Early detection of Parkinson's disease through multimodal features using machine learning approaches

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Abstract: This research establishes a relation between objective biomarkers of Parkinson's disease (PD) based on T1-weighted MRI scans and other clinical biomarkers. It shall aid doctors in identifying the onset and progression of PD among the patients. Voxel-based morphometry has been used for feature extraction from MRI scans. These extracted features are combined with biochemical biomarkers for dataset enrichment. A genetic algorithm is applied to this dataset to remove the redundancies and to obtain an optimal set of features. Subsequently, we used Self-adaptive resource allocation network (SRAN), extreme learning machine (ELM) and support vector machines (SVM) to classify different subjects. It is observed that SRAN classifier gave the best performance when compared with ELM and SVM. Finally, it is found that a variation of grey matter in Thalamus is responsible for PD. The obtained results corroborate the earlier findings from the literature.

Keywords: Parkinson's disease; magnetic resonance imaging; MRI; proteomic biomarkers; genetic algorithms; GA; classification; self-adaptive resource allocation network; SRAN; extreme learning machine; ELM; support vector machines; SVM.

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1 Introduction

Parkinson's disease (PD) is considered as the second most common progressive neurodegenerative disorder that leads to various problems like defects in body movements including speech (Bolat and Bolat, 2010). It is believed that genetic (Samii et al., 2004) and environmental factors like polluted environment and water (De Lau and Breteler, 2006) are the important causes of PD. Early diagnosis of PD is very important; otherwise, it is difficult to cure as 60% of the damage to a dopaminergic neuron is already done. Today, no single blood test or laboratory test has been identified for recognising PD and its progression. UPDRS and Mini-mental state examination are some of the methods that have been used by the neurologists for diagnosing PD in its initial stages. However, these methods have limitations like: the need of experienced and skilled doctors, cooperation from the patients, and plenty of time required for investigation. To overcome these limitations, neuroimaging techniques are preferred to visually evaluate and quantify the loss of neurons in different regions of the brain. Some of the commonly used neuroimaging techniques are: magnetic resonance imaging (MRI), functional MRI (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) (Ravina et al., 2005; Brooks et al., 2003; Segovia et al., 2015). Among these techniques, PET and SPECT have limitations such as poor spatial resolution, cost (PET is expensive) and most importantly is the use of radioactive nucleotides onsite. Thus, there is a need for a non-invasive and high-resolution method that would help doctors to monitor the development, progression, and treatment of neurodegenerative diseases. Based on the studies done so far, it is observed that MRI can be used for PD diagnosis due to its high spatial resolution, non-invasiveness, low cost, and wider availability (Thiel, 2009; Rasmussen, 2010). In addition to the above, MRI also provides accurate information about brain morphometry (i.e., shape, mass, and volume of the brain). Literature shows that the use of MRI for reliable and accurate diagnosis of PD and other brain-related diseases like brain tumour (Kharrat et al., 2014; Sheela and Babu, 2016) has become very vigorous (Chaplot et al., 2006; Kassubek et al., 2002; Gama et al., 2014). Identification of a subject as a healthy person or PD patient is a 2-class/binary classification problem and hence it is a suitable candidate for implementing Machine Learning (ML) techniques. According to Lavrac (1998), medical datasets consists of incomplete, incorrect, and sparse information. Therefore, to deal with these kinds of problems, ML approaches play a vital role. In addition, ML techniques can easily relate the changes in brain volume while a person is suffering from this disease. Two methods that are used to extract features from MRI scan and relate the brain volume changes are region-of-interest (ROI) based approach and Whole-brain morphometric approach.

ROI based approach describes the shape and size of specific preselected brain regions. Although good classification results were obtained, still there are certain limitations like subject expertise requirement for drawing ROIs. Therefore, the process is time-consuming and needs large datasets to generalise the results. To overcome the limitations posed by this, Whole-brain voxel-based morphometric approach is used. The dictionary meaning of Morphometry is quantitative analysis of form, a concept that encompasses size and shape; brain morphometry is a subfield of morphometry which deals with the quantification of brain in terms of shape, mass, tissue volume changes in individual brains or between the brains of normal and abnormal persons during development, learning, disease and evolution. Two techniques for analysing the brain morphometry are: voxel-based morphometry (VBM) and surface-based morphometry (SBM). SBM is a technique for the construction and analysis of structural boundaries within the brain. VBM employs voxel-wise comparison of tissue probability volumetric maps between two groups of subjects

(Ashburner and Friston, 2000). A Voxel represents the volume element whose intensity is defined in 3D spaces and is different from pixel (2D spaces). In this paper, VBM approach has been used to identify the grey matter (GM) differences among normal and abnormal persons' (PD patients') brain.

PD detection studies have been extensively carried out by various researchers using morphometric features. Kassubek et al. (2002) analysed GM volume differences between the patients and healthy subjects using SPM99/VBM. It was observed that the Thalamus is involved in the generation of Parkinsonian tremor. Similarly, a group study to find the change in GM, white matter (WM), and CSF, using VBM, among the patients and normal people, was performed by Brenneis et al. (2003). Significant cluster of volume loss in putamen, midbrain, primary sensorimotor cortices bilateral, supplementary motor areas bilateral, right premotor cortex, prefrontal cortex bilateral and insular cortices bilateral and subcortical atrophy occurred bilaterally in caudate nuclei have been observed in PD patients. Lai (2013) performed a meta-analysis of GM findings in major depressive disorder using VBM. The author observed GM defects in right anterior cingulated cortex and left anterior cortex in PD patients as compared to controls. Another investigation has been carried out by Gama et al. (2014) for evaluating the changes in CSF in PD patients with diurnal visual hallucinations using VBM. The authors found that the GM volume had been reduced in left insula and left trigonal frontal gyrus in the abnormal cases without cognitive dysfunction.

Further, Babu et al. (2014) identified that a loss of GM in superior temporal gyrus is responsible for the onset of PD. Their approach was based on morphometric features (SPM/VBM) and meta-cognitive radial basis function network classifier. The high computational cost was incurred in this approach although the results were good. Similar kinds of results have been obtained for Alzheimer's disease as well (Seixas et al., 2009). Recently, Korolev et al. (2016) developed a model for predicting the Alzheimer disease progression using probabilistic multiple kernel learning classification approach from the data of 259 patients. 80% accuracy was achieved using cognitive markers and MRI markers. Thus, it is clear from the literature that VBM approach and ML algorithms are playing a vital role in detection and classification of neurodegenerative diseases.

