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Multi Variate Feature Extraction and Feature Selection using LGKFS Algorithm for Detecting Alzheimer's Disease

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Abstract

Objectives: This study focuses on machine learning techniques to classify various stages of Alzheimer's Disease(AD). **Methods:** Absolutely, 1,997 PD weighted Resting State Functional MRI (rsFMRI) images were acquired from ADNI-3 dataset for the classification of AD. First, input rsFMRI images from the dataset were preprocessed and segmented. After segmentation, we have extracted multi variate features. Then, we have proposed Lasso with Graph Kernel Feature Selection (LGKFS) algorithm for selecting the best features. Finally, Radom Forest algorithm is applied to perform multi class classification for classifying all the stages of AD. **Findings:** In order to find the accuracy of this approach, cross validations were performed in the ADNI 3 dataset. We have measured the accuracy of RF classifier using three feature selection algorithms. The RF classifier with LASSO achieved 79.94% accuracy, 79.31% precision, 79.69% recall and 79.48% F1 score. The RF classifier with GK-FS achieved 76.52% accuracy, 84.0% precision, 79.19% recall and 79.77% F1 score respectively. By using our LGKFS algorithm, 90.8% accuracy, 82.4% precision ,81.6% recall and 81.6% F1 score was achieved by RF classifier which is higher than the existing feature selection techniques such as LASSO and GK-FS. **Novelty:** In this, a new hybrid feature selection algorithm namely LGKFS algorithm is introduced which combines two well-known feature selection algorithms Lasso Regression and GK-FS algorithm to improve classification accuracy.

Keywords: Alzheimer disease; Feature Extraction; Feature Selection Machine Learning; Mild Cognitive Impairment; Statistical Parameter Mapping

1 Introduction

A chronic neuro degenerative disease occurs in senior citizens called Alzheimer's disease (AD). Generally, it starts gradually and degrades over time by destroying brain cells. Nowadays, around 15 of people whose age is above 65 years is affected by AD [(1)].

It is estimated that 1/9 of people whose age >65 years and 1/3 of people whose age >85 years suffer from AD. By 2050, this count will be quadrupled[(2)].

Mild Cognitive Impairment(MCI) is a prodromal symptoms of AD in which people have slight but quantifiable changes in cognitive thinking capabilities that are traceable to the patients. Nearly, fifteen to twenty percentages of people above 65 years are affected by MCI[(2)]. The current researches have focused on identifying which MCI persons are most probable to progress Alzheimer's.

Now a day, neuroimaging has become a powerful tool to analyze brain structure and its functional changes[(3)]. Recently, a Neuroimaging modality such as Resting State Functional MRI (rsfMRI) is used to examine the functional fluctuations in brain regions, because of its non-invasive nature. In rsfMRI, the calculation of functional connectivity among different regions of brain is done by estimating correlation of BOLD (Blood Oxygen Level Dependent) signals. Instead of focusing on structural changes, rsfMRI connecting methods are focusing on brain functions to detect early cognitive degeneration. It also allows monitoring the progression of disease by means of functional connectivity disorders.

Artificial Intelligence techniques have been incorporating significant growths in health care industry. Many Machine Learning (ML) algorithms are currently being used in health care to predict and diagnose many diseases. Also, in neuro imaging, multivariate pattern analysis (MVPA) is applied to rsFMRI data to different cognitive stages by using brain activity patterns. There are three stages in MVPA approach to process rsFMRI. The first step is Feature Extraction which transforms the BOLD rsFMRI signals into features which are used to train and test the classification model. Secondly, Feature Selection which selects the best features that will be used to increase the accuracy of classification. Thirdly, Cross Validation which determines classification accuracy according to new data.

With the evolution of neuroimaging and artificial intelligence techniques, many researchers have used lot of machine learning methods to find structural or functional changes in brain region. Moreover, rsfMRI and machine learning models has played a significant part in finding biomarkers of AD[(4)]. In previous researches, various features have extracted to diagnose AD. Ngugen etal.,[(4)] have extracted maps of 3D regional coherence such as degree centrality(DC), Seed based resting Functional Connectivity (rsFC) and Regional homogeneity(ReHo) from every subjects in the dataset. In[(5)], the authors have extracted 68 cortical features using free surfer and have used these features to construct the model to classify AD and MCI. They have used various machine learning methods for classification among these, SVM (RBF kernel) produced the better results. The limitation was only cortical thickness features were considered for classification. Hao et al., have extracted three local properties of rs-fMRI such as degree centrality, betweeness centrality and nodal efficiency and used SVM classifier for detecting patients with depressive disorder[(6)]. Y.Shi etal., have used functional connectivity between voxels in the brain region[(7)].

