Early Prediction of Alzheimer's Disease Using Low Complexity Techniques for High Data Classification.

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ABSTRACT

Alzheimer's disease is one of the most common Neuro Degenerative diseases that commonly affects people above age of 60. The disease is progressive in nature and affects the grey matter of brain cells, causing permanent damage to the thinking capability. This paper proposes a new technique for identification and observing progression of Alzheimer's disease using contours and clustering technique. The number of MRI used for classification is 900 in which 400 is of Alzheimer's disease (AD) and 500 is of cognitive normal (CN) and the classification is done using random forest. The feature used for classification is shape and structure of brain and the end result showed a significant improvement in the classification of AD patient and CN patient. This paper compares our method with current methods in the field of Alzheimer's disease detection using machine learning to show the reliability of our method. The proposed method shows improvement in accuracy when compared with existing machine learning methods. The accuracy of this proposed method calculated using 5-fold cross validation is found to be 91.6%.

Introduction:

Alzheimer's disease is one of the most common Neuro Degenerative diseases that commonly affects people above age of 60. Currently there are more than 60 million people worldwide who are affected by AD and it is growing at the rate of 10 million people per year. So by the end of 2050 the AD patients are expected to grow 4 fold [1]. The development of AD starts few years before the first symptom starts to appear and it remains undetected in most of the cases. The conversion stage between normal aging and dementia is considered as Mild Cognitive

Impairment (MCI). However, this condition is heterogeneous. MCI patients progressively results in development of AD or some other dementias, while the rest stay as MCI effected for several years [25]. There is a need for the doctor's and clinicians in the identification of the disease for effectively giving medication for slowing down the progression of the disease and to check the effectiveness and further growth. There are several techniques that are being developed using a single biomarker of combination of different biomarkers in detecting the disease[2].

The structural irregularities induced in the brain by AD can be monitored non-invasively by making use of magnetic resonance imaging (MRI) in order to estimate cerebral atrophy or ventricular expansion. Loss of volume in the hippocampal area can be connected with AD, and dissection studies have shown that hippocampus, amygdala and entorhinal cortex are extremely at risk to AD anatomy. Hippocampal atrophy set side by side with healthy brain was measured using MRI in AD and MCI subjects [3]. The computing resource usage have greatly improved in monitoring the health of patients as it can record the patient's data electronically instead of the old scenario of pen and paper.

Machine learning techniques can be put to electronic health records (EHR) to intensify the quality of medicine and healthcare centers [5]. Data mining aims in finding the patterns or similarities in the existing data. Extracted patterns are then used to classifying the inputted new data and also in generating summaries of data. By following this pattern of data mining helps in identification of patterns in data and helps in grouping the data on the basis of resemblance of the data [6].

Image denoising is a usual problem in medical image processing. When different wavelets are iteratively considered for decomposition and reconstruction of the image while denoising, it is found that the Haar base has given the best output here. By comparing different multiscale transforms, it is suggested that, Contour let is outperforming all other techniques for medical image denoising [7]. In last few years' data mining is widely used in various fields such as medicine, marketing, stock marker etc. [30]. The algorithms used for data mining can be made into use for grouping and differentiating subjects based on the resemblance in patterns. The use of Machine learning techniques has been significantly found in medicine and their application in the same helps in accurate identification of several diseases and classification of disease. In this

paper we use Gaussian noise removal technique in order to remove the noise from the MRI images followed by skull stripping for removing the non-brain tissues from the image. Feature segmentation is done using K Means clustering followed by Feature extraction using active contours and Prewitt operator. Classification of AD and CN images is done using Random Forest classifier.

Materials and Methods:

Dataset.