Although MRI scans are helpful in PD detection, a single test does not reveal the existence of PD. Further, to improve PD classification accuracy, we have incorporated additional biomarkers. The intent of using Biomarkers is to support neurologists in disease diagnosis, track disease progression, and help to identify therapeutic targets. Three categories in which biomarkers can be categorised are: imaging, clinical testing procedures, and biochemical and genetic biomarkers (Michell et al., 2004). Thus our main focus in this study is on using cost-effective and minimal-invasive data sources that include:

- clinical data
- voxel based morphometric measures obtained from structural T1-weighted MRI scans
- plasma-based proteomic data.

We developed a model to classify the subjects, as healthy person or PD patient, by integrating heterogeneous data. Heterogeneous dataset resembles the features obtained from a combination of MRI, clinical and plasma proteomic biomarkers. VBM approach has been used to find the GM differences between the group of PD patients and healthy subjects. To validate our hypothesis, matched biomarkers related data and imaging data of 164 persons (82 PD patients and 82 normal persons) was collected from PPMI organisation. Using VBM approach, 2200 features were extracted from MRI scans and an additional 11 biomarkers were combined to form a heterogeneous dataset. Since the features' space is very large and samples are few, there is degradation in machine learning due to the curse of dimensionality. Therefore an optimal set of features are absolutely needed to claim the performance of the algorithms. To reduce the dimensionality of the feature space, first, principal component analysis (PCA) was implemented in this study. Although dimensionality was reduced, the time taken to extract the features was still high. Since the number of samples was less than the number of features; PCA reduced features may not give the accurate results as studied in the literature. To overcome this limitation, we used an evolutionary approach based on genetic algorithm (GA) to select the optimal number of voxels and a sequential learning algorithm (SRAN) that used the self-adaptive thresholds to select and discard the training samples so that overfitting does not occur. For performance evaluation, GA-SRAN classifier is used to select the best 56, 29, 16, 14, and 10 voxels out of 2211 features. Further, the performance of GA-SRAN model (Babu and Suresh, 2012) is compared with those of GA-ELM (Huang et al., 2006) and GA-SVM models (Ozcift, 2012). The results clearly show that SRAN outperforms ELM and SVM in terms of accuracy, sensitivity, and specificity. We have also conducted a statistical test using ANOVA to show the significance of the obtained results. The P-value signifies that the results are systematic and are not received by chance.

The rest of the paper is structured as follows: Section 2 describes the materials and methods used in this study. Section 3 explains how classification is done using SRAN, SVM, and ELM classifiers. Section 4 describes the experimental setup, the performance comparison of GA-SRAN classifier with the aforementioned classifiers, and validation of results. Section 5 concludes the study.

2 Material and methods

The problem of PD detection and classification using heterogeneous features consists of three steps:

- The first step is to extract the features from T1-weighted MRI scans using VBM approach.
- Second, to find the correlation between different biomarkers and then integrate those with VBM extracted features to get an enriched dataset.
- Third, to employ GA on the enriched dataset to get the optimal voxels followed by PD classification using SRAN/ELM/SVM classifiers. After this, the results are validated statistically as well as neurologically. This section explains the first 2 steps in detail along with data description used in this study.

2.1 Parkinson's progression markers initiative (PPMI)

Subject datasets for healthy persons and PD patients have been obtained from PPMI database (http://www.ppmi-info.org). PPMI was launched in 2002 by The Michael J. Fox Foundation for Parkinson's Research (MJFF) (https://www.michaeljfox.org/foundation). The objective of PPMI is to support researchers, industry, and governments for creating efficient and effective ways for PD detection by socialising genetic biomarkers, cognitive assessments, and image modalities data.

2.2 Structural MRI data

The demographic details of the subjects used in our study are shown in Table 1. We have collected more than 164 T1-weighted MRI samples from the available dataset. Due to non-availability of matched clinical, proteomic biomarkers and failure of segmentation method, some of the normal persons' and PD patients' MRI images are excluded. Also, to overcome the limitations of the imbalanced dataset (Belarouci et al., 2016), an equal number of scans from both the categories are taken. Dataset corresponding to the 3D sequence of magnetisation prepared rapid acquisition gradient echo MRI images with slice thickness ranging from 1–1.5 mm were acquired using 1.5 Tesla scanners with some echo delay time between 2–6 ms. Two-way ANOVA test is performed to calculate the difference between age and gender of the control group and PD group. However, it was found that the difference between these groups is insignificant because P-values are greater than 0.05.

Table 1 Details of the subjects used in this study

	T1-weighted MRI data					*Clinical AND plasma proteomic data*					
Subjects	*Number of persons*	*Sex (M/F)*	*Age (range)*	*Slice thickness* (mm)	*Voxel dimensions* (mm)	*CSF (ml) (mean volume)*	*RNA (ml) (mean volume)*	*Plasma (ml) (mean volume)*	*Serum (ml) (mean volume)*	*DNA (ml) (mean volume)*	*Urine (ml) (mean volume)*
Control	82	58/24	31-82	1-1.5	1_1_1.20	14.1	0.1	4.3	3.9	0.40	13.01
PD	82	60/22	34-77	1-1.5	1_1_1.20	13.9	0.138	4.097	3.613	0.49	12.48

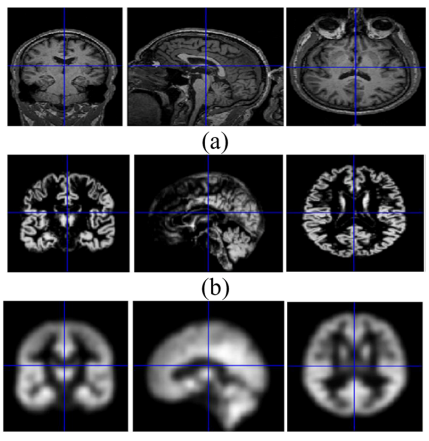
CSF: cerebral spinal fluid; DNA: deoxyribonucleic acid; RNA: ribonucleic acid.

2.3 Voxel-based morphometric (VBM) approach for feature extraction

In this study, 'optimised' VBM analysis of T1 weighted images based on unified segmentation (Ashburner and Friston, 2005) has been used for finding the GM differences among the population of subjects. The steps involved in VBM analysis are: unified segmentation, smoothing, and statistical analysis (Kurth et al., 2015). Statistical Parametric Mapping version 8 (SPM8) is used for pre-processing the MRI images. For this, the conversion of Digital Imaging and Communications in Medicine (DICOM) images to single 3D NIFTI format is performed first. After the conversion, 'normalisation' of all 3D T1-weighted MR volumes is performed by keeping all the volume preserved. Normalisation warps each individual subject into standard space based on Montreal Neurological Institute (MNI) template. After that, all normalised volumes are 'modulated segmented' into GM tissue probability maps (TPMs) which are further 'smoothed' by a 10 mm isotropic full width at half maximum (FWHM) Gaussian kernel to increase the signal-to-noise ratio. Subsequently, VBM has been utilised for feature extraction from smoothed modulated Grey Matter TPMs. Family wise error with $p < 0.05$ has been applied to get the voxels. Significant voxels having maximum intensity projections can then be used to extract the features for further analysis.

