector machines, decision tree learner, Random Forest, Multilayer Perceptron are implemented to detect AD.

1) *Support Vector Machine:* Support Vector Machine (SVM) is a supervised machine learning algorithm used for both classifications. In SVM, each data item is plotted as a point in n-dimensional space (where n is number of features you have) with the value of each feature being the value of a particular coordinate. Then, classification is done by finding the hyper-plane to differentiate the classes very well.

The QP formulation for SVM classification is presented as follows.

SV classification:

$$\min_{f, \xi_i} \|f\|_K^2 + C \sum_{i=1}^{l} \xi_i \qquad y_i f(\mathbf{x}_i) \geq 1 - \xi_i, \ \text{for all } i \quad \xi_i \geq 0 \quad \text{...…… (6)}$$

SVM classification, Dual formulation:

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$$\min_{\alpha_i} \sum_{i=1}^{l} \alpha_i - \frac{1}{2} \sum_{i=1}^{l} \sum_{j=1}^{l} \alpha_i \alpha_j y_i y_j K(\mathbf{x}_i, \mathbf{x}_j)$$

……… (7)

Where $0 \le \alpha_i \le C$, for all i;

$$\sum_{i=1}^{l} \alpha_i y_i = 0$$

Variables ξ_i are called slack variables and they measure the error made at point $(\mathbf{x}_i, y_i)$.

2) *Decision Tree Algorithm:* The fundamental algorithm for building decision trees called C**4.5** which employs a top-down, greedy search through the space of possible branches with no backtracking. In C4.5, *Entropy* and *Information Gain* is used to construct a decision tree. Decision trees classify instances by sorting them based on feature values. Each node in a decision tree represents a feature, and each branch represents a value of the feature. classification starts from the root node and sorted based on their feature values. Recursively partitioning the data space and fitting a simple prediction model within each partition to construct the model.

Two types of entropy are calculated using frequency tables to build a decision tree as follows:

a) Entropy using the frequency table of one attribute:

$$\mathbf{E(S)} = \sum_{i=1}^{c} - \mathbf{Pi} \log_2 \mathbf{p_i} \quad \text{…………(8)}$$

b) Entropy using the frequency table of two attributes:

$$\mathbf{E(T,X)} = \sum_{c \in X} P(c) E(c), \quad \text{…………(9)}$$

The information gain is based on the decrease in entropy after a dataset is split on an attribute. While constructing a decision tree, we have to find the attribute that returns the highest information gain.

- *Step 1*: Calculate entropy of the target.
- *Step 2*: Split the dataset on the different attributes and calculate the entropy for each branch. Then it is added proportionally, to get total entropy for the split. The resulting entropy is subtracted from the entropy before the split. The result is the decrease in entropy called Information Gain. Gain (T, X) = Entropy(T) – Entropy (T, X)
- Step *3*:Assign attribute that contains the largest information gain as the decision node.
- Step *4a*: Assign a branch with entropy of 0 is a leaf node.
- *Step 4b*: Split the branch with entropy more than 0
- *Step 5*: Run ID3 algorithm recursively on the non-leaf branches, until all the data is classified.

3) *Random Forest:* Random Forest Algorithm(RF) is a supervised organization algorithm. It creates the forest with an amount of trees. If more trees are there in the forest, the more robust the forest look like, likewise in the random forest classifier, high accuracy results when the higher amount of trees in the forest. In RFA, the process of finding the root node, and splitting the feature nodes will have done randomly instead of using information gain for calculating the root node.
4) *Multilayer perceptron (MLP):* There are different types of neural networks, but they are generally classified into feed-forward and feed-back networks. A feed-forward network is a non-recurrent network in which the signals can only travel in one direction. Feed-forward networks include perceptron (linear and non-linear) and RBF networks. In data mining, feed-forward networks are frequently used. In feed-back network, the signals are traveling in both directions. It allows all possible connections between neurons. Feed-back networks are frequently used in associative memories and optimization problems where the network looks for the best arrangement of interconnected factors. Nodes in intermediate layers use sigmoid (logistic) function. Nodes in the output layer use soft max function. The number of nodes NN in the output layer corresponds to the number of classes. The different layer function of MLP is shown in figure

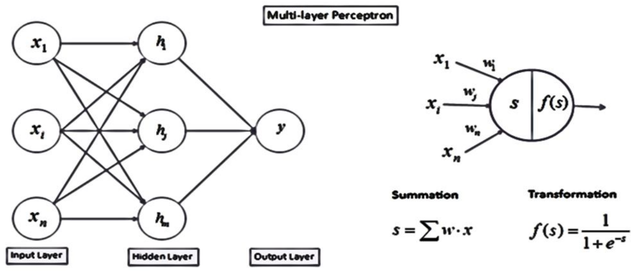

Fig3. Multilayer Perceptron

MLP is a classifier based on the feedforward artificial neural network. MLP consists of multiple layers of nodes. Each layer is fully connected to the next layer in the network. Nodes in the input layer represent the input data. Mapping of inputs to the outputs is performed by the linear combination of the inputs with the node's weights ww and bias bb and applying an activation function.