In[(8)], the authors have extracted both cortical and sub cortical features to detect AD from structural MRI and they have combined Principal Component Analysis(PCA) and Recursive Feature Elimination(RFE) method to reduce the feature dimension.

Machine Learning (ML) models take benefit of multi variate nature of rsfMRI dataset to recognize spatial patterns. Functional connectivity analysis was used to calculate the functional changes among AD groups.In[(9)], the functional feature such as nodal degree(ND), between connectivity(BC) and nodal path length(NL) were extracted. They have used fishers code for feature selection and the best features were given to four well known classification algorithms such as Support Vector Machine, Decision Tree, Random Forest and Multi-Layer Perceptron to diagnose AD patients. Solano B et al., have implemented 3D dense net 121 and attained the classification accuracy of 87% in[(10)]. The authors have used 3D CNN to obtain the accuracy of 85.27% to distinguish AD from CN in[(11)]. Reddy G et al., have implemented VGG 19 and transfer learning to classify AD stages and achieved 85% accuracy in[(12)]

Feature selection methods are the key component in AI assisted diagnosis. Several feature selection algorithms have been developed so far[(13)]. Feature Selection algorithms aims to the reduction of the feature dimension and computation time to improve the classification accuracy by eliminating irrelevant, redundant and noisy features[(14)]. Generally, two kinds of feature reduction techniques are applied to reduce the feature dimesions. ie rank based feature reduction and subset based feature reduction. In rank based method, rank is calculated for all features and then best features are chosen based on specific condition. Features ranking algorithms such as Fisher score, t-test and infinite latent feature selection were commonly used. The limitation of feature ranking algorithm is that they focused only on each individual features. Hojjati et al.,[(15)] have used two feature selection algorithms i.e. sequential feature selection (SFC) and Discriminant Correlation Analysis (DCA) for choosing best features.

In subset based feature reduction, selection of feature subset is done by optimization. The well-known subset algorithms namely Lasso regression method was applied in[(16)]. The authors have selected the optimal features by using gk-SFS approach to increase classification performance[(17)].

In [18], multimodal feature selection algorithm was applied to classify MCI and AD. It has some limitations. First, only the relatively common method was considered for calculating correlation coefficient. Second, only the linear fusion of multi model features was given as input to SVM classifier. Liu et al. have developed a model that combines deep feature selection, casual inference and genetic imaging data analysis to predict AD [19].

Many researches in the literature were focused on extracting specific features and performed binary classification. From the literature review, we found that subset based feature reduction algorithms performed well than rank based feature selection algorithms. To focus on multivariate features and five-way classification of AD, this research work focuses on multivariate pattern analysis in which multi variate features such as textual features and functional features are extracted from rsFMRI data and hybrid version of subset based feature selection is applied to produce higher classification accuracy. Finally, a well-known machine learning algorithm namely Random Forest is applied for classification. The results of the proposed work are compared with LASSO method and GK_SFS method.

2 Methodology

This work has proposed a multivariate feature extraction and hybrid feature selection approach to detect various stages of AD and to improve the accuracy. Figure 1 depicts the Architecture which represents the various modules of the proposed system.