Figure 1 shows (a) MRI of PD patient, (b) segmented GM tissue class, and (c) smoothed GM image.

Figure 1 (a) MRI of PD patient; (b) segmented GM tissue class and(c) smoothed GM image (see online version for colours)



(a)

(b)

(c)

Three planar views viz., coronal, sagittal, and axial of MRI images have been shown in Figure 1. Figure 2 describes the feature extraction steps using VBM. From Figure 3, it is clear that there are significant areas with decreased GM tissue in the patients as compared to normal persons. A total of 2200 features have been extracted using VBM approach. After feature extraction from MRI, we had combined the clinical and proteomic features. Now, this integrated set of features shall be used for classification purpose. The number of features obtained by different researchers using VBM approach may not be the same (Whitwell, 2009) because there are a large number of factors that can vary and thus influence the results. These factors include the

- use of different degrees of smoothing, registration, and segmentation algorithms
- lack of standard conventions for what '*p*' value to be used for statistical analysis, and
- different group of persons, different covariates, and different contrast.

A 3D volume-rendered display of the significant areas (increased GM density in normal persons as compared to PD patients) is shown in Figure 4. From these figures, it is clear that the affected region of brains with less volume of GM can be easily inferred.

Figure 2 Feature extraction using SPM8/VBM (see online version for colours)

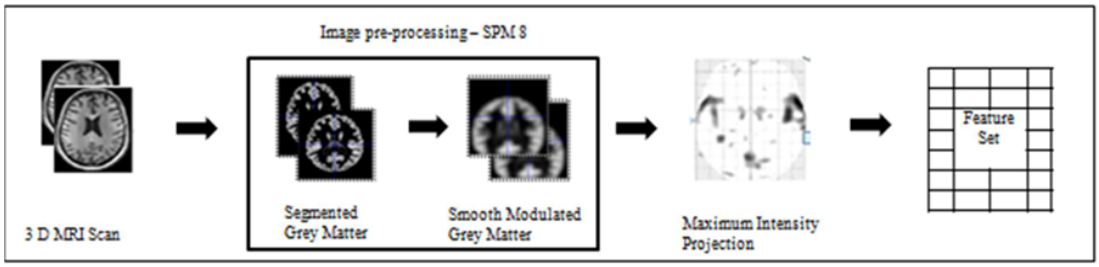


Figure 3 Maximum intensity projections of significant areas with increased GM density in normal persons relative to PD patients (see online version for colours)

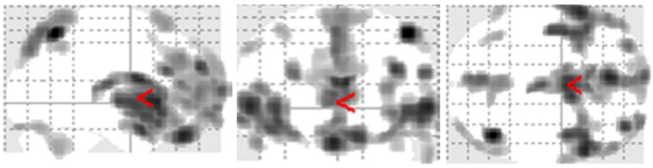
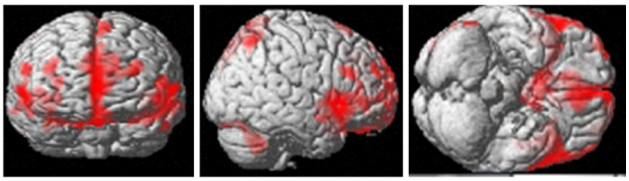


Figure 4 3D Rendered displays of significant areas with increased GM density in normal persons relative to PD patients (see online version for colours)



2.4 Clinical and plasma proteomic data

Variations in biomarkers are reflective of the changes that the subject is undergoing. Hence, its study can facilitate in identifying the subjects at risk and support the clinicians of quick decision making. The biomarkers reflective of PD can be categorised into imaging, clinical testing procedures, and biochemical and genetic biomarkers (Michell et al., 2004). Clinical testing procedures are further classified into risk factors and assessment markers. Our classification analysis focuses only on risk factors. Current literature shows that a decrease in uric acid levels and high plasma concentration leads to the onset of PD (Weisskopf et al., 2007; Bogdanov et al., 2008). Hence, we focused on plasma to identify the correlation with other bio-markers like RNA, CSF, and Serum. This correlation between different biospecimens (Pahuja and Nagabhushan, 2016) is represented by the following formula:

$$\text{Plasma (ml)} = 2.49 - 0.142\text{CSF (ml)} + 10.42\text{RNA (ml)} + 0.5873\text{Serum (ml)}. \quad (1)$$

The significance of various biomarkers responsible for the onset of PD has been depicted in Figure 5. The accuracy of the model varies with the biomarker values and characteristics. This can further be made more consistent by increasing the dataset. Finally, these results should be used along with human intelligence for practical implementation. In this research, we incorporated the aforementioned features along with the features extracted from MRI scans. Since the number of features obtained is large, optimisation methods are required to speed up the process by reducing the irrelevant, redundant, and noisy data while keeping the most relevant ones. After studying the literature, it was observed that GA is one of the most useful multi-criterion optimisation techniques (Yang and Honavar, 1998). Multi-criterion algorithms not only optimise the classification accuracy but can also consider other factors like cost, risk, etc. GA is defined as a heuristic method that is based on 'survival of the fittest'. The structure of GA (Haupt and Haupt, 2004) is depicted in Figure 6. The results of implementing the evolutionary algorithm strategies for discriminating PD and age-matched controls have been found to be more promising than conventional algorithms (Smith et al., 2007). Also, various researchers have indicated the use and effectiveness of GA for optimal feature selection (Siedlecki and Sklansky, 1989; Martínez-Murcia et al., 2014; AlMuhaideb and Menai, 2014). Thus, in this paper, GA has

been employed to select the optimal number of voxels. In addition, we have implemented three classifiers viz., SVM (Vladimir and Vapnik, 1995), ELM (Huang et al., 2006), and SRAN (Suresh et al., 2010) on the reduced feature set. For the purpose of performance evaluation, the classifiers are used to select 56, 29, 16, 14, and 10 voxels out of the total number of features.