IV. RESULTS AND DISCUSSION

A classifier is learned on training data and then tested on unseen test data. There exist many measures to evaluate performance of a classifier and a lot of techniques to create training and test data in order to estimate generalization ability of a classifier on test data. Evaluating the performance of a model with the training data is not acceptable in data mining because it can easily generate overoptimistic and over fitted models. The Cross-Validation is performed using 70/30 CV to evaluate model performance. That is, 70% of data is taken for training and 30% of data is used for testing.

A. Simulation Results

The dataset was pre-processed and the machine learning algorithms were implemented on the pre-processed dataset. BC, ND AND NL features were extracted and the best features were selected by fisher's criterion. Best features are applied to each algorithm consequently and the results were tabulated.

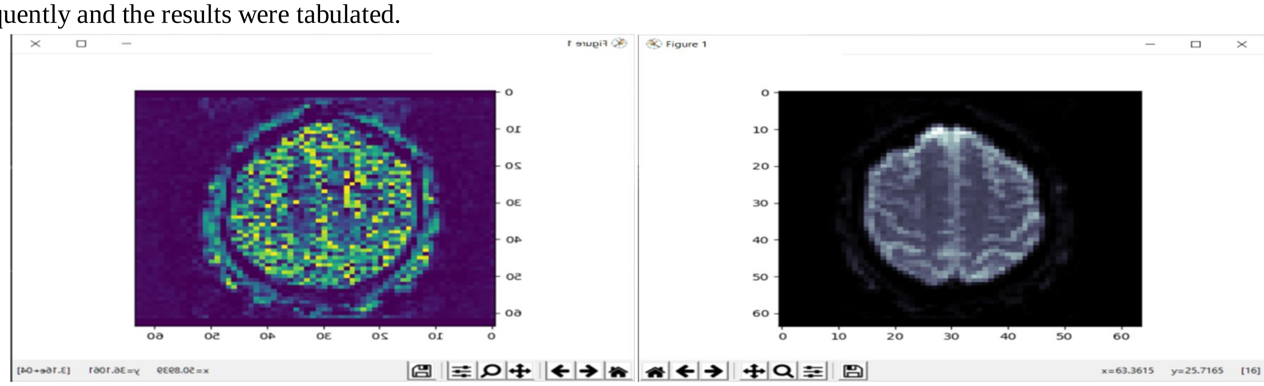

Fig.4 Pre-processed Image

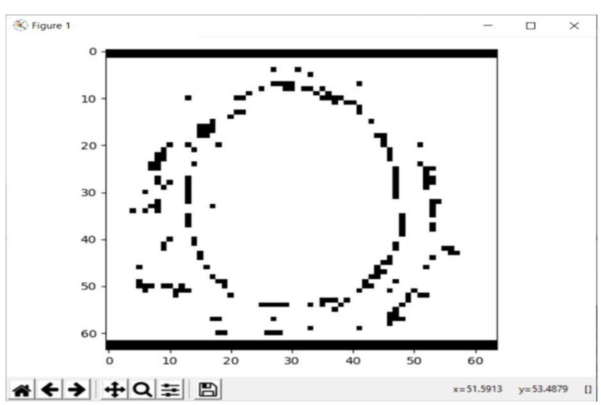

Fig.5a Segmentation

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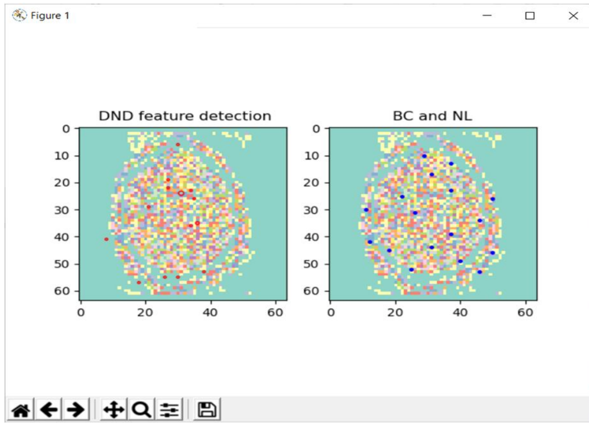

Fig 5.b Feature Extraction

B. *Performance Evaluation*

The evaluation metrics for biomarker used in AD are Accuracy, Precision and Recall.