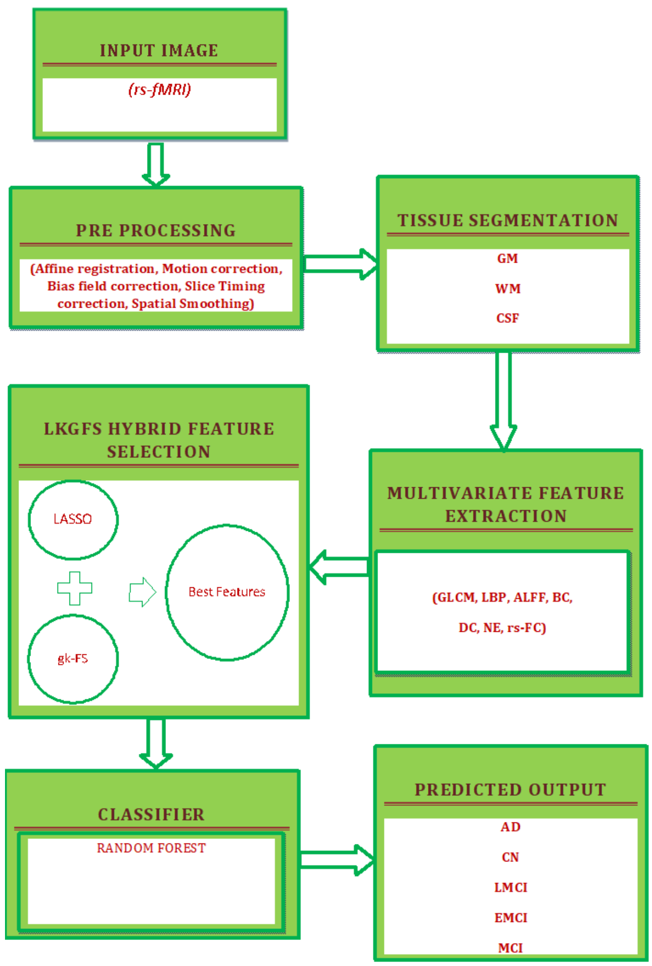

Fig 1. Proposed System Architecture

The preprocessing and segmentation of rsfMRI dataset is carried out using Statistical Parameter Mapping tool (SPM12). From the segmented regions, the multivariate features such as ALFF (Amplitude of Low Frequency Fluctuations), BC (Betweeness Centrality), NE (Node Efficiency), DC (Degree Centrality), rsFC (resting state Functional connectivity) and textual features such as LBP and GLCM are extracted. After that, we have proposed a new hybrid algorithm Lasso with Graph Kernel Feature Selection (LGKFS) for selecting best feature among the feature set. Lastly, the best features are given to Random Forest (RF) algorithm to detect various stages of AD. The performance Validation of proposed approach is carried out using 10-fold cross validation and LOOCV.

2.1 Materials used

In this study, PD weighted rsFMRI images taken in axial plane with slice thickness 3.4 are acquired from Alzheimer's Disease Neuro Imaging dataset(ADNI-3). All images are downloaded in DICOM format. The dataset contains 1,997 DICOM images over five groups of classes Cognitively Normal (CN), MCI, Early MCI (EMCI), Late MCI (LMCI) and AD. The details of the collected rsFMRI data set from ADNI3 is represented in Table 1.

Table 1. rsFMRI Dataset Details

Subject Group	No of Subjects	Sex(M/F)	Age
CN	400	200/200	79±84
EMCI	397	197/200	72±74
MCI	397	197/200	84±89
LMCI	403	203/200	76±81
AD	400	200/200	70±77

2.2 Preprocessing

The preprocessing steps are performed with SPM 12 tool implemented in Mat lab. SPM is a package developed for neuroimaging data such as FMRI, PET etc., This is available for free in the link (https://www.fil.ion.ucl.ac.uk/spm /)[20]. Using SPM tool, the input rsfMRI DICOM images are converted into NifTi format. Then, the functional scans are preprocessed with the following preprocessing steps such as affine registration, motion correction, biased field correction, slice time correction normalization and spatial smoothing.

2.3 Tissue segmentation

In SPM, the segmentation process will be carried out via SPM toolboxes namely VBM8, CAT12 and AAL3. In our work; we have used CAT12 toolbox for segmentation. The input rsfMRI images are first converted into NifTi format. Then the images are segmented into Cerebrospinal Fluid (CSF), Gray Matter (GM) and White Matter (WM). They are displayed in Figure 2.