The Data set used for the preparation of this paper was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI was launched in the year 2003 as a public private partnership which was led by Principal Investigator Michael W. Weiner, MD [33]. The aim of ADNI was to know if MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of AD. ADNI database contains a large amount data of MRI and PET images, blood biomarkers such as cerebrospinal fluid analyses, for healthy individuals (NC), AD patients and patients suffering from MCI symptoms [31]. ADNI provides T1, T2 and T3 MRI which is based on the time duration of the Repetition Time and Time to Echo. Repetition Time (TR) is defined as the amount of time duration between successive pulse sequences applied to the same slice. Time to Echo (TE) is defined as the time duration between the delivery of the RF pulse and the receipt of the echo signal. The database that is considered for this work, contains a total of 900 patients' data. In this proposed method only the T2 weighted slices of the MRI images are considered since T2 provide better partisanship power between the AD and CN [38].
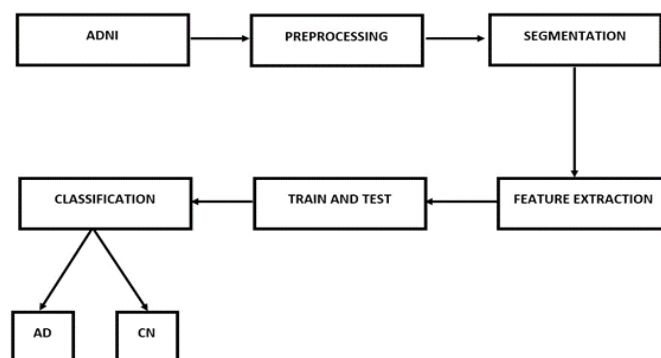

Figure 1. Flow Diagram of the proposed method

Out of these 900 patients 400 patients had Alzheimer's disease and rest 500 were cognitively normal people. Furthermore, the data was divided according to the necessity of an analysis for the process of training and testing shown in Table 1.

Table 1. Dataset Splitting

Data	Train	Test
AD	320	80
CN	400	100

Data Preprocessing.

The steps involved in the preprocessing are Gaussian noise removal and skull stripping.

1) Gaussian noise removal: A Gaussian Filter is a low pass filter used in images for filtering out noise and blurring regions of an image. The filter is implemented as an Odd Sized Symmetric Kernel which is passed through each pixel of the Region of Interest to get the desired effect [12]. This kernel will not be forceful towards the edges, due to this pixel towards the center of the kernel will be having more weight towards the final value than the borderline. A Gaussian Filter can be contemplated as an estimate of the Gaussian Function. This is additive in nature [9] and it follows Gaussian distribution, which indicates that each pixel in the noisy image is the sum of the true pixel value and a random, Gaussian distributed noise value. The noise in the image will be self-sufficient of intensity of pixel value at each point.

2) Skull stripping: The Magnetic resonance image (MR)brain images consists of tissues that are not in importance in the terms of detecting Alzheimer's disease. Some of them are skin, fat, muscles etc. These are not usually found in in other biomarkers such as PET, SPECT, fMRI etc. [17]. Thus, these non-important regions found in the MRI need to be removed before proceeding with further steps. Some of the common methods used for skull stripping used for MRI's are methods based on morphology, methods based on the image intensities, methods based on Altas or combination on any two-method known as hybrid method.The morphological methods use dilation operations and morphological erosion in order to remove the skull region from the area of interest in an MRI. This method uses a combination of thresholding and edge detection technique in finding the region of interest.
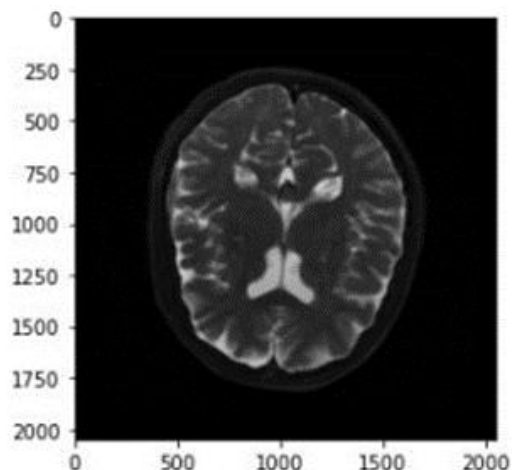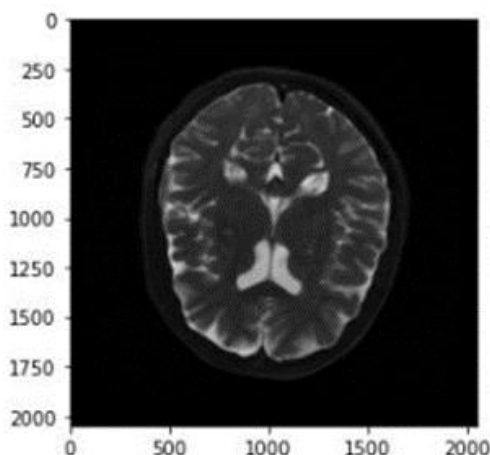
Figure 2. Original MRI   **Figure 3.** MRI after applying Gaussian blurring