1) *Accuracy:* The pixel accuracy is commonly reported for each class separately as well as globally across all classes. When considering the per-class pixel accuracy, a true positive represents a pixel that is correctly predicted to belong to the given class whereas a true negative represents a pixel that is correctly identified as not belonging to the given class.

$$\text{Accuracy(AC)} = \left[\frac{TP+TN}{TP+TN+FP+FN}\right] \quad \ldots\ldots\ldots\ldots(10)$$

2) *Precision:* Precision is the purity of positive detections relative to the ground truth.

$$\text{Precision} = \left[\frac{TP}{TP+FN}\right] \quad \ldots\ldots\ldots\ldots(11)$$

3) *Recall:* Recall is the completeness of positive predictions relative to the ground truth.

$$\text{Recall} = \left[\frac{TN}{TN+FP}\right] \quad \ldots\ldots\ldots\ldots(12)$$

Where

True Positive rate (*TP*) - the proportion of positive cases that were correctly identified

False Positive rate (*FP*)- the proportion of negatives cases that were incorrectly classified as positive

True Negative rate (*TN*) - the proportion of negatives cases that were classified correctly

False Negative rate (*FN*) -the proportion of positives cases that were incorrectly classified as negative

Table.1 shows the performance evaluation values of the classifiers Decision tree, SVM, Random Forest and MLP. The results shown here have been attained using a 70/30 cross-validation. Accuracy, Recall and Precision have been computed.

Table.1 Performance Evaluation Values of Classifiers

Performance Metrics	DT	SVM	RF	MLP
Accuracy	97.413	84.8542	86.6	74.66
Precision	95.452	70.9042	92	90
Recall	97.7919	85.5353	88	77
F-Measure	76.63	69.1123	90	80

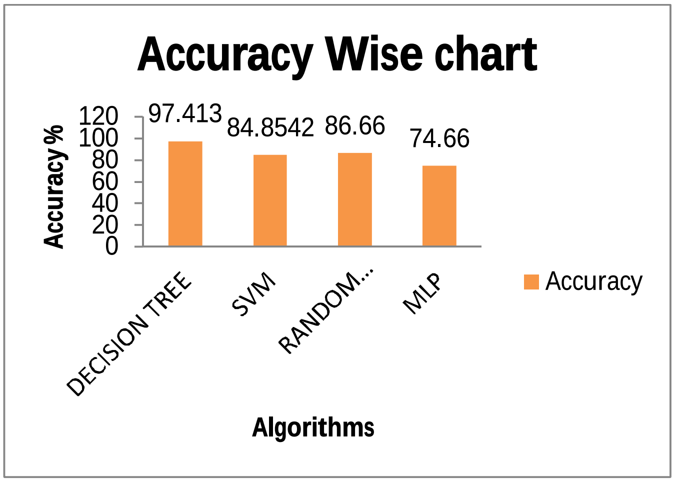

Fig.6.Accuracy chart

Now analyzing Fig.6, we can see that, Decision Tree Classifier provides 97.41% of accuracy, SVM provides 84.85%, RF provides 86.66% and MLP provides 74.66. Thus, Decision Tree Classifier provides more accuracy.

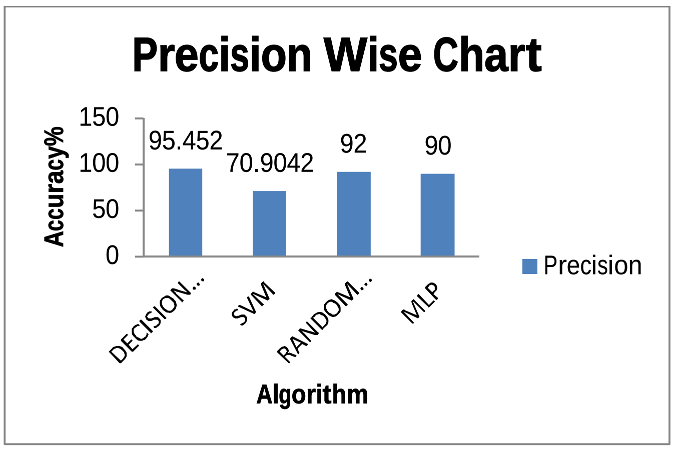

Fig.7 Precision chart

We then analysed the Precision values obtained by DT, SVM, RF and MLP classifiers and are depicted in Fig.7. This analysis showed that Decision Tree Classifier has 95.45% of Precision, MLP has 90% of Precision, RF has 92% of Precision, but SVM has 70.90% only.