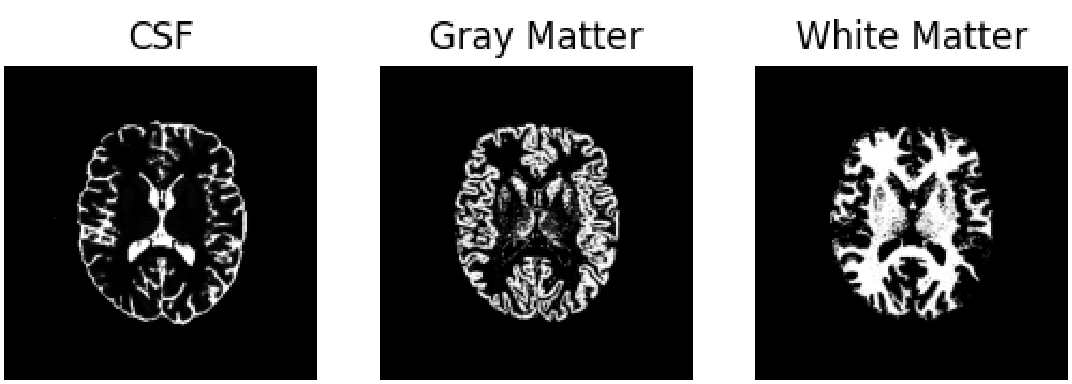

Fig 2. Tissue segmentation

The Figure 3 shows the sample output of the segmentation process for all the stages of AD.

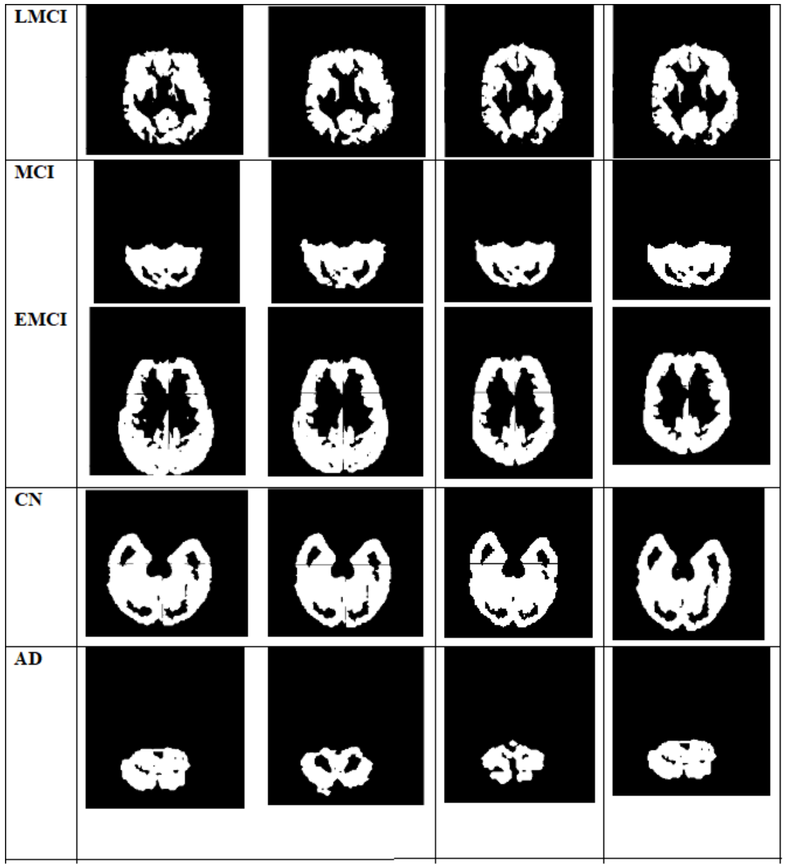

Fig 3. Output of the Segmentation Process

2.4 Multivariate feature extraction

From the segmented regions, we have extracted the following multi variate features.

a) GLCM

It is used to calculate the gray level spatial dependences in an image. In an image, the number of gray levels are accurately equal to the number of rows and columns. Co-occurrence matrices are constructed in four orientations (0^0,45^0,90^0, 135^0). Various textual features are calculated namely energy, correlation, dissimilarity, contrast, entropy, mean, standard deviation and variance.

LBP is a commonly used textual descriptor which describes the local text patterns of an image. The formula for LBP calculation is defined as

$$\mathrm{LBP} = \sum_{j=0}^{p-1} S(Nj - Gc)2^{j} \tag{1}$$

Where,

p - represents number of neighborhood pixels
c - Represents center pixel
Nj - represents j^{th} neighboring pixel

c) ALFF

It is used to measure unstructured variations in rsfMRI images. ALFF defines the local unstructured brain activity through the entire brain. In every voxel, the average amplitude value lies between 0.01 and 0.08Hz was calculated to give ALFF measure.

d) BC

For each vertex, the measurement of number of the shortest path passing through that vertex is called Betweeness Centrality.

e) DC

DC is a measure based on graph[21] which calculates the number of direct links of each voxel and reflects the functional connectivity within the entire brain network. DC has been extensive application in neuropsychiatric disorders.

f) NE

NE is used to capture the center of each node in a network. For a given node i, Nodal efficiency is calculated as

$$E_j = \frac{1}{n-1} \sum_{j \neq k \in G} \frac{1}{d_{k,j}} \tag{2}$$

NE measures the information propagation between nodes in a network.

g) RsFC

rsFC measures temporal correlation of impulsive BOLD signals among spatially disseminated brain regions. Here, we have used seed based rsFC to inspect un depth the differences of rsFC among AD, MCI and all its stages at regional level.

