CHAPTER 2

REVIEW OF THE LITERATURE

In this chapter briefly describes the Alzheimer's disease related to the studies in this thesis and similar studies found in the literature. This information serves as motivation for the work described in this thesis. The diagnosis of Alzheimer's disease is a global problem. Automated image based classification for individual patient's plays a pivotal role in computer assisted diagnosis.

An emphasis in ongoing AD research is identifying biomarkers which best predict future cognitive decline, especially at the earliest stages of disease progression. The development of automated detection procedures based on MRI and other medical imaging techniques is of high interest in clinical medicine [17]. It is important to note that these techniques are aimed to help clinicians with more statistical evidence for the diagnosis, ultimately, it is hoped that these biomarkers can serve as early markers for AD diagnosis.

In clinical diagnosis, the robustness and accuracy of the CAD techniques are very important, for the reason that the result is crucial for treatment of patients. There are many different types of classification and clustering algorithms are available for the diagnosis as early as possible through MR images. The goal of clustering a medical image is to simplify the representation of an image into a meaningful image and make it easier to analyze. These methods promise to fully automated, standard PC-based clinical decisions, unbiased by variable radiological expertise. In this study compare the results to those obtained by radiologists.

2.1 ALZHEIMER’S DISEASE

Dementia is a chronic syndrome, characterized by a progressive, global deterioration in intellect including memory, learning, orientation, language, comprehension and judgment due to disease of the brain [18]. In 2010 dementia India reports estimate that over 3.7 million people are affected by dementia in our country. Alzheimer's disease is the commonest type of dementia. AD is not always a disease of old age; many individuals younger than age 65 can also develop the disease. It is irreversible, and progressively destroys memory and thinking skills which results in decline of memory and mental function. Symptoms include confusion, irritability, aggression, mood swings, language breakdown, long-term
memory loss and the decline of the sufferer’s senses. Ultimately, this leads to the loss of bodily functions and death. Neurofibrillary tangles and amyloid plaques are the histopathological hallmark of AD and are associated with neuronal loss and brain volume reductions [19].

The prevalence of AD is expected to increase dramatically as the population around the globe continues to age. Better understanding of this demanding disease, therefore, is essential, and early diagnosis combined with a comprehensive management strategy initiated early in the course of the cognitive decline will likely be the most effective method of controlling the progression of AD [20]. The incidence of AD ranges from 6.44% in south India to 4.86% in Shanghai, China to 3.92% in Sri Lanka for populations above 65 years. Currently one of the major handicaps towards achieving this is the difficulty in early and definitive diagnosis of AD [13-15].

Current treatments cannot stop Alzheimer’s from progressing, but can slow down the worsening of symptoms. Early diagnosis of AD can help improve the quality of life of the patients and their families; it also helps researchers to deeply understand the causes of the disease to reverse or slow down the progress of AD and offers more chances to treatments in the early stages. The clinical diagnosis of Alzheimer’s is based on the investigation of the complete medical history, conducting lab tests, physical exam and neuropsychological tests that measure memory, attention, language skills and problem solving abilities. The accurate diagnosis of Alzheimer's disease is challenging since there are other causes of dementia that could have the same symptoms. Severe cognitive deficit and autopsy confirmation of histopathological changes in the brain confirms the diagnosis of AD. For a living person the diagnosis confirms if the deficits are severe enough that they interfere with normal daily functions. Recent studies show that AD has a pre-symptomatic phase likely lasting for years, and during this phase, there is a high probability of preserving the cognitive functions through proper treatment [21]. However, during this stage clinical symptoms are not apparent. These early signs of the degenerative process that are most likely to evolve to AD are characterized as mild cognitive impairment. Subjects with MCI have a high risk of AD and it is considered as a transitional zone between normal aging and AD [22].
2.1.1 Mild Cognitive Impairment