An automated system for the contour detection from brain MRI images is proposed in [14]. The method base on the intensity works on the basis of grey matter and white matter. Authors in [34] and [35] introduces various intensity-based method for skull stripping.

Methods based on Atlas depends on placing atlas on target image in order to remove the skull from the brain. Leung et al [36] presented a multi-atlas method that generates brain segmentation by combination of many segmentations made by atlas. The hybrid method make use of one or more methods results in order to fulfil the shortcoming of methods that used single approaches. The fig 4, shows the skull stripping that is done on the Gaussian filtered brain. Here, intensity-based method to remove the skull particles from the MRI is used since it gives better result when compared to other methods [39]. The initial phase was to separate the foreground from the background with the help of Otsu thresholding method. The next step was to find skull in the image. For this, background separated image and the original image were combined to find the connected components. Finally connected components are removed from the blended image by masking process to extract the non-skull brain.
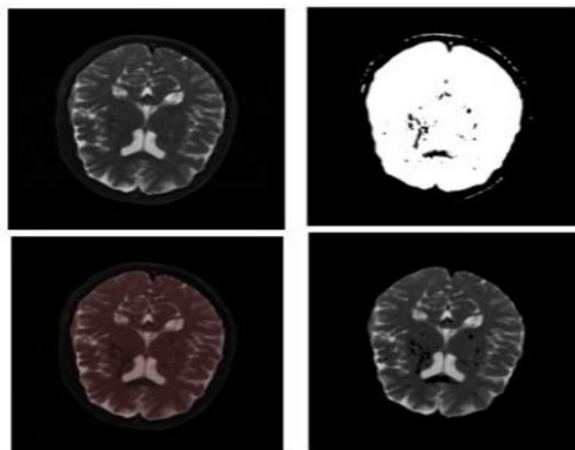
Figure 4. Indicates the original image and the results after each stage. (a) original image with skull (b) separating the foreground and background (c) blended image of first two images (d) final skull stripped brain image.

Feature Segmentation.

Feature Segmentation splits an image to different domain depending upon its property. Each region is different in terms of brightness, color, texture, and reactivity etc. Basically, segmentation recognizes the regions of interest in mechanizing or supporting the description of anatomic structures. This results in detecting masses, micro calcification's, and speculated lesions. Also, it helps in approximating denseness depending on the segmenting dense tissue regions. In this paper for the purpose of feature segmentation K means is used.

K means clustering.

K-Means is an algorithm that comes under unsupervised learning that is used to solve clustering problem. The steps begin with the classification of the data set to a certain number of clusters with a constant priority of their own. The aim of this method is to define k centroids, one for each of the clusters [17]. It should be planted in a well-defined way to avoid the effect of different locations leading to different results. The better way is to separate them not within the reach of each other.

Further the next process is to associate each point in the given dataset to its nearest centroid.