2.5 Feature Selection using LGKFS

Feature selection can be used to improve accuracy by reducing the feature dimensions in the Functional Connectivity Networks (FCN) constructed on rsFMRI. The proposed LGKFS (Lasso with Graph Kernel Feature Selection) algorithm is implemented for selecting best features for reducing the feature dimensions and to increase the accuracy. The pseudocode of the proposed algorithm is described below.

Pseudocode of LGKFS Algorithm

Input: X (F1, F2………. Fk , Fc)
Output: FsBest Features
Begin
Estimate the correlation coefficient
For i=1 to k do begin
$r_{co\ rr} = \frac{\sum(Xi - \overline{Xl})(Yi - \overline{Yl})}{\sqrt{(Xi - \overline{Xl})^2 (Yi - \overline{Yl})^2}}$
if rcorr =0 then remove feature
Xi= (correlation features) rcorr
y=F,
ρ =0
La $= \min \frac{1}{N} W_i L \left(y_i, \beta_0 + \beta^T Xi + \aleph[1-\alpha) \|\beta\|^2/2 + \alpha \|\beta\|\right)$
Over a grid of values of ⊠ covering the entering range
L (y, η) is the negative log
$\alpha = 1 \rightarrow La$
for i=1 to k do begin
t=calculate threshold (rcorr, ρ)
if La< t
assign FSBest=SList
end
LaBest= FSBest
for i=1 to k do begin
set Mi(V)= La(V)= La(V)2
if i>0 then $M_i(V) = \{\{La_{i-1} - (u) \mid u \in N(v)\}\}$
end
end
res=Sort (Mi(V))

Concatenate res into string Si(V)
add La_{i-1} with string Si(V)and store the result in Si(V)
do compression
From G and G' sort string Si(V)
using a function, assign each string in Si(V) to a new label
$f : \Sigma^* \rightarrow \Sigma$such that f(Si(V)) = f(Si(x)) if and only if Si(V)=Si(x)
Set Li(V)= f(Si(V)) ε G,G'
end
LKG$_{best}$= Li
return LKG$_{best}$
end

This algorithm considers the feature selection steps taken by two widely used feature reduction techniques namely LASSO regression and GK-SFS algorithm. LASSO regression is commonly used in machine learning for selecting subset of variables. LASSO is used for eliminating irrelevant parameters to help the concentration of selection and regularization of the model. It uses shrinkage operation in which coefficients get shrunk towards the central point as mean to enable the identification of variables strongly associated with variables corresponding to the target. Lasso regression uses absolute weighs to provide greater accuracy.

The formula for LASSO regression is given as

D=residual sum of squares or Least Squares Lamda*aggregate of absolute values of coefficients

Where Lamda represents shrinkage amount.

GK_SFS algorithm uses three functions namely quadratic loss function to measure the difference between estimated and actual values for training data, graph kernel based laplacian regularizer to maintain the structural information and sparsity regularizer with l1-norm to get a sparse solution of the model. The features which contains non-zero factor will be considered as best features.

2.6 Classification

Finally, we have applied a well-known supervised classification algorithm namely Random Forest(RF)to classify different stages of MCI and AD. Random Forest algorithm is a machine learning algorithm widely used for classification and regression problems. It can handle the dataset containing categorical variables in case of classification problems and in case of regression problems it can handle continuous variables. The steps involved in the random forest is depicted in Figure 4 .