The field of normal aging and dementia is focused on the characterization of the earliest stages of cognitive impairment. Recent research studies have identified that mild cognitive impairment could be a pre-dementia condition between normal aging and AD during which persons experience memory loss to a greater extent than one would expect for age, they are not meeting presently accepted criteria for clinically probable AD [23]. The main clinical characterization of MCI is memory complaint, normal activities of daily livings (ADLs), normal general cognitive function; abnormal memory for age [24]. MCI subjects had comparable memory impairment, but less impairment in other domains than mild AD patients. MCI subjects suffered fewer declines over time than mild AD patients. Unlike AD where cognitive abilities progressively decline, the memory deficits in MCI may remain stable for years. However, some people with MCI develop cognitive deficits and functional impairment in keeping with AD. The MCI patients are observed longitudinally, they reach to clinically probable AD at a significantly accelerated rate compared with healthy age-matched people. In the Mayo clinic, a longitudinal study performed in a community based clinical setting showed that a progression rate of almost 12% per year was seen in declining from MCI to dementia or to probable AD. The healthy elderly subjects declined to MCI or to AD with a rate of only 2% per year [25]. The American Academy of Neurology(AAN), reviewed in 2001 a number of studies and, even though these studies had used various criteria for MCI, they indicated an annual conversion rate of MCI to AD may even be as high as 25 % [26]. The heterogeneous nature of MCI subjects correctly identified those MCI subjects likely to convert to AD, as they are a target group for early therapeutic interventions in AD using the best biomarker.

2.1.2 Diagnostic Criteria for AD

For research purposes the AD diagnosis is based on general criteria usually defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and specifically by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) [27][28] and by the Alzheimer’s disease and Related Disorders Association (ADRDA). These criteria have been extremely useful and have survived intact, without modification for more than a quarter of a century. According to them, the following requirements are needed to
support a dementia diagnosis. Early diagnosis of AD allows time to plan for the future and to treat patients before marked deterioration occurs. MR imaging technique must be consistently differentiated AD from normal aging in individual scans [29].

2.1.3 Approaches of Biomarker Studies for Early Detection of AD

Biomarkers have diagnostic and prognostic value in the early detection of AD. Various candidate biomarkers for AD have been developed that can detect patients with AD at an early stage. Structural MRI studies and functional studies such as PET and SPECT are being widely researched in the diagnosis of AD [30]. Structural and functional imaging may be useful for the early diagnosis of AD [8]. With increasing research in disease modifying therapy in AD and recognition of mild cognitive impairment as a very incipient stage of AD, early diagnosis of AD will assist in early initiation of disease modifying therapy. This in turn will aid in improving the quality of life of patients with AD.

MRI is one of the non-invasive imaging techniques for the structural analysis of AD brains. The decline from normal to MCI and to AD has been investigated mainly using MRI studies [31]. Structural MRI analysis has demonstrated that medial temporal atrophy is associated with increased risk of developing AD and can predict future memory decline in healthy adults [32]. Current research focuses on some of the volumetric analysis techniques for the early detection of AD. Earliest techniques where the visual impression which evolved to manual volumetry and later into automated volumetry.

2.2 COMPUTER AIDED DIAGNOSIS (CAD) OF ALZHEIMER’S DISEASE

Computer Aided Diagnosis (CAD) allows physicians to detect early stages of the disease, and functional brain images have been proved to be very useful in this task. An accurate and early diagnosis of the Alzheimer’s disease is of fundamental importance for the development of effective treatments to palliate the effects of the disease in quantitative brain magnetic resonance imaging analysis. Many clinical applications rely on the segmentation of MRI scans which allows describing how brain anatomy changes over time, of aging or disease. However, manually labeling by clinical experts is a laborious, time consuming task and, above all, it is subject to inter and intra rater variability. That is why automatic techniques
are desirable to enable a routine analysis of brain MRIs in clinical use, especially for the brain segmentation. A fully automatic segmentation procedure would allow medical structures to obtain fast and economic diagnosis tools; besides, an automatic procedure would guarantee the standardization of the segmentation which would be no longer dependent on the intrinsic variability’s involved with the use of human experts. The proposed system is to perform 3D image segmentation of original 3D MRI neuroimaging brain data. There are many existing segmentation techniques applied to medical image segmentation, including statistical methods, thresholding, edge detection, region-based techniques and more recently multi-resolution using wavelet techniques[33] [34]. The choice of the method depends on the type and quality of the image.

Machine learning and computer-aided diagnosis have gained increasing attention in the medical field [35]. A machine learning algorithm is trained using a set of examples to produce a desired output. Those examples are divided into different classes. When a new instance is presented to the learning algorithm, it assigns it a class according to the set of classification rules. The only information given to the algorithm is a set of labeled examples. These classification algorithms induce the classification rules from the data. In the early stages of AD brain atrophy may be subtle and spatially distributed over many brain regions, including the entorhinal cortex, the hippocampus, lateral and inferior temporal structures, as well as the anterior and posterior cingulate.

