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Classification of Alzheimer's disease based on RBF-SVM classifier with multimodality methods

Graduate School of Chosun University

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멀티모달리티 방법으로 RBF-SVM 분류기 기반으로 한 알츠하이머 병 분류

Advisor: Prof. Goo-Rak Kwon

This thesis work submitted in partial contentment of the necessities for a master's degree in Chosun University

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This is to certify that the master's thesis of

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has been approved by examining committee for the thesis requirement for the master's degree in Engineering.

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요약

멀티모달리티 방법으로 RBF-SVM 분류기 기반으로 한 알츠하이머 병 분류

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최근 수십년 동안 매년 알츠하이머 병 (AD)은 전세계의 노인들에게 퍼지고 있다. 20 년 이내에 두 배 이상 증가할 것으로 예상된다. 이 질환은 뇌의 신경 퇴행성 이상으로서 적절한 언어 능력의 상실, 기억력 문제 및 환자 행동의 변화가 있는 약간의 인지 장애 (MCI)의 증상이 있는 단계로 인식된다. 이 질병에 대한 명확한 치료 방법은 없으며, 자가돌봄에 있어서 많은 돈을 요구한다. 따라서 이 질병은 조기 진단이 필요하다.

본 논문에서는 혈액의 단백질 (SerumAab), 5 가지 유형의 인지 점수, 구조적 자기 공명 이미지(sMRI)의 3 가지 바이오 마커를 이용하여 각각의 분류 그룹과 AD 를 구별 할 수 있는 멀티 모달 방법을 만들었다. SerumAab 의 값은 GenePix 스캐너를 통해 얻을 수 있으며, 인지 점수는 전문가에 의해 제공받고, sMRI 에서 외피질 및 내피질의 특징은 MALPEM (Multi-Atlas Label Propagation with Expectation-Maximization) 의 ToolBox 를 사용하여 추출한다. 그런 다음에, AD 분류를 위해 기계 학습 기술을 사용하여 구현한다. 또한, 이 기계 학습 기술은 AD 에 대해 다른 분류 그룹과 자동으로 AD 를 분류하고 멀티 모달리티 접근 방식을

사용하여 AD 의 조기 진단 및 MCI 에 대해 임상적 변화를 예측할 수 있다. 분류 부분에서는 RBF-SVM (Radial Basis Function-Support Vector Machine) 을 이용한 기계 학습 알고리즘을 구축하여 검증한다. 이 작업을 위한 학습 데이터로는 ADNI 데이터 세트를 사용한다.

마지막으로, 대부분의 AD 의 조기 예측을 위한 연구 방법들은 특별한 형식의 바이오 마커를 사용한다. 단일 형식의 바이오 마커를 사용하면 정보가 불충분하기 때문에 AD 또는 MCI 의 그룹에 대한 구별을 하는데 부정확하게 검증된다. 따라서, 본 논문에서는 3 가지 종류의 바이오 마커를 하나의 형태로 융합하여 복합체 분류군의 분류를 지원하는 멀티 모달 기법의 구현을 제안한다. 제안된 머신러닝 방법에 따라서, 이 접근법은 MCI vs CN 그룹에 대해 97.62%의 최대 정확도를 달성하였다. 그다음에, AD vs CN 은 91.43%, AD vs MCI 는 88.57%의 정확도를 보였으며, 같은 다른 그룹에 비교하여 우수한 정확도를 얻었다. 추가적으로 제안된 방법은 두 SVM 커널과 두종류의 기계 학습 분류 방법으로 구현하고 비교하였다.

핵심 문구: 알츠하이머 병, 멀티 모달 바이오마커, 기계 학습, RBF-SVM 분류기, 인지 점수, 혈청의 단백질, GenePix 스캐너, Polynomial-SVM, KNN, RF.

Abstract

Classification of Alzheimer's disease based on RBF-SVM classifier with multimodality methods

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Alzheimer's disease (AD) is spreading over the elderly people in the world year by year in recent decades. It is being expected to increase more than double rates in two decades. This disease is neurodegenerative abnormality of brain with often been recognized as prodromal mild cognitive impairment (MCI) phase, which are loss of proper language ability, memory problem and the change of patient behavior. However, it is not clarified treatment or cure for this disease and self-caring requests much money. Therefore, early diagnosis of this disease is needed.

In this thesis, multimodality method was created, which could differentiate AD with other classification groups by utilizing three kinds of biomarkers which are (Blood protein (SerumAab), five types of cognitive scores, structural magnetic resonance image (sMRI)). The SerumAab volumes are achieved from GenePix scanner, Cognitive scores are given by specialist and subcortical and cortical features of sMRI have been extracted by using Multi-Atlas Label Propagation with Expectation-Maximization (MALPEM) toolbox. Then, machine learning technique was implemented for classification of AD. Furthermore, this machine learning technique can classify automatically for AD with other groups and predict early diagnosis of AD and

prognosis clinical changes of MCI subjects by employing multimodality approach. In classification part, it has built and validated a machine learning algorithm by utilizing radial basis function kernel algorithm in support vector machine (RBF-SVM) classifier. Moreover, this work has done by using Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset.