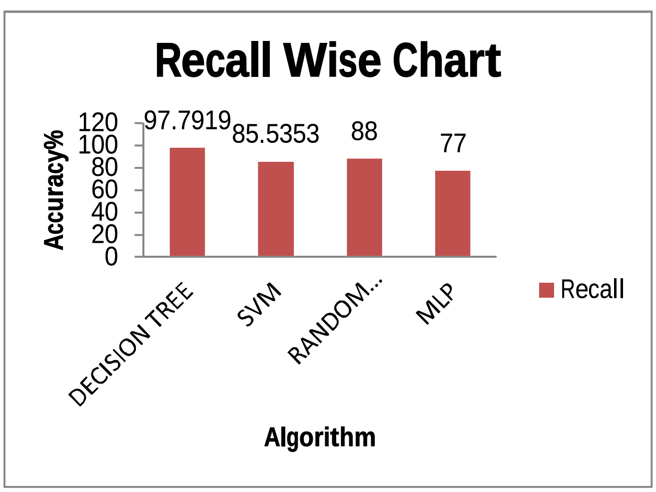

Fig.8.Recall chart

The recall values of DT, SVM, RF and MLP classifiers are shown in Figure 8. It shows that Decision Tree Classifier has more recall values when compared with other algorithms.

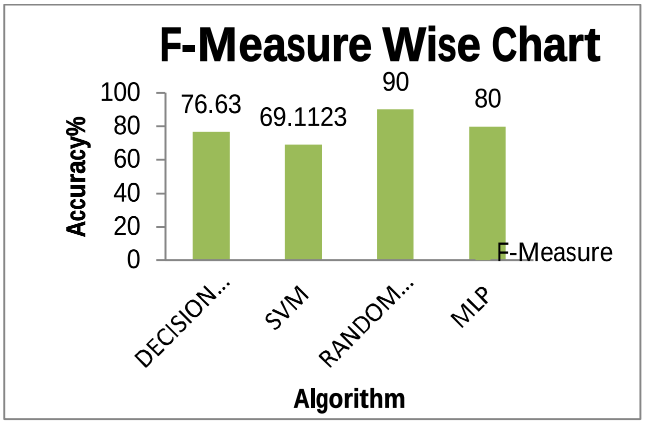

Fig.9 F1Measure chart

The F1-measure of DT, SVM, RF and MLP classifiers are shown in Figure 9. It shows that Decision Tree Classifier has 76.63% of F-Measure, RF has 90% of F-Measure, MLP has 80% of F-Measure but SVM got 69.11% of F-measure only.

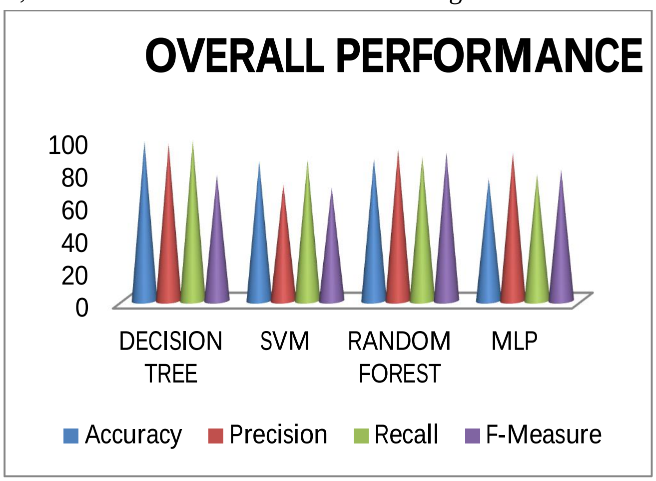

Fig.10 Overall Performance comparison of DT, SVM, RF and MLP

The overall performance comparison of DT, SVM, RF and MLP algorithms are shown in Figure10. Decision Tree Classifier provides more accuracy, precision, recall, f-measure than SVM, RF and MLP classifiers. Hence, we concluded that Decision Tree classifier gives better results than other classifier such as SVM, RF and MLP to classify the AD patients from Normal Control(NC).