When there is no further point is left, the initial step is done and an early group is created. Now, it needs to again calculate the k new centroids as centers of the clusters from the previous process. After the calculation of the k new centroids, a new tie should be made between the same data points and the nearest new centroid and a loop is generated. As a result of this loop, it may be noticed that the k centroids alter their location in each step till no more changes are done. That is the centroids are now fixed [22]. The aim of this is to keep down the objective function.
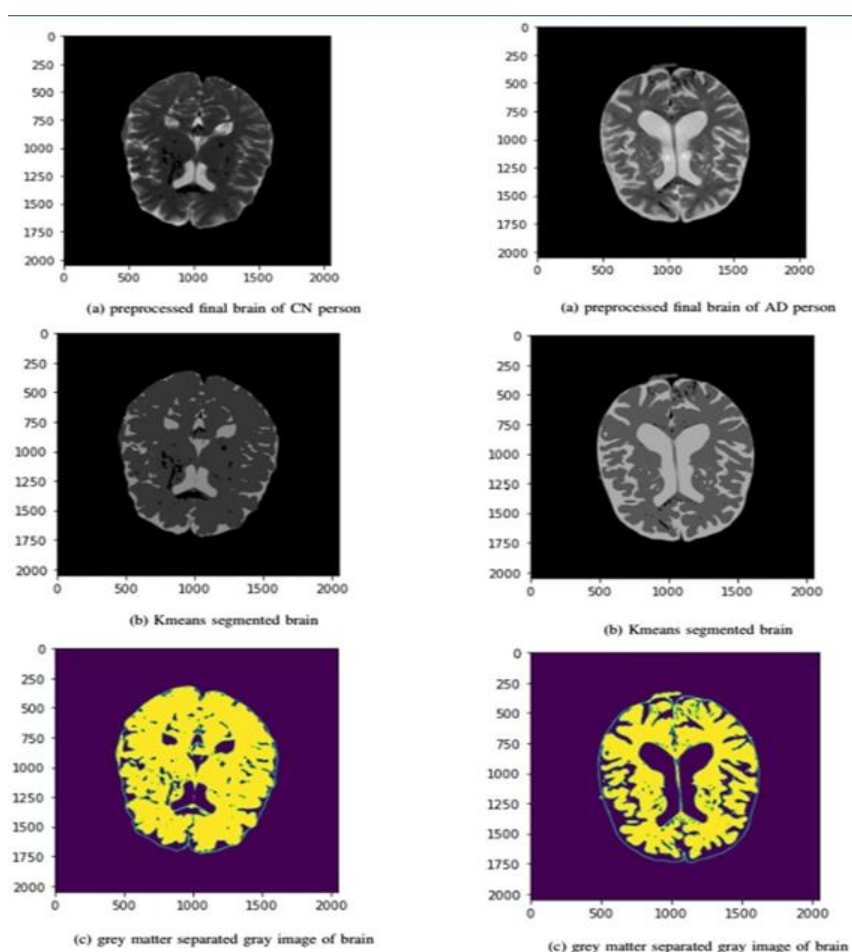

Figure 5. Brain MRI images after feature segmentation of CN and AD

A fundamental step for any Machine learning algorithm is to determine the optimal number of clusters into which the data may be clustered. The Elbow Method is one of methods to determine the optimal value of k. Elbow method is used in this paper for determining the true number of

clusters in a data set [2]. Figure 5 shows the K mean clustering done on an AD and CN brain. The second part in the figure 5 represent the segmented brain and the last part is the grey matter of brain without any white matter present in it.

Feature extraction.

Feature extraction comes under dimensionality reduction process in which the original data is reduced into a group which can be easily managed without losing much information. Machine learning techniques requires lot of data for its functioning but processing a large amount of data is considered to be very difficult. A simple image will consist of lot of data in them so to learn for a lot of such image is very difficult and leads to high computational time. To overcome this feature extraction is made into use where we can decide what type of feature form a data need to be extracted for our particular task. Different feature extraction techniques used in this paper are as follows:

Active Contours: Shape as prediction factor

A line that joins all the local point along the boundaries of an image which have same pixel intensity is called a contour. A contour means a pixel in the boundary which have the same color and same pixel intensity. Contours are mainly used in shape analysis or for finding the size of the object of interest as well as for detecting objects from images. Image contour extraction is one of the key measurement factors in computer vision measurement [26].
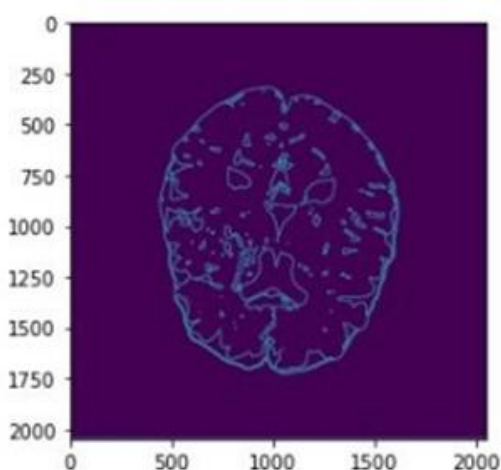

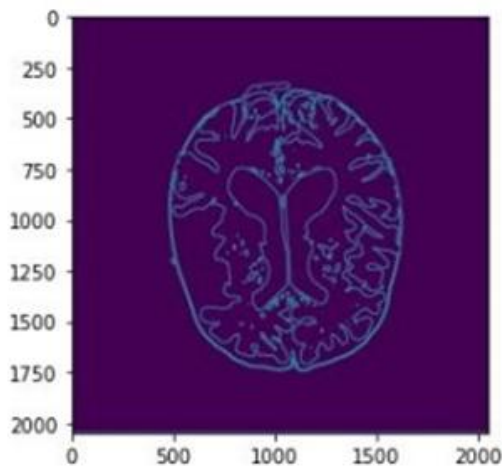
Figure 6. CN brain Results   **Figure 7.** AD brain Results

The structure of MRI image is extracted from the figure 5 by using contours. The contours are drawn across the edges which gives the amount of shrinkage in the grey matter of brain. Once the contours are drawn across the grey matter of brain, amount of shrinkage need to be checked by observing the amount of pixel content in that preprocessed image. A normal brain grey matter shrinkage will be very less compared to an Alzheimer's disease affected person brain. In figure 6 and figure 7 shape of the AD and CN brain after applying the contour can be shown. The main characteristics that differentiate between an AD and CN person is the folds in the gray matter of brain which suggest the shrinkage process happening in the brain.

For an AD patient, his gray matter will be less due to constant degradation of brain. This can be clearly visible in the contour drawn across the AD patient brain MRI scan. Similarly, for a CN person, the degradation in brain cells will be less which can be seen from the contour drawn across CN person brain, as there are very less folds in the brain. Also, the amount of pixel content present in the gray part of brain gives a clear picture of Alzheimer's disease.

4.2. Prewitt operator: Edges as prediction factor

In this paper we make use of Prewitt operator for detecting the edge of the image. It can detect Horizontal edges, as well as Vertical Edges. The edges are nosed out by calculating the variability in pixel intensities with the neighboring pixels. Masks used and the operators used are otherwise called derivative operators or derivative masks [28]. The operator offers two masks one for vertical edge detection and the other for horizontal edge detection.
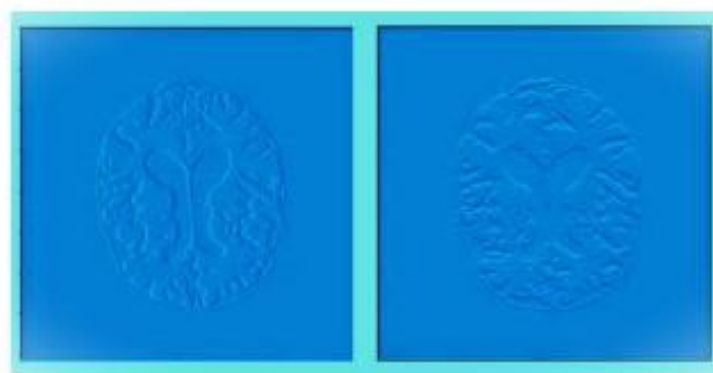

Figure 8. Horizontal and vertical Prewitt of AD patient

Figure 8 shows the Prewitt edges (both vertical and horizontal) taken for AD patients MRI scan. The impressions in the green background are the emphasized edges which are collected as the feature for the classification purposes.