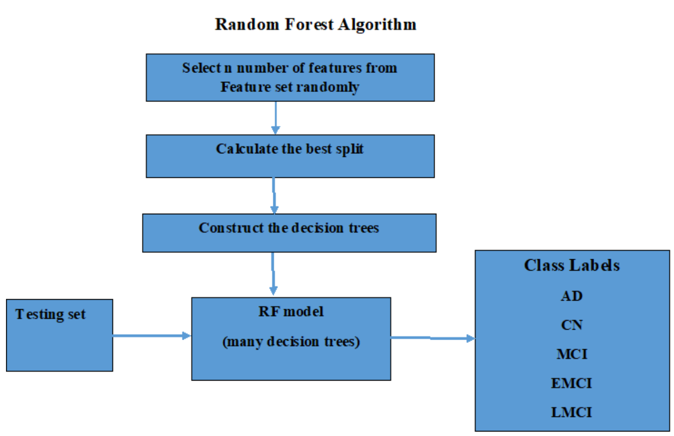

Fig 4. Random Forest Algorithm

Step1: In Random Forest, n number of features are selected for constructing decision tree.
Step2: Feature splitting are done randomly to calculate the best split.
Step3: Individual decision trees are constructed for each sample.
Step4: Each decision tree will generate an output.
Step 5: Final classification is done based on majority voting.

If numbers of trees are high in the random forest, robustness and accuracy will be high. The main advantage of RF algorithm is that it can handle large dataset efficiently and it provides high accuracy in predicting class labels over the decision tree algorithm.

3 Results and Discussion

This research work is aimed to classify five stages of AD using rsfMRI data. Before doing the experiment, various preprocessing methods were applied to rsfMRI dataset. In this section, we have performed two kinds of cross validation of our approach. In 10 Fold Cross Validation, the entire dataset is splitted into 10 folds of equal size randomly. From that, nine folds are taken as training data and one fold is taken as test data. This is repeated for all the 10 folds. In LOOCV, out of n subjects in the dataset, one subject is considered as test data and n-1 subjects are considered as training data. For all the n subjects, this procedure is repeated to give the final result. In our experiment, we have evaluated the performance of disease classification using the evaluation metrics mentioned below.

- **Accuracy (ACC)**

$$\mathrm{ACC}=\frac{TP+TN}{TP+TN+FP+FN} \tag{3}$$

- **Sensitivity (SEN)**

$$\mathrm{SEN}=\frac{TP}{TP+FN} \tag{4}$$

- **Positive Predictive Value (PPV)**

$$\mathrm{PPV}=\frac{TP}{TP+FP} \tag{5}$$

- **F1 Score**

$$\text{F1 Score }=2*\frac{PPV*SEN}{PPV+SEN} \tag{6}$$

- **Specificity (SPEC)**

$$\mathrm{SPEC}=\frac{TN}{TN+FP} \tag{7}$$

- **Balanced Accuracy (BAC)**

$$\mathrm{BAC}=\frac{SEN+SPEC}{2} \tag{8}$$

- **ROC_AUC**

$$\mathrm{AUC}=\frac{TPR-FPR+1}{2} \tag{9}$$

Fig 5. a) Analysis chart of performance metrics (10Fold validation), b) Analysis chartof performance metrics (LOOCV)

Where,

TP - True Positives FP - False Positives

TN - True Negatives FN - False Negatives

TPR -True Positive Rate FPR -False Positive Rate

All the above mentioned evaluation metrics have been computed for RF classifier using 10-fold CV and LOOCV. Based on the calculated values of metrics, we have analyzed the metrics individually and the results are graphically represented below. Figure 5 (a) demonstrates the analysis of accuracy, positive prediction value, sensitivity, f1 score, specificity and balanced accuracy obtained in 10 Folds.

In Figure 5 (b), the analysis of results of various metrics obtained in LOOCV validation is clearly displayed. It is clearly showing that LOOCV produces high accuracy than 10-fold validation.

The Receiver Operating Characteristic for multi class data classification using RF classifier is plotted against TPR and FPR. Figure 6 describes the AUC value of RF classifier and AUC of five classes of Alzheimer's disease classification are 0.99 for CN,0.81 for EMCI,0.85 for MCI,0.95 for LMCI and 0.94 for AD.