V. CONCLUSION AND FUTURE ENHANCEMENT

This work provided an extensive overview of Prediction of Alzheimer’s disease by using different machine learning based methods, also provided the process of classification of Brain images and a summary of the results acquired by various researchers to predict Alzheimer’s disease. As recognized from the literature research, much research has been done in early detection of Alzheimer’s disease, but the crucial need remains to identify appropriate features that could detect Alzheimer in early stage. This work describes four machine learning classifiers SVM, DT, RF and MLP and its performance evaluation on different metrics and finally concluded that Decision Tree classifier gives better results than other classifiers such as SVM, RF and MLP. Future research encompasses extracting reasonable set of features for early identification of Alzheimer's disease and also to decrease the insignificant and redundant conventional feature sets to enhance Alzheimer's detection methods effectively and also the features of neural network weights are studied in depth through the unsupervised feature learning techniques.

VI. ACKNOWLEGEMENT

Dataset used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu/).

The investigators within the ADNI, who can be found at http://ADNI.loni.usc.edu/study-design/ongoing-investigations, contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or the writing of this article

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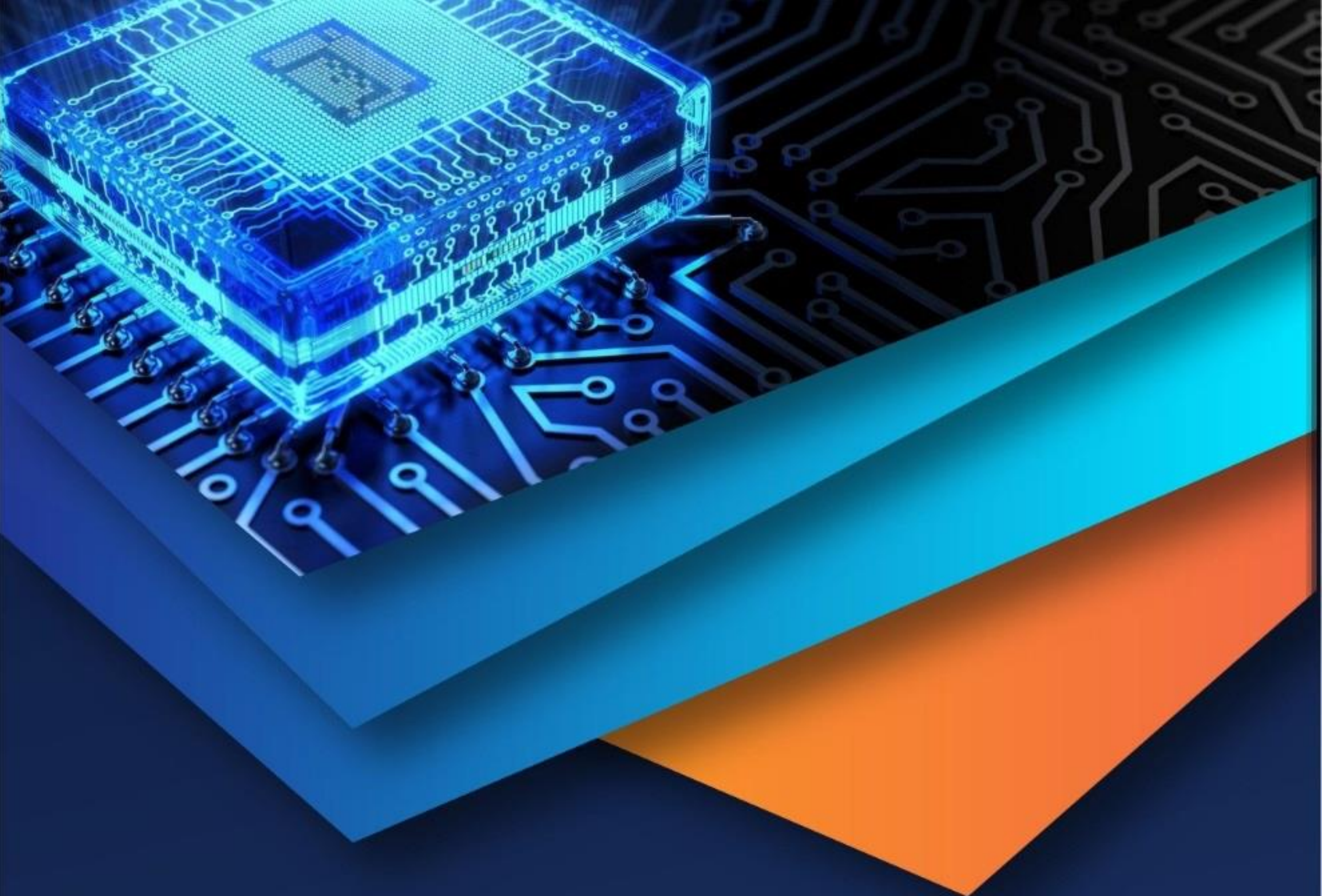

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