Feature classification

The process of arranging image into groups or classes according to some common characteristics present in its feature is called feature classification. In this paper the classification is about distinguishing the AD and CN based MRI images based on the features extracted. There are various feature classification techniques like Stochastic gradient, Decision tree, Random forest etc. Random forest as classifier is used in this paper for the classification purposes since it provides precise and accurate results and the overfitting is less due to usage of multiple trees.

Random Forest

Random forest can be defined as a Supervised Machine Learning Algorithm that can be used for Classification and Regression problems. The random forest algorithm builds decision trees for different inputted samples and majority vote is considered for the classification purpose. Random forest (RF) classifier is used in this paper to classify the source brain MR image into either CN or AD image since RF reduces overfitting in decision trees and helps to improving the accuracy of the model. This RF classifier uses weighted voting technique to classify the brain images for severity diagnosis. The image classification done by RF classifier is based on the training and testing features [20]. In this classification be the total number of trees in forest and S be the training set which constitutes the features which are extracted from AD and CN brain MR images. The weight updating computation for RF classifier is represented as:

$$w_i = w_i^0 - \frac{1}{S}\sum_{j=1}^{S} |p_i^{c_j} - p_i^{c_j}| \quad (1)$$

Where starting weight of classifier is represented as w_i^0 and s denotes set of features from training feature set. The random index is represented as i and it is varied from 1 to total number of tress considered in the forest. The class label of the classifier during the process of training is represented by:

$$C_j = argmax \sum_{i=1}^{T} w_i p_i^c \, (j)(2)$$

The algorithm followed by a Random Forest classifier are as follows:

Step 1: An amount of' n' data is taken from a large dataset of' k'.

Step 2: Distinct decision trees are set up for each sample that is for AD as well as CN.

Step 3: Each distinct decision trees will be generating an output of its own.

Step 4: Majority Voting for classification is use for the final output that is AD or CN.

The result obtained after inserting the extracted features into the classifier will be either zero or one. 'zero' will be outputted if the MRI inputted belongs to CN category. The output will be 'one' if the inputted MRI belongs to a disease effected patient.

Results and Discussion

For every analysis, the data was divided in the ratio of 8:2, i.e., 80 % of the total MRI data was used for the purpose of training and rest 20 % of the MRI data was put into for the purpose of testing. For general case of analysis, the number of data used is 300. So, a total of 240 patients' data was used for training and the rest 60 was used for the testing purposes. And for other cases, it is mentioned along with the analysis.

Performance Analysis Based On Feature

The first analysis is between the shape, edges or the outline of the MRI image. Table 2 gives the analysis of different feature extraction technique in terms of accuracy, sensitivity, specificity and F1 scores. The classifier used for classification in all techniques was random forest. It can be seen that contour or shape-based classification can give a better accuracy, sensitivity and specificity compared to other feature extraction techniques. This comparison also indicates that the grey matter shrinking in brain of an AD patient can be exactly described with the help of contours drawn across the grey matter of brain. In the case of specificity, there is higher increase showing the false positive rate is very less signifying the prediction rate for cognitive normal persons are good which makes our method feasible as the amount of people going further procedures are reduced. Since the amount of variation in sensitivity and specificity is high, F1 score is also

added as another analysis parameter to show the effectiveness of our method. As expected, the F1 score is approximately equal to the accuracy, which shows the reliability of our method.

Table 2. Analysis based on different Feature Extraction

Random Forest Classifier				
Feature Extraction Technique	Accuracy (%)	Sensitivity(%)	Specificity (%)	F1 score (%)
Contours	91.6	88.7	96.1	90.09
Prewitt's edges	84.5	82.3	86.7	83.1
Otsu threshold	79.4	74	81.5	77.6

Performance Analysis Based On Different Classifiers:

Since there are many classifiers available, methods that can classify individually instead of batches are only considered for comparison. Methods that do all the steps in one single operation like Convolutional neural network (CNN), Deep neural network (DNN) etc. are also not considered.