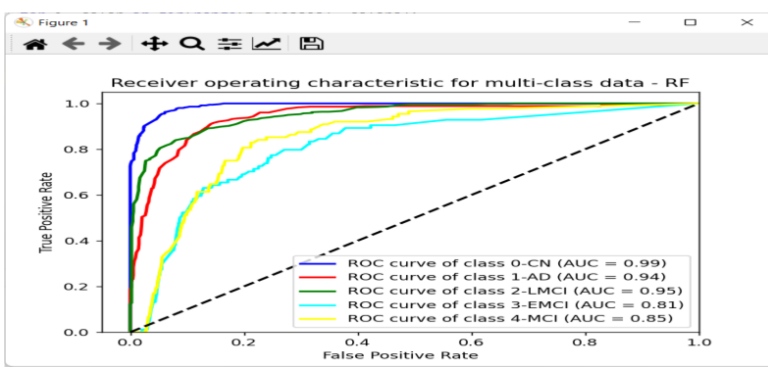

Fig 6. AUC value for multi class data –RF classifier using LGKFS

The Lasso method performance in 10 Fold validation is illustrated in Figure 7 (a) and (b) shows the performance of GK-FS technique in 10 Fold cv.

Next, we compared our proposed LGKFS Feature selection based RF classification performance with two existing feature selection techniques LASSO and GK-FS and it is depicted in Table 2. It is clearly shows that the proposed LGKFS based RF classifier gives improved classification accuracy than RF using LASSO and RF using GK-FS feature selection techniques.

We also analyzed the performance of our multi variate feature extraction approach with deep learning approaches used earlier which is shown in Table 3.

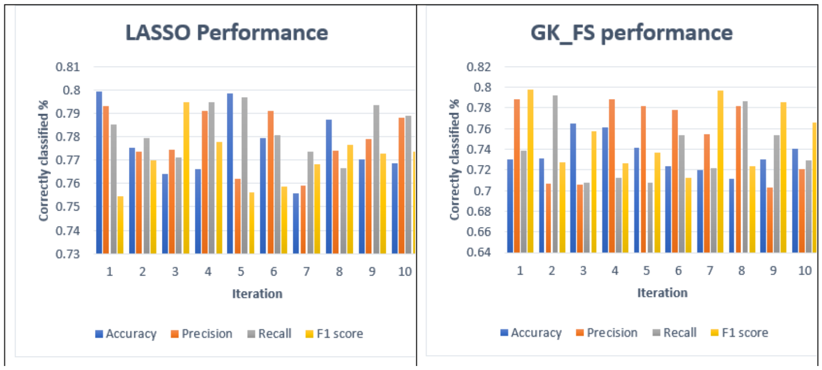

Fig 7. a) Performance of RF using LASSO method, (b). Performance of RF using GK-FS method

Table 2. LGKFS Vs LASSO Vs GK-FS Techniques Comparison

Feature Selection Technique	Accuracy %	Precision %	Recall %	F1 Score %
LASSO	79.94	79.31	79.69	79.48
GK-FS	76.52	84.0	79.19	79.77
LGKFS (Proposed)	90.8	82.4	81.6	81.6

Table 3. Analysis of accuracy obtained by deep learning approaches

Authors	Method	Accuracy %
Solano B et al [10]	3D dense net 121	87%
Duc N T etal., [11]	3D CNN	85.27%
Reddy G et al., [12]	VGG 19	85%
Proposed	Multivariate feature extraction with LGKFS feature selection	90.8%

Even though the above works were done using deep learning, they produced less accuracy. Therefore, we have proposed LKGFS approach to enhance the classification accuracy of the model. Using this approach, we have achieved the average accuracy of our multi class classification is 90.8% to classify five stages of AD which is higher than that of previous methods.

4 Conclusion

This work employed multivariate approach for feature extraction by extracting graph based connectivity features and texture features and proposed a novel approach lasso with Graph Kernel Feature Selection(LGKFS) algorithm to reduce the feature dimension that can be attained by combining LASSO and GK_SFS feature selection techniques. To perform multi class classification, the selected best features are given to Random forest classification algorithm. It classifies the test data into different classes namely class 0-CN, class1-AD, class2-LMCI, class3-EMCI and class4-MCI and attained an average accuracy of 90.8%. For cross validating the result, we employed 10 Fold validation and LOOCV. The results show that the proposed multi variate feature extraction and LGKFS selection approach based RF classifier increases the classification accuracy than RF using LASSO and RF using GK-FS feature selection techniques and also detect disease related brain regions. These detected regions are acted as an early indicator of developing AD. The limitation is that the features are only extracted from WM, GM and CSF. In future, it is planned to make use of deep learning framework for feature extraction to produce better classification performance and also planned to use multi model dataset to investigate the performance of our approach in different ways.

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