Figure 5 Depicting the significance (P-value) of biomarkers responsible for the onset of PD: (a) run chart for plasma; (b) run chart for serum; (c) run chart for cerebral spinal fluid (CSF) and (d) run chart for ribonucleic acid (RNA) (see online version for colours)

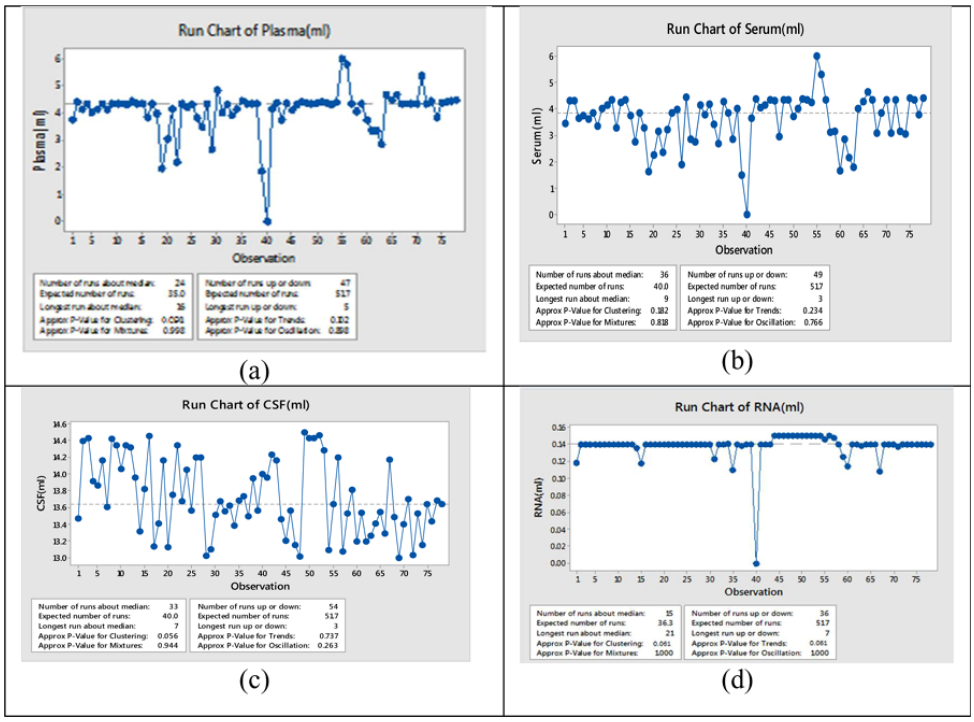
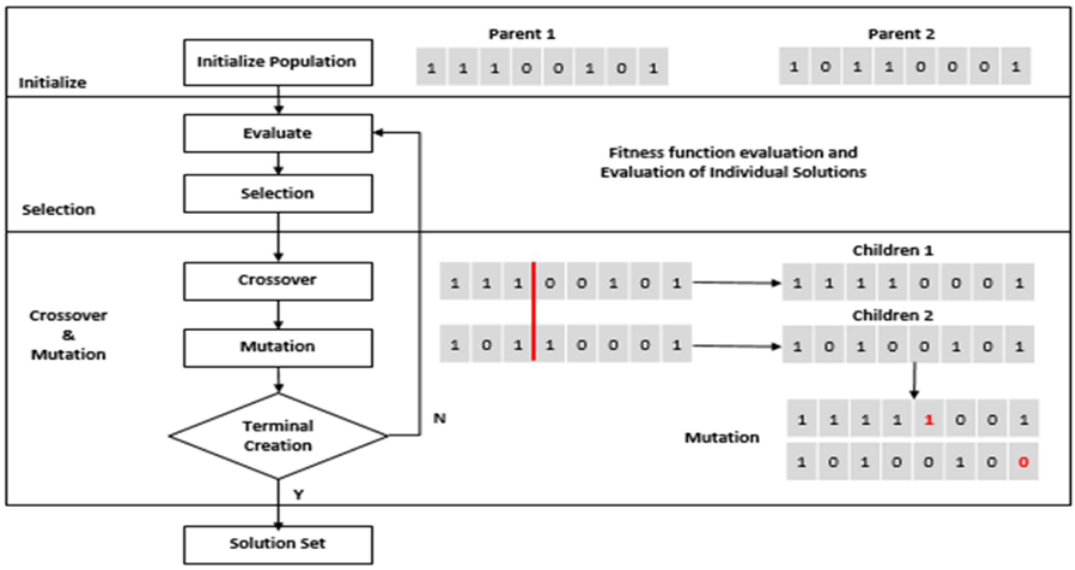


Figure 6 Phases of genetic algorithm (see online version for colours)



3 PD classification using SRAN/ELM/SVM classifiers

3.1 Self-adaptive resource allocation network (SRAN)

Online/sequential machine learning and batch learning are the two different methods of machine learning. Batch learning techniques generate the best predictor by learning on the entire training dataset at once as opposed to sequential learning in which training samples arrive one-by-one and are deleted after learning. Sequential learning has found its application in medical applications (Bala and Vijayachitra, 2014) and real-time scenarios like stock market prediction, where it is computationally infeasible to train over the entire dataset. For these kinds of situations, it is necessary for the algorithm to dynamically adapt to new

patterns in the data. Thus, the batch learning algorithm may not be suitable for such applications and online/sequential learning algorithms can be used instead. SRAN (Suresh et al., 2010), a sequential learning algorithm, is found to be more appropriate for medical applications because getting the complete set of data priori is very difficult. SRAN overcomes the problem of overfitting and also reduces the training time and minimises the computational time. It makes use of self-adaptive control parameters to change the training data sequence and learn the network parameters. In this research, we are using SRAN as one of the classifiers to classify the PD patients. Sequential learning for binary classification problem can be stated as follows: The observation data is represented by $\{(x_1, y_1), \ldots, (x_n, y_n)\}$, where x_i is 2211 dimensional features vector. Since we are trying to classify the subjects as normal or abnormal persons, here, SRAN classifier is used for 2-category classification. Thus $y_n \in \{1, -1\}$ and it represents the class labels $y_n = 1$ for PD persons and $y_n = -1$ for normal persons. For new training sample, the predicted class label $\hat{c}$ is calculated using the formula: $\hat{c} = \arg\max_{i=1,\ldots,n}(\hat{y}_i)$. The output of SRAN is the decision function that correlates the random samples (feature space) with their category/class labels. The pseudo code of how the network adapts its control parameters is provided below.

START

Initialization: Assign the first sample as first neuron (K=1).
Start learning for samples i = 2, 3, 4, ….