Table 3. Analysis based in different classifiers

Contour				
Classifiers	Accuracy (%)	Sensitivity (%)	Specificity (%)	F1 score (%)
Decision Tree	88.2	85.1	91.9	87.4
Random Forest	91.9	88.7	96.1	90.9

The main reason is that they are computationally expensive and needs a GPU for faster training. For the effectiveness of neural network, it needs large amount of data that are difficult to obtain. Also, the neural network will simply decimate the interoperability of the feature to the point where it becomes meaningless. The proposed method was implemented in Intel i7 CPU with 8GB of RAM and time taken for the training was about 7 minutes. Table 3 shows the analysis of different classifiers used in the proposed method. So, classifiers which are convenient and less

expensive such as stochastic gradient, random forest and decision tree are only considered. The inclusion of decision tree is to showcase the potency of random forest classifier in classifying instance much more accurately and precisely. Even though, stochastic gradient has higher accuracy than random forest, random forest is preferred since accuracy is based on true positive and true negative. The main interest lies in the prediction of false negative and false positive which combine together to give us the F1 score. So better the F1 score means less unnecessary treatment and further procedures, which in turn reduces the cost.

Performance Analysis Based On Different Sample Points:

This part deals with the comparison of the proposed technique with respect to sample points i.e., whether the suggested technique fails if data points are increased and also to analyze the change in the accuracy parameter along with increase in number of sample points. Figure 9 shows that the accuracy bar graph have not changed much and has stayed between the 80 to 100 percent range showing the reliability of method for higher number of samples. Also, decision tree to check whether the performance graph remain the same is included and it can be seen that the technique performance has not diminished.

Comparison of Our Model withPrevious Models:

In 'K- skip-n-gram' technique by Lei Xu [19] instead of normal MRI image structural genes, they have gone with the use protein to extract their sequence information. The classification task is done by random forest. The total number of samples they considered for the experiment is around 620 samples with equal number of AD and Non-AD patients. And the final result after the experiment was around 85% accuracy. But the work was done only for accuracy and the accuracy of this method is slightly lesser than our proposed method. Also, comparison is made with some of other classifiers like Stochastic Gradient Descent (SGD), Decision tree etc. and have taken into consideration of sensitivity, specificity and F1 score in the analysis.
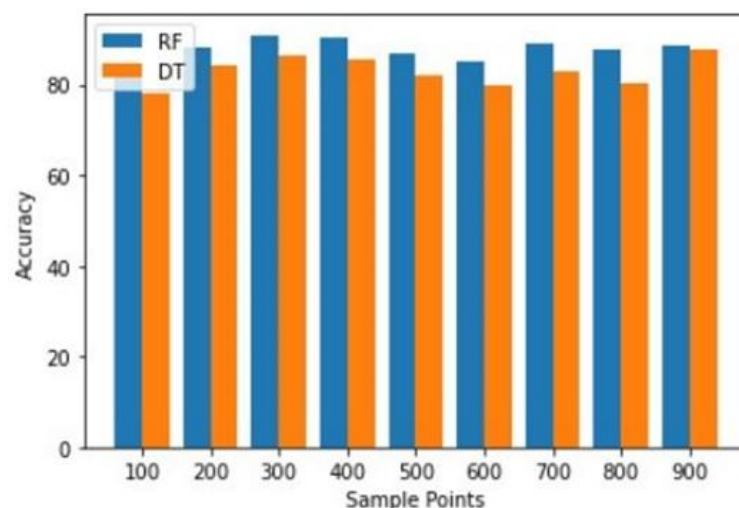
Figure 9. Analysis based on sample points

Graph signal processing combined with deep learning for classification Alzheimer's disease was proposed by Himanshu Padole [20]. A modified version based on dynamic connectivity model for detecting the disease was proposed. The feature extracted using the same was combined with the static connectivity-based features using the multimodal deep learning method to construct the integrated AD detection model. The maximum accuracy obtained using this model is 85% which is lesser compared to our method.
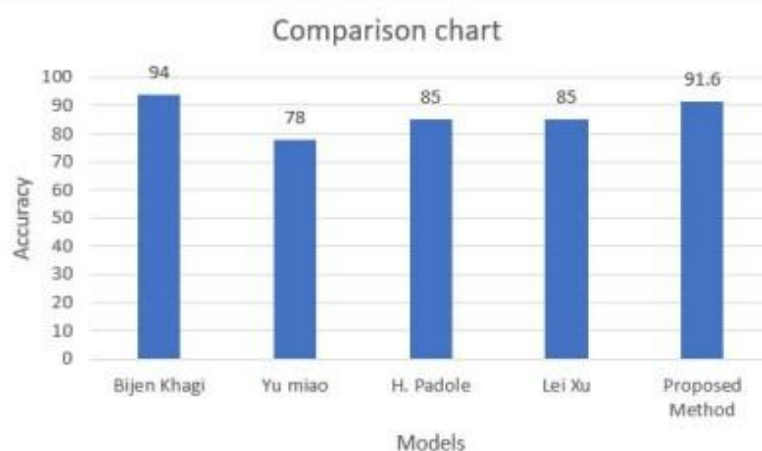

Figure 10. Accuracy comparison with similar works

CNN for the prediction of AD was proposed by Bijen Khagi [36]. Data set is obtained from Open Access series of Imaging Studies (OASIS). Since feature extraction is done using CNN the amount of data taken for the training and testing purposes are very large, i.e. in the range of 1800 data points. They used various CNN networks for the prediction like Alex net, Google net, Resnet50 etc. The method gives a good result in terms of prediction which is in the range of 94%. But the method is too costly due to many hidden layers and the amount of time needed for estimation is also very high. Comparing the model in phrases of complexity as well as cost effectiveness the proposed method has a slight advantage over it. The amount of data used for this method is in the range of 1800 which is another drawback of this method.

Relief method for the identification of the feature from MRI was proposed by Miao [22]. These features are then passed into the two-cascade layer classifier, where, in the first layer the feature vectors are taken and from that it is passed into classifier for classification. The classifier used for the purposes are Support Vector Machine (SVM), extreme learning and random forest. Based on the voting scheme it takes the best accurate classified classifier output. They have taken only 27 patients for their estimation which is very less for generalization and the feature extraction is based on Relief network alone. So the chances of missing the edges and the relevant part of grey matter of brain is more. The accuracy of this method is only 78% and specificity and sensitivity are 74.3% and 83% respectively. The proposed method has higher accuracy, specificity and sensitivity since it uses clustering technique to make sure that grey matter is separated out before feature extraction is applied.

Conclusions:

Alzheimer's is a disease which affects only the grey matter of brain. The proposed method takes into consideration of only the grey matter of brain for Alzheimer's disease prediction by using K means clustering techniques. Also, the feature taken into consideration for the prediction is shape or structure of grey matter of brain which is the main part in Alzheimer's disease prediction. Also, preprocessing of brain to separate the skull from brain tissue in the MRI image is applied. To validate our method several comparisons which includes comparison of different feature extraction technique with the proposed method is made. Also, prediction is done with different

classifier to find the best classifier for prediction. Finally, the proposed method is compared with existing technique to show that proposed method can compete with other methods. Like every experiment, our method has some drawbacks the first one is necessity of continuous analysis to check the progression of the disease. The other drawback is that in preprocessing step normal Gaussian filter is applied. Since a Gaussian filter smooths the edges of the image, the Prewitt edge detection method has shown significant drop in the classification. Also, there is a chance that the contour drawn across all the irregularities won't be accurate due to smoothing effect. Finally, the method can be improved with the help of different stage classifier and predicting the output with voting scheme. Also preprocessing and addition of more features are some areas that can be taken into account

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