Elaheh Moradi et al (2014) propose a semi-supervised learning method for dementia classification based brain MR images. The features used are extracted with sparse logistic regression from a large pool of voxel-wise gray matter densities computed based on MRIs registered in stereotactic space. The classifier uses a low density separation algorithm. This algorithm estimated accuracy of 76.7% for the ADNI database data [36].

Andrés Ortiz et al (2013) presents segmentation techniques based on unsupervised vector quantization and fuzzy clustering techniques using 3D statistical features extracted from the volume image. The feature vectors associated with each non-background voxel are unsupervised modeled by a Self Organizing Map(SOM). The resulting fuzzy segmentation method addresses the problem of Partial volume Effect (PVE) and has been assessed using Internet Brain Image Repository (IBSR) data base [37].
Jieping Ye et al (2012) study employed sparse learning and stability selection for predicting MCI to AD conversion using baseline ADNI data. The longitudinal conversion was considered over the course of a 4-year follow-up period. A combination of 15 features including those from MRI scans, APOE genotyping, and cognitive measures achieves the best prediction with an AUC score of 0.8587. These results also demonstrate the effectiveness of stability selection for feature selection in the context of sparse logistic regression[38].

Javier Escudero et al (2011) investigated the classification of AD, MCI and control subjects using the MRI features of ADNI database with classification techniques of logistic regression, SVM, Radial Basis Function (RBF) and C4.5 tree learner techniques. The highest accuracy rates for the classification of controls against ADs and MCIs were 89.2% and 72.7%, respectively [36].

S. Matoug (2011) proposed predicting Alzheimer’s disease by classifying 3D-Brain MRI images using SVM and other well defined classifiers. The ADNI dataset is used for testing. This study presents a pseudo automatic scheme that reads volumetric MRI, extracts the middle slices of the brain region, performs segmentation in order to detect the region of brain ventricle, generates a feature vector that characterizes this region, creates an SQL database that contains the generated data, and finally classifies the images based on the extracted features [39].

Andrea Chincarin et al (2011) study identified automated methodologies of RF and SVM classifier able to extract accurate classification of AD. The MRI based features are extracted and analyzed using RF classifier and subsequently processed with an SVM classifier. The performance of the classification based on the features extracted. The classification index is able to discriminate controls from AD with an AUC 0.97, sensitivity 89% at specificity 94% and Controls from MCI-converters with an AUC = 0.92 sensitivity 89% at specificity 80%. MCI-converters are separated from MCI-non converters with AUC = 0.74 sensitivity 72% in specificity 65% [40].

Claudia Plant et al (2010) developed automated detection of brain atrophy patterns based on MRI uses VBM and a combination with three different classifiers SVM, bayes statistics, and voting feature intervals techniques for the discrimination of AD patients from healthy controls and also predict the conversion from MCI to AD. The brain regions showing the highest accuracy (92%) for the discrimination between AD and HC were identified in the voting feature selection
algorithms also 75% accuracy for the prediction of the conversion from MCI to AD analysis [41].

Xiaojing Long et al (2010) study proposed an automatic unsupervised classification approach to distinguish brain MR images of AD patients from those of elderly normal controls. This study used the symmetric log-domain diffeomorphic demons algorithm and the spectral embedding algorithm to project images onto a low-dimensional space where each image is represented as a point and its neighboring points correspond to images of high anatomical similarity. Finally, the quick shift clustering method is employed in the embedded space to partition the dataset into subgroups for the diagnosis of AD [42].

Rémi Cuingnet et al (2010) investigated automatic classification of patients with Alzheimer's disease from structural MRI using ten methods in the ADNI database. This study evaluated the performance of five voxel-based methods, three methods based on cortical thickness and two methods based on the hippocampus. AD vs controls detect high accuracies with whole brain methods up to 81% sensitivity and 95% specificity. For the detection of prodromal Alzheimer, the sensitivity was substantially lower and for the prediction of conversion, the accuracy was only slightly higher than chance [29].

M. Lopez (2009) proposed SVM-based CAD system for early detection of the Alzheimer's disease using kernel PCA and LDA for the dimension reduction and feature extraction application in the SPECT images. The kernel based methods achieved 92.31% accuracy rate and PCA based methods yields 80.22% for the discrimination of AD from normal subjects for the same database [43].