Do

Compute the sample significance to the network

Compute the network output $\hat{y}_i$

$(\hat{y}_i = \sum_{j=1}^{K} \alpha_{ij} \exp((-\|x - \mu_j{}^m\|^2)/(\sigma_j{}^m)^2))$

for i = 1, 2, …, n

Find the maximum absolute hinge error E and predicted class label. $e_i = \begin{cases} y_i - \hat{y}_i, & if\ y.\hat{y}_i \le 1 \\ 0, & otherwise \end{cases}$.

Delete redundant samples

IF E≤ 0.05 THEN

Delete the sample from sequence without learning.

ENDIF

IF $\hat{c} \neq c$ AND E ≥ ηa, THEN

ADD a neuron to the network (K= K + 1)

Choose the network parameters and update control adding parameters.

ELSEIF $\hat{c}$ == c AND E ≥ η1 THEN

Update the network parameters using Extended Kalman filter

Update the control parameters.

ELSE

The current sample is pushed to the end of the stack for learning in future.

END IF

END DO

END

where μ_j and σ_j are respectively the neuron centre and width of the jth neuron. $\alpha_{i,j}$ is the weight connecting the ith output neuron to the jth Gaussian neuron. e represents the sample error while E represents the absolute maximum error in the current sample. K is a positive constant which controls the overlap between the hidden neurons and c is the actual class label of the current sample.

If there are no more samples to be presented to the network then training stops in ideal conditions. SRAN produces compact and efficient network with better generalisation; computational efforts get minimised as the self-regulated control parameters ($\eta a, \eta 1$) results in the selection of less number of neurons.

3.2 Support vector machine (SVM) classifier

SVM, also called non-probabilistic binary linear classifiers, was first proposed by Vladimir and Vapnik (1995). SVM does classification or regression by constructing a hyperplane between different class labels (Figure 7). The steps for classification are described below:

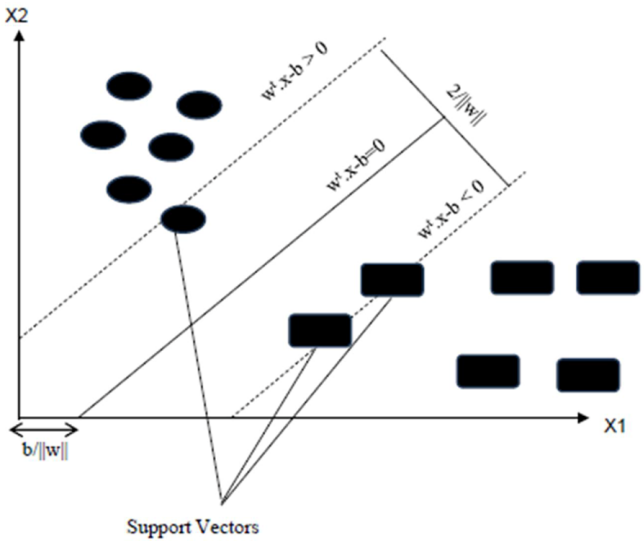
Input: For PD detection, the training data is represented by $\{(x_1, y_1), \ldots, (x_n, y_n)\}$, where x_i is 2211 dimensional features vector and $y_n \in \{1, -1\}$ and represents the class labels.

Output: The test data is classified as a patient or normal person. The equation for separating the hyperplane in case of linear SVM is given by $w^t.x - b = 0$, where w is the weight vector and b is the bias. Depending on the decision boundary, $w^t.x - b > 0$ or $w^t.x - b < 0$, the test sample is classified as abnormal or normal.

Tuning an SVM classifier: Cross-validation and retraining of SVM classifier are done by adjusting various control parameters to yield the lowest classification error.

Classification based on SVM algorithms have been widely accepted in medical imaging because of their robustness, good out-of-sample generalisation capability, and non-linear transformation property (Akay, 2009; Haller et al., 2012). 10-fold cross-validation has been used in this study.

Figure 7 SVM for binary classification



3.3 Extreme learning machines (ELM)

Similar to SVM, ELMs have also fascinated a lot of research interest due to their better generalisation performance and faster learning speed than traditional gradient-based learning algorithms. Huang et al. (2006) first proposed ELM for single–hidden-layer feed-forward neural network. In traditional gradient-based learning approaches, the weights keep on updating until the difference between the desired and actual output will not be minimum. However, in ELM, the weights connecting the inputs to the hidden nodes are randomly assigned and never updated. The weights between the hidden nodes and outputs are learned in a single step. Mathematically, it can be represented as

$$Y = w_2\sigma(w_1 x), \tag{2}$$

where w_1 is the input-to-hidden-layer weight matrix, σ is the activation function, w_2 is the hidden-to-output-layer weight matrix, and x is the input.

For classification purpose, our problem can be formulated as: $D = \{(x_1, y_1), \ldots, (x_n, y_n)\}$ where $y_n \in \{1,-1\}$ and it represents the class labels. The steps involved for classification using ELM are:

- The optimal output weights are calculated using

$$\hat{\beta} = H^{+}Y, \tag{3}$$

where H^+ is the Moore-Penrose generalised inverse of H and H is called the output matrix of the hidden layer, $\hat{\beta}$ is the output weight connecting the hidden node to output node.

- Estimate the prediction of class given by

$$\hat{C} = h_i\hat{\beta}. \tag{4}$$

- Predict the class labels y_i by

$$\widehat{yi} = \arg\max_{i=1,2,\ldots,n}(\hat{c}_i). \tag{5}$$

As stated earlier, ELM has been extensively used in various real-time applications. ELM algorithm has been employed for classification of other neurodegenerative diseases also because it is computationally efficient and more robust than SVM as the sample size increases (Peng et al., 2013).

4 Experimental setup

In this PD classification study, SPM8/VBM (SPM8, 2011) has been used for extracting the features. Since the dimensionality of the feature set is high as compared to the number of samples, there is a need to remove the irrelevant/redundant voxels by applying the feature subset selection method. After studying the literature, GA was found to be one of the appropriate optimisation methods for feature subset selection in MIP (Smith et al., 2007, Guo et al., 2010). The subset of features obtained by applying GA can then be used for classification of PD patients and healthy controls. The convergence of GA depends upon crossover probability (Pc), mutation probability (Pm), and selection probability (Ps). As reported in various studies, the crossover rate generally should be high, about 80–95%. On the other side, mutation rate should be very low. Best rates reported are about 0.5–1%. The values of the parameters used in this study are: Pc is 0.8, Pm is 0.5, and Ps is 0.08. Next, we evaluate the performance of SRAN, ELM, and SVM classifiers and compare the results. All the experiments are carried out using Matlab 2013a in the windows environment. Image Processing Toolbox from Matlab 2013a, SPM8 (SPM8, 2011), and WFU Pickatlas (Maldjian et al., 2003) are also used for experimentation purpose. Figure 8 describes the complete methodology used for Parkinson's disease detection and classification.