In conclusion, most of research methods employed unique modality biomarkers for prediction on early classification of AD. It is not properly validated for distinguishing of AD or MCI groups because of insufficient information while using single modality biomarkers. Therefore, this work proposed using of multimodal technique, which are fused three different kinds of biomarkers into one form and to classify compound classification groups. According to proposed machine learning method, this approach has achieved the best accuracy of 97.62% for MCI vs CN group. Then, it has obtained good accuracy for other groups such as AD vs CN is 91.43%, AD vs MCI is 88.57% accuracy as well. Additionally, it is implemented and compared our proposed work with two kernels of SVM and two kinds of machine learning classification methods.

Key phrases: Alzheimer's disease, Multi-modal biomarkers, Machine Learning, RBF-SVM classifier, Cognitive score, SerumAab protein, GenePix scanner. Polynomial-SVM, KNN, RF

1. Introduction

Alzheimer's disease (AD), which is liberal, an irretrievable neurodegenerative syndrome of the dominant nervous structure and most common form of dementia categorized by rare gathering of amyloid plaques and neurofibrillary knots in the dominant nervous system, which no treatment or succeed to find treatment for this disease, the most serious and unusual neurodegenerative disease Alzheimer's (AD) is dramatically going up among elderly generation which is 24.3 million suffering among 60 to 84 ages [1]. The early diagnosis and prognosis of AD and the best projection of age-associated disease mains increasing list of possible biomarkers (from genetics, proteins, cognition, proteomics and neuroimaging) [2]. Alzheimer's disease the rate of morality is more and is increasing every year compare with other neurological disease. Nowadays, many works have been done to analysis neurological and biological biomarkers for prognosis of Alzheimer's disease in many methods, finding and doing this kind of works allow early prediction of disease might postpone or delay of AD, as well as mild cognitive [3].

Even though, biomarkers are used for the analyzing of Alzheimer's disease, on the other hand in imaging modality method or cognitive score, clinical reflection is utilized for diagnosis of AD as a traditionally way. Moreover, recent research shows fusion modality techniques (multimodality imaging and biomarkers) are demonstrated better performance compare to single image modality technique [4]. Nowadays, most of the researchers prefer to combine imaging modality with more than one biomarker and implementing by deep learning or machine learning method to show automatic prediction of Alzheimer's disease. Alzheimer's Disease Neuroimaging Initiative (ADNI) is one of the dominant research projects in the area of AD in the world, it has

subsidized expressively process on the area of AD. This dataset gives opportunity for researchers to do research clinical purposes which is consist on different kind of patients group from various of analytical groups includes in sMRI and fMRI, PET images modality. Furthermore, many researchers have achieved better results on different image modality while using imaging scanners from ADNI dataset by using machine learning and deep learning techniques [5-6].

Deep learning and Machine learning (ML) methods are implemented to preclinical and clinical analysis of patients as well as diagnosis support in the area of medical part and there are a lot of curiosity in ML technology for utilizing in many fields such as oncology, radiology and cardiology, etc. nowadays ML is known and effective method for predictions and distinguishing high-dimensional data which are from MRI or another image modality [7-8]. As it is known, nowadays most of the researcher pay attention more to deep learning (DL) algorithms and it is being gained better result compare to machine learning method in many AD and healthy control classifications [9].

Lately, image modality and neuroimaging investigation with the T1-weighted MRI features for brain disease mainly for AD vs MCI has been demonstrated preferable result especially it is given anatomical features such as (subcortical and cortical features, grey and white matter, CSF volumes) engendered from T1 MRI image modality could be utilized to compute the brain dementia part and it will be support to predict early prognosis of MCI/AD [10-11]. Precise predict of Alzheimer's disease has been confirmed to be problematic to accomplish. Nowadays, diagnostic observes consists on neuropsychiatric tests, neuroimaging methods and behavioral history

assessments [12]. Any of these techniques by alone or in fusion methods of them do not provide for early predict or yield better accuracy or result. Newly, more researchers greatly deal with emphasis on the prognosis for blood-borne and protein biomarkers indicative of AD dementia, however most challenges have detected just incomplete accomplishment [12]. The Alzheimer's municipal is continuously in dreadful necessary of a prognosis technique which is inexpensive, relatively non-invasive and proper accurate [13].

1.1 Overview and Motivation

Currently analytic imaging, structural Magnetic Resonance Imaging (MRI) is studied