D. Salas-Gonzale (2009) proposed Computer-aided diagnosis of Alzheimer's disease using support vector machines and classification trees techniques for improving the accuracy of early diagnosis of Alzheimer-type dementia. The mean and standard deviation of intensity values are calculated for selected voxels and chosen as feature vectors for these two different classifiers. This study reaches greater than 95% accuracy in the classification task.

Christos Davatzikos et al (2008) developed deformation based morphometry and SVM pattern classification of magnetic resonance imaging detects patterns of brain structure characterizing Alzheimer's disease. This study Recursive Feature Elimination (RFE) technique was used to rank computed features from the extracted regions, according to their effect on the leave-one-out error bound. Using
cross-validation and longitudinal analysis, 90% diagnostic accuracy was achieved [17].

C. Davatzikos et al (2008) proposed a MRI-based high-dimensional pattern classification analysis between patients with AD, FTD and healthy controls, on an individual patient basis. The ability to correctly distinguish AD from FTD averaged 84.3%. The AD and FTD specific patterns of brain atrophy can be detected with high accuracy using high-dimensional pattern classification of MRI scans obtained in a typical clinical setting [44].

A Stefan Koppel et al study in 2008 presents a direct comparison between radiologists and a computerized method for the diagnosis of dementia. This study has a binary diagnostic classification was made by six radiologists with different levels of experience in the same scans and information that had been analyzed with SVM. SVM techniques correctly classified 95% of sporadic AD and controls into their respective groups. Radiologists correctly classified 65-95% of scans. SVMs were better at separating patients with sporadic AD from those with Frontotemporal Dementia (FTD) with 89%. These results showed that well-trained Neuroradiologist classifies typical Alzheimer’s disease-associated scans comparable to SVMs. These results are encouraging and indicate a role for computerized diagnostic methods in clinical practice [45].

DeCarli C et al (1995) presents a multivariate discriminant analysis of brain volumes obtained from semi automated magnetic resonance image quantification was used in an attempt to identify demented patients very early in the course of the disease. Quantitative MRI and multivariate discriminant analysis showed promise in distinguishing the dementing process from healthy aging in a group but the sensitivity of any single measure was limited to 87% with a specificity of 83%. Initial multivariate discriminate analysis revealed significant gender differences among the healthy subjects, but not the AD patients [46].

2.2.1 Voxel Based Morphometry studies in AD

Voxel based morphometric technique allows the evaluation of gray matter volumes in subjects with AD or classification of AD related conditions compared with healthy elderly controls in an automated fashion, across the whole brain. In previous MRI studies using VBM findings include gray matter deficits in medial temporal structures and corresponding volume change assessed using
different manual region of interest measurements [47]. In this study, here conducted original MR images from the SCTIMST memory clinic to test the discrimination of MCI from NCI and AD from NCI and also predict the conversion from MCI to AD based on the gray matter structural changes assessing using VBM with statistical parametric map and ROI based volumetry. This is the first cohort study in southern Indian population for the longitudinal prediction of MCI to AD conversion.

The two approaches most widely employed to perform such quantitative measurements and between group comparisons are volume change assessed using atlas based automated ROI based approaches and voxel-by-voxel analysis methods. In literature Several VBM studies have assessed differences in regional gray matter volumes in AD subjects compared with healthy elderly controls. This is very time consuming. In morphometric MRI studies of AD, the manual ROI based approaches have been employed to provide volumetric changes most often in the hippocampus and related medial temporal lobe structures. This is very labor intensive, time consuming and subject to observer bias. Recently, automated methods have been developed for measuring hippocampus and related structures, volume in a faster way, including the determination of shape models and morphometric measurements [48] [49]. The application of the voxel-based approach for comparisons of regional gray matter volumes between controls and patient group studied with MRI is referred to as voxel-based morphometry [50]. The voxel-based approach presents advantages in comparison to ROI methods as it is fully automated rater independent and capable of investigating the presence of AD related morphometric gray matter abnormalities across the whole brain. In AD, the most consistent findings across all studies is the medial temporal lobe structures, including hippocampus, amygdala, entorhinal cortex and parahippocampal gyrus are the atrophy presented at the early stages of the disease [52]. In literature, a number of VBM studies have confirmed MCI related regional gray matter abnormalities similar to those seen in AD patients relative to healthy controls [53]. In VBM analysis, different category of AD patients is associated with gray matter reductions affecting mainly medial temporal lobe structures [54]. Over the disease course, and at the progression from MCI to clinical AD, such atrophic changes may spread to other brain regions, preferentially to the frontal and temporoparietal association cortices, cingulate gyrus, insular and precuneus, as well as to the thalamus and basal ganglia [55].
2.2.2 Literature survey on classification Algorithms

The computer-based high dimensional pattern classification of MRI detects patterns of brain structure characterizing MCI, often a prodromal phase of AD. Detecting complex patterns of brain abnormality in very early stages of cognitive impairment has pivotal importance for the detection and management of AD.

Yehu Shen (2014) studied K-means algorithm and image post processing techniques are applied to the hair segmentation and automatic facial caricature synthesis. The initial hair region so that the final hair region can be segmented precisely in this algorithm. Experimental results show that the average processing time for each image is about 280ms and the average hair region detection accuracy is above 90% [56].

Anuradha et al (2013) presents an automatic supervised classification of MR images for the diagnosis of oral cancer. This method includes four stages: preprocessing, segmentation, feature extraction and classification. The extraction of texture features in the detected tumor has been achieved by using Gray Level Co-occurrence Matrix (GLCM). In the extracted features are fed as input to SVM classifier. It classifies the images between normal and abnormal depending upon features[57].

Fouad Khan (2012) et al proposed an initial seed selection algorithm for K-means clustering of georeferenced data to improve reliability of cluster assignments for mapping application. This improves the reliability of cluster assignments by as much as 100% over K-means and K-means++, virtually reducing the variance over different runs to zero, without introducing any additional parameters to the clustering process [58]. LIU Yingqiu et al (2007) investigated K-means clustering techniques can obtain up to 80% overall accuracy, and, after a log transformation, the accuracy is improved to 90% or more [59].

Nivedita Chaudhary et al (2013) used back propagation artificial neural network model has been designed to classify neurodegenerative disorders according to their symptoms. This ANN network was based on the C++ programming language on a computer. The proposed ANN model has to be classified the different types of neurodegenerative disease with an overall performance of 96.42% [60]

Shih-Ting Yang et al (2013) proposed SOM, the combination of Particle Swarm Optimization (PSO) and SVM classifier for the discrimination between AD
and MCI. Combining PSO-SVM with statistical analysis and PCA algorithm classification result was improved up to 94.12% and 88.89% in patients with AD and MCI [16].

R. Sheela Kumari et al (2013) identified Genetic Algorithm (GA) tuned ANN to measure the structural changes of brain in dementia patients, specifically FTD patients using MR images. The features are extracted using gray level co-occurrences matrix and segmentation based on GA-ANN. The performance of this computerized scheme is evaluated and compared with the ground truth information, achieved an average classification accuracy of 95.5%, 96.5% and 98% of GM, WM and CSF respectively [61].

Varghese, T et al (2012) study proposed a longitudinal study is to identify the structural characteristic of Gray Matter, White Matter and Cerebrospinal fluid at baseline and structural changes after one year that could serve as accurate predictors of future development of MCI in the normal aging controls and AD in the MCI patients. This study explored the efficacy of different approaches such as K-means, FCM and VBM for the segmentation and the comparative analysis of longitudinal MR images of AD patients and controls [62].

Javier Escudero (2011) proposes the creation of the bioprofile of AD using K-means clustering to date features taken from the ADNI database. This study the subjects are divided into pathologic and non-pathologic groups in five clinical scenarios. The bioprofile could help in the early detection of AD at the MCI stage since it divided the MCI subjects into groups with different rates of conversion to AD [63].

Ali Farzan et al (2011) presents the potential of K-mean and fuzzy clustering method (FCM) in diagnosing Alzheimer’s disease based on the longitudinal whole brain atrophy percentage with MRI technique. The discriminating power of this measure is statistically analyzed and it is used as a feature in classifying subject using K-mean and FCM. Both classifiers have the same specificity, but FCM (86.67%) shows higher sensitivity and hence higher accuracy besides K-mean (83.3%) [64].

María Quintana et al (2011) investigate a Linear Discriminant Analysis (LDA) and ANN to differentiate NCI, MCI and AD, and to study the relevant variables in MCI and AD diagnosis. The ANNs with 12 input neurons selected based on the neuropsychological parameters, age and education and 4 hidden neurons, and
output neuron were used to classify the patients. The ANNs were superior (98.33%-100%) to LDA (80%-96.4%) in its ability to classify correctly patients and showed better predictive performance [65].

Alexandre Savio et al (2009) proposed a study for the detection of Alzheimer's disease on brain magnetic resonance imaging used four different models of ANN. The Back propagation (BP), Radial Basis Networks (RBF), Learning Vector Quantization Networks (LVQ) and Probabilistic Neural Networks (PNN) to perform classification of patients of mild Alzheimer's disease vs. control subjects. Features are extracted from the brain volume data using VBM detection clusters. This study has evaluated feature vectors computed from the GM segmentation volumes using the VBM clusters as voxel selection masks. The study has been performed on MR images from the Open Access Series of Imaging Studies (OASIS) database [66].

Y. Zhang and L. Wu (2008) studies found that improved Bacterial Chemotaxis Optimization (BCO) approach as a possible alternative to the problematic BP algorithm, along with improving the efficiency of the traditional BCO. In the comparison of classical XOR problem and ‘sinc’ function, the convergence rate and precision rate is superior with other training algorithms. It also has some possible solution to the hard optimization problems [67].

Enzo Grossi et al (2007) study discovered the hidden and non-linear associations among AD pathognomonic brain lesions and the clinical diagnosis of AD in participants in the nun study through ANN analysis. The Neuropathological findings processed by artificial neural networks can perfectly distinguish Alzheimer's patients from controls in the nun study. By taking the four neuropathological features, the overall predictive capability of ANNs in sorting out AD cases from normal controls reached 100%. The corresponding accuracy obtained by linear discriminant analysis was 92.30% [68].

Christian Habeck et al (2007) have proposed neural network approaches and their reproducibility in the study of verbal working memory and Alzheimer’s disease. But this study not reported the correct classification accuracy on patients and controls [69].

Ng, H.P. et al (2006) proposed a methodology that incorporates K-means and improved watershed segmentation algorithm for medical image segmentation. The K-means clustering is an unsupervised learning algorithm, while the improved
watershed segmentation algorithm makes use of automated thresholding on the gradient magnitude map and post-segmentation merging on the initial partitions to reduce the number of false edges and over-segmentation. The proposed methodology produced segmentation maps which have 92% fewer partitions than the segmentation maps produced by the conventional watershed algorithm [70].

Reeti Tandon et al (2004) study proposed a new type of neural network called the Mixed Effects Neural Network (MENN) model for the longitudinal progression of AD. A back-propagation algorithm modified for longitudinal data is used to obtain the weight parameters of the MENN. This study is comparing the performance of the MENN with linear mixed effects models and standard neural networks. MENN show better as compared to standard NN and linear mixed effects models [71].

Santa Di Cataldo proposed a fully-automated method based on unsupervised clustering that performs pathological tissue segmentations highly comparable with those provided by a skilled operator, achieving an average an accuracy of 90% [72]. Anil K. Jain in 2009 presented a review paper on 50 years beyond K-means clustering were proposed over 50 years ago and thousands of clustering algorithms have been published since then, K-means is still widely used [73].

Kyle et al study compared and analyzed three different methods including K Nearest- Neighbors (k-NN), naïve Bayes, SVM for the classification of dementia from brain MRI. Data were obtained from the Oasis Brain Dataset and custom extraction algorithms for feature extraction purposes. The KNN method accuracy up to 91.70% compared from naïve bayes (80.60%) and SVM (83.80%)[74]

J. Shane Kippenhan (1994) et al investigates neural network classification of normal and Alzheimer's disease subjects using high-resolution and low resolution PET Cameras. Neural networks were trained to distinguish between normal and abnormal subjects from the database on the basis of regional metabolic pattern. The optimal classification accuracy up to 87% to 95% [75].

Hamilton, D (1997) presents an evaluation of the performance of artificial neural networks for the classification of probable Alzheimer's disease patients was undertaken using data extracted from four regions of interest constructed on single photon emission tomographic cerebral perfusion images. Two
studies using feed-forward neural networks were undertaken. The FFNN successfully classified all datasets in the first study, achieving an area under the ROC curve of 1.00, whereas discriminant analysis achieved 0.94. When tested on data from the second group, the areas under the ROC curves varied between 0.86 and 1.00 for the FFNN, whereas that for discriminant analysis was 0.99 [76].

2.3 IMPROVING COMPUTER AIDED DIAGNOSIS OF ALZHEIMER’S DISEASE WITH PROPOSED CLASSIFICATION ALGORITHMS

Structural brain imaging is playing a vital role in identification of changes that occur in the brain associated with Alzheimer’s disease. There is an active research going on to delay the onset or slow down the progression of AD. Early diagnosis of AD helps both the patients and their caregivers to improve the quality of their lives. There are treatments that slow down the disease progression and help in prevention. However, this is only possible if the AD is diagnosed with high accuracy in its early symptomatic stage. Many scientists believe that there is a transitional stage between normal aging and AD termed as mild cognitive impairment. During this stage a person experiences more memory loss that cannot be linked to aging problems, but also not severe enough to point to probable AD. MCI has higher chance to turn to AD. This thesis proposes an automated image processing based approach for the early identification of AD and to predict the possible conversion from MCI to AD from MRI of the brain. This study conducted many experiments with various CAD techniques and achieved performance levels comparable to the existing approaches in this domain. The results are very promising and demonstrate the utility of CAD methods in this domain. In this study earlier diagnosis in not only challenging, but also crucial for progression of conversion from MCI to AD.

The proposed framework makes use of image processing and pattern recognition techniques to help practitioners identify the disease from neuroimages at an earlier stage before irreversible loss of brain has occurred. The diagnosis process is strengthened by incorporating clinical and neuropsychological data that lead to improvement in the prediction accuracy. Owning to its clinical convenience, T1-weighted MRI has been extensively studied in the past decades for prediction of AD and MCI. The volumetric assessment of gray matter, white matter and Cerebro-spinal fluid are the most commonly used measurements, resulting in many successful
applications of early diagnosis and tracking the progression of AD. Structural MR imaging investigations commonly apply a segmentation step followed by the extraction of feature data that can be used to compare or discriminate groups.

The proposed system presents a framework for such a study based on automated CAD system for segmentation using the extracted features for the discrimination of AD patients with MCI and NCI also tracking the progression of MCI to AD. In particular, this study describes a texture features are extracted using 2D Gabor filters and it is used for and cross sectional and longitudinal analysis of AD patients and controls using unsupervised classifiers like K-Means clustering and supervised classifiers like RBFNN, GRNN, PNN, BPNN, MSVM and BFOANN. Learning in the supervised classifiers is done using back propagation (BP) learning algorithm. The BP algorithm completely depends on the initial settings. In order to improve the training process and accuracy, this research work investigates novel intelligent classifiers that use texture information based on the 2D Gabor filter as input to classify the AD patients from MCI and MCI patients from NCI. So optimization techniques applied in the BP learning to optimize the hidden layer neurons (Nh), learning rate (Lr) and Momentum constant (Mc) initial parameters. The optimization algorithms increase the classification performance of ANN. Therefore the FFNN trained by the BP system chosen the optimal network parameters of Bacterial Foraging Optimization algorithm.

Before introducing our proposed approach, it is worth highlighting the advantages of the volumetric assessment of GM, WM and CSF based approach over the conventional performance measurement approaches. Since volumetric MRI can detect changes in the size of brain regions, measuring those regions that atrophy during the progress of Alzheimer's disease can help the neurologist in his diagnosis. The cohort study subjects used in the preparation of this thesis were obtained from the original MR images from the SCTIMST memory clinic.

### 2.4 SUMMARY

In summary, in this chapter presents a review of the clinical diagnosis of dementia, AD and the concept of MCI. This chapter also discusses the recent progress in selected biomarkers for early diagnosis, classification, and progression, of AD and the different segmentation techniques as applied to brain MRI over the past decades is revisited in this chapter. Survey on the CAD system in the diagnosis
is given in the second section. This section reviews about different CAD system for early AD and tracking progression of AD and also survey on optimization approaches for clustering and classification were done.

Based on the above survey, the proposed system presents automatic CAD techniques for the volumetric segmentation methods in order to segment gray matter, white matter and Cerebro-spinal fluid for the analysis of AD diagnosis at an early stage. This study used the real MRI dataset from the cohort study of SCTIMST. The strength of the present study is the first in analyzing original MR images of AD, MCI and NCI sample derived from population-based cohorts in a southern Indian province, Kerala for early AD diagnosis and tracking the progression of MCI to AD using various CAD based volumetric techniques. The main contributions of the thesis are in the methodology of the Bacterial Foraging Algorithm (BFA) to optimize ANN parameters to improve the classification accuracy in early AD detection thereby reducing the misclassification rate. This proposed system also maps the progression of GM loss in MCI patients over time and to help detect brain changes between MCI patients who may convert and may not convert to AD.