The complete dataset is divided in the ratio of 80% and 20% i.e., for training and testing 80% and 20% samples are randomly chosen. Since we are dealing with medical image classification problem, it is very important to calculate the misclassification rate along with correct classification. For evaluating the classifier performance, 3 parameters, namely accuracy, sensitivity, and specificity, have been used.

$$\text{ACCURACY} = \frac{TP+TN}{TP+TN+FP+FN}\times 100$$

$$\text{SENSITIVITY} = \frac{TP}{TP+FN}\times 100$$

$$\text{SPECIFICITY} = \frac{TN}{TN+FP}\times 100,$$

where TP is true positive i.e., the number of PD patients correctly classified; TN is true negative i.e., the number of healthy persons correctly classified; FP is false positive i.e., the number of healthy persons classified as abnormal/patient; and FN represents false negative i.e., the number of PD patients classified as normal persons.

Sensitivity measures how many positive cases are correctly recognised out of the total positive cases, and specificity measures the proportions of negative cases correctly identified out of the total negative cases. Ideally, a higher value of sensitivity and specificity is desirable. However, there exists a trade-off between these two in real time. For a balanced dataset, accuracy is equal to the arithmetic mean of sensitivity and specificity. On the other hand, for an imbalanced dataset, accuracy is biased towards sensitivity and specificity. The mean, best training and testing efficiencies for each of the above-mentioned classifiers are presented next.

4.1 Performance comparison and discussions

This section describes the classifier's performance on the best solution (features) obtained using GA after a specified number of generations. The performances of SRAN, ELM, and SVM classifiers are evaluated using a random combination of training and testing data. The values of accuracy, sensitivity, and specificity achieved on different random combinations of features' subset have been represented in Table 2. Figure 9 highlights the feature reduction post each iteration.

Figure 8 Steps for PD classification

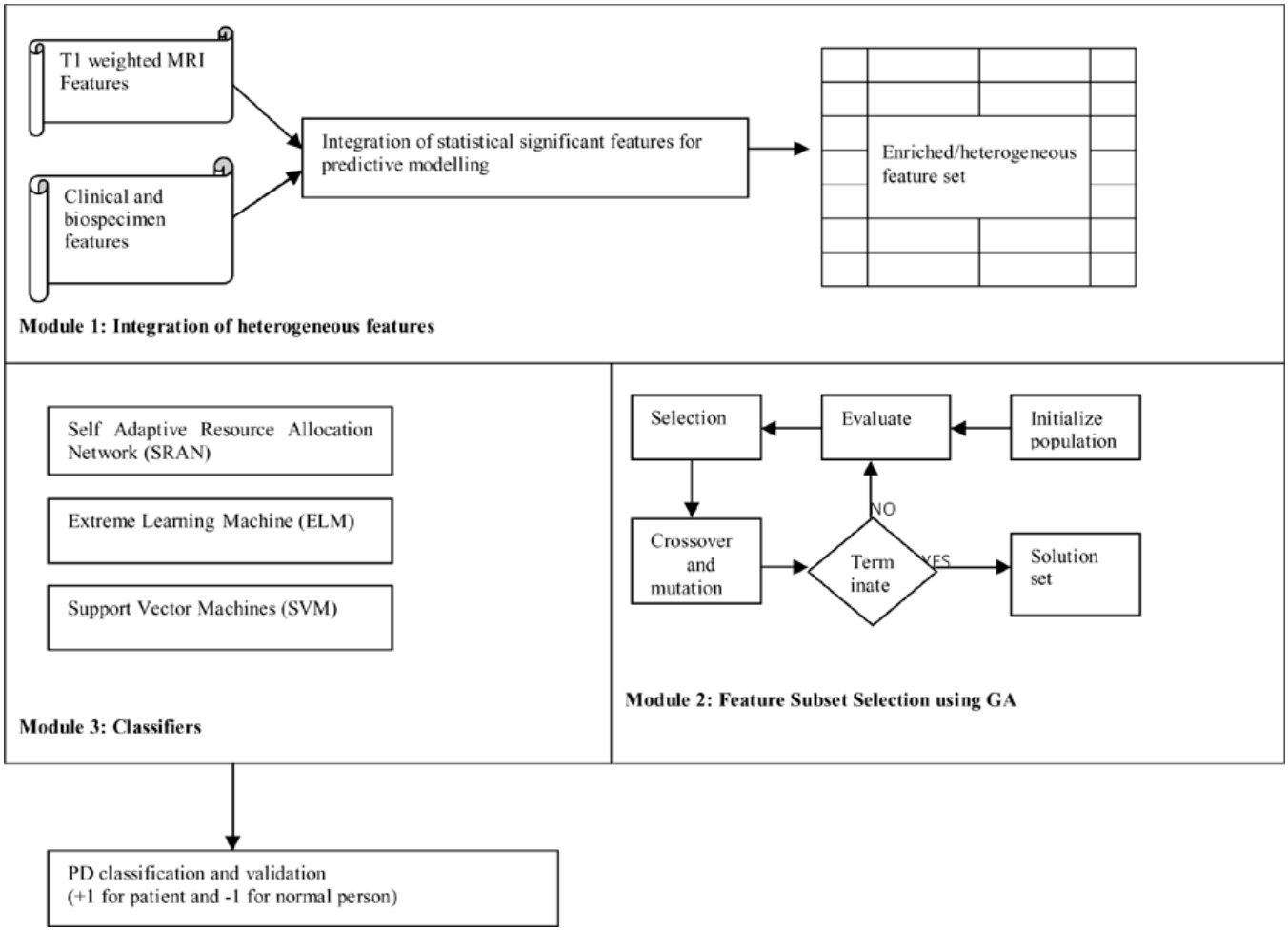
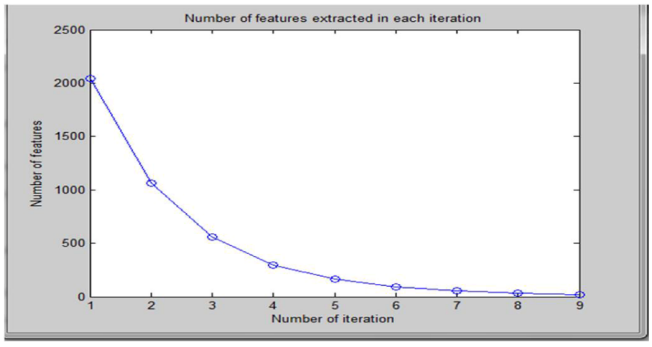


Figure 9 Number of features reduction using GA (see online version for colours)



It is observed from Table 2 that SRAN gives 98.17% accurate results on 10 selected heterogeneous (Morphometric + clinical + Plasma Proteomic data) features. Also, the time taken to extract the features is 0.25 s, which is very less as compared to the time taken in extracting the features by PCA. Using ELM and SVM, the best testing accuracy of 97.95% and 96.95% was observed on Genetic Algorithm selected features (Table 3). Thus it can be concluded from Tables 2 and 3 that the mean testing accuracy of SRAN classifier is higher than that of ELM and SVM for the same set of selected features.

Figures 10–12 depict the sensitivity, specificity, and accuracy comparison of SRAN, ELM, and SVM classifiers on GA selected features, where the number of features extracted is shown along the X-axis and the sensitivity, specificity, and accuracy are represented along the Y-axis. From Table 3 and Figures 10 and 11, it is observed that a mean sensitivity of 97.80% and a mean specificity of 96.47% are obtained using the SRAN classifier on the GA selected features. Similarly, the values of the mean sensitivity for ELM and SVM are 97.07% and 95.60% respectively. Also, it is analysed that the mean accuracy produced by SRAN is more than that of the other two classifiers. Thus SRAN is more efficient, in terms of accuracy, than the other two classifiers for PD detection. Hence, it can be concluded from the discussed results that the SRAN classifier can do accurate detection of PD with some selected features rather than using the large feature set obtained from structural MRI, clinical and plasma proteomic data.

In contrast to the related works available in the literature, in which the attributes (features) either from the image biomarkers or from the clinical biomarkers or from the biochemical biomarkers have been used for PD detection (Samii et al., 2004; Halliday, 2009; Whitwell, 2009; Lai, 2013; Delenclos et al., 2016), we have tried to combine all these features in this research. When

classification is done on the enriched dataset, we observed an enhanced accuracy in classifying PD from healthy subjects as depicted in Table 4. Although higher accuracies and sensitivity have been observed as compared to related works, it must be noted that the dataset is different from other studies.

Table 2 Performance parameter comparison of different classifiers

Iteration	*Number of features*	*Algorithm*	*Sensitivity* (%)	*Specificity* (%)	*Accuracy* (%) *(Training)*	*Accuracy* (%) *(Testing)*
1	56	SVM	96.34	95.12	97.83	95.73
		ELM	97.56	97.56	98.56	97.56
		SRAN	98.78	96.34	*99.66*	97.56
2	29	SVM	93.9	97.56	96.83	95.73
		ELM	95.12	98.78	97.49	96.59
		SRAN	96.34	97.78	99.56	97.56
3	16	SVM	96.34	93.9	97.24	95.12
		ELM	98.78	96.34	98.45	96.34
		SRAN	97.56	95.12	99.41	97.44
4	14	SVM	95.12	96.34	96.73	95.73
		ELM	96.34	97.56	97.95	96.95
		SRAN	97.56	97.56	99.56	97.56
5	10	SVM	96.34	97.56	97.75	96.95
		ELM	97.56	98.78	98.95	97.95
		SRAN	*98.78*	97.56	99.27	*98.17*

SRAN: self-adaptive resource allocation network; SVM: support vector machines; ELM: extreme learning machines.

Table 3 Performance comparison of SVM, ELM, and SRAN

	Sensitivity (%)		*Specificity* (%)		*Accuracy* (%) *(Testing)*	
Algorithm	*Mean*	*Best*	*Mean*	*Best*	*Mean*	*Best*
SVM	95.61	96.34	96.10	97.56	95.85	96.95
ELM	97.07	98.78	97.80	98.78	97.08	97.95
SRAN	97.80	98.78	96.47	97.78	97.66	98.17

Table 4 Performance comparison

	GA extracted features from heterogeneous data (combination of VBM extract and biochemical biomarkers)			*GA extracted VBM features from MRI*		
Algorithm	*Accuracy* (%)	*Sensitivity* (%)	*Specificity* (%)	*Accuracy* (%)	*Sensitivity* (%)	*Specificity* (%)
SVM	96.95	96.34	97.56	91.45	92.01	91.19
ELM	97.95	98.78	98.78	93.05	94.11	92.81
SRAN	98.17	98.78	97.78	97.43	97.80	97.07

4.2 Evaluation and validation of results

The evaluation and validation of the results have been done in the following two different ways:

- Neurological significance (by considering, only GA selected VBM extracted features from MRI): The features extracted from MRI using VBM technique (not from heterogeneous dataset) are further processed through GA to get a reduced subset of features; with this reduced subset of features, we carried out a neurological study for identifying the brain regions responsible for PD. When the selected features are again mapped to standard MNI brain space, it is observed that these selected features are from 'Thalamus' (TD Broadmann area: Medial Dorsal Nucleus; TD lobe: Sub lobar; TD hemisphere: Right Cerebrum; TD type: Grey Matter). The same has been verified by various researchers (Kassubek et al., 2002; Halliday, 2009). An injury to thalamus results in sensory defects. The medial dorsal nucleus, which is a large nucleus in the thalamus, plays a role in memory. Damage to the medial dorsal nucleus has been associated with Korsakoff's syndrome. Korsakoff's means damage to neurons in the central nervous system. We know that PD is caused by loss of neurons in central nervous

system. Thus the observed AAL 'Thalamus' proves our study.

- Considering the complete heterogeneous dataset: For evaluating and analysing the results, analysis of variance (ANOVA) statistical test has been employed. It was first developed by statistician and evolutionary biologist, Ronald Fisher, to analyse the differences among the group means and their related procedures like variations among and between the groups. Validating the results by ANOVA needs null hypothesis and alternative hypothesis. The null and alternative hypothesis formulated in this work are:

  Null Hypothesis: The obtained results are not systematic and they are received by chance.

  Alternative Hypothesis: The obtained results are systematic and they are not received by chance.

Figure 10 Sensitivity comparison of SRAN, ELM, and SVM on GA selected features (see online version for colours)

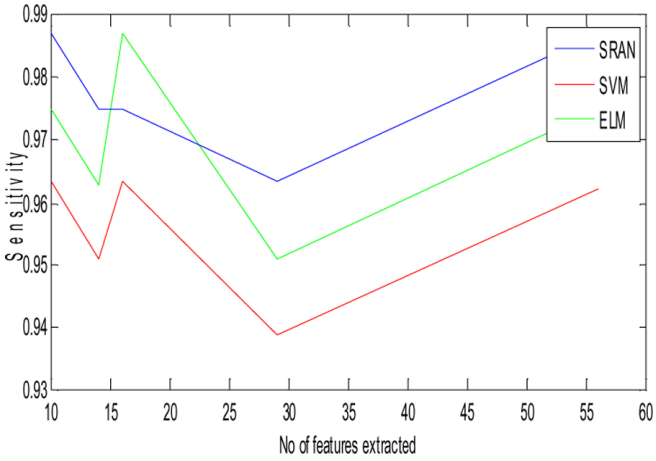
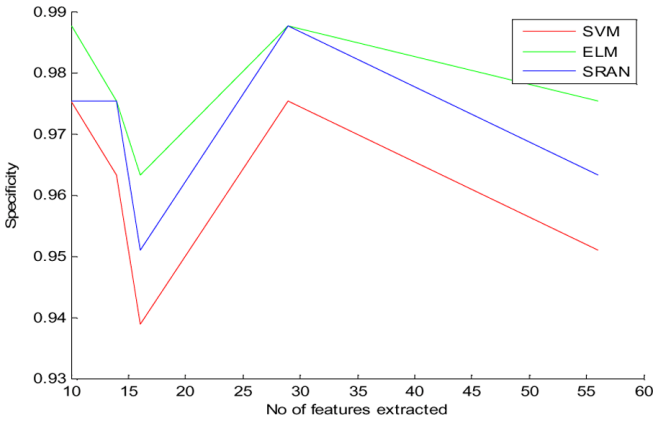


Figure 11 Specificity comparison of different classifiers on GA selected features (see online version for colours)



To evaluate and validate the results, the average value of accuracy obtained by the classifiers is calculated and submitted to ANOVA. The results obtained from ANOVA test are reported in Table 5, where P-value or calculated probability is less than the significance level (0.05). If the P-value is less than or equal to significance level, the null hypothesis is rejected and the alternative hypothesis is accepted. From Table 5, it is clear that the obtained P-values are less than 0.05, therefore, we can reject our null hypothesis that we are getting the results by chance. Thus it is concluded that the obtained results are systematic and are not received by chance.

Figure 12 Accuracy comparison of different classifiers on GA selected features (see online version for colours)

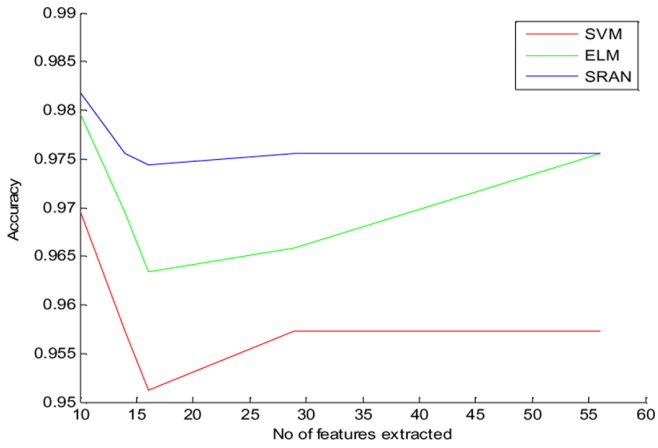


Table 5 ANOVA test results

Dataset	*Mean square error (MS)*	*F value*	*P-value*
Enriched dataset (VBM extracted MRI PD Dataset + Biomarkers)	2.00E-04	14.45277	5.08E-03

5 Conclusions

In this research, a new approach has been presented for PD detection and classification based on the integration of heterogeneous features from T1 weighted MRI images, clinical and Plasma Proteomic data. VBM has been used to obtain the voxels from MRI of patients as well as normal persons. Features are constructed from GM values of voxels. Further, an optimised algorithm GA has been used to select relevant and significant features. The classification model is built using three well-known machine learning algorithms: SRAN, ELM, and SVM. For performance analysis, a clinical and plasma related matched balanced dataset of 82 healthy persons and 82 PD patients has been acquired from PPMI and has been used to check the efficiency of the above-mentioned classifiers. Sensitivity, specificity, and accuracy have been evaluated for the above classifiers. The best classification accuracy is achieved with SRAN when GA selected features are used in addition to other biomarkers responsible for the onset of PD.

A similar study using SPECT and non-motor features have been carried out by Prashanth et al. (2016). The authors observed that the best performance is provided by SVM. Although the results analysed using SPECT are good;

from the literature, it is clear that MRI is preferable over SPECT due to its non-invasiveness and other advantages. Therefore, we used MRI modality for PD detection. Further, in the field of medicine, it is better to use an algorithm that will dynamically capture or adapt to new patterns. Therefore we have used SRAN as a classifier. An accuracy of 98.17% has been observed on test data which is more than the accuracy mentioned in the study done by Prashanth et al. (2016).

To summarise, in comparison to the existing research works, our contributions in the classification of PD are as follows:

- Comparatively large balanced dataset of 164 persons (82 normal persons and 82 PD patients) has been studied and employed to overcome bias.
- In addition to VBM extracted features from T1-weighted MRI scans, we have used the biochemical biomarkers, which are cost-effective and non-invasive, for classification purpose.
- Before combining the biomarkers with VBM extracted features, analysis has been done to find the correlation between age, gender, Plasma, RNA, Serum and CSF of different groups using ANOVA. The P-values obtained for age and gender is greater than 0.05, which states that there is no significant difference between the groups. The P-values for Plasma, RNA, and Serum is less than 0.05, therefore, it is concluded that these biomarkers are contributing towards PD.
- Further, an evolutionary approach (GA) has been used here for determining the optimal set of features which are further used as input to classifiers.
- Implemented, analysed, and compared three extensively used classifiers: SRAN, ELM, and SVM.
- To validate the results, GA selected features (only from VBM extracted features) are remapped to standard MNI template and we have identified that the brain regions responsible for PD is thalamus region, which has also been mentioned in the literature.
- ANOVA test has been applied on the heterogeneous dataset, to check the significance of the results. The lesser P-value (less than 0.05) signifies that it is unlikely that the improvement in classifiers accuracy happened by chance.

Although better results have been obtained using SRAN, there are certain limitations for this study. First, the features have been extracted from the whole brain, but one may also look at any variations in GM/WM/CSF in the brain regions using SBM and ROI based approaches. Second, though a large heterogeneous dataset has been acquired, still it is limited in size and more data is desired to make the results more generalised. Third, the method may be employed for other image modalities like DaTScan, fMRI, etc. for PD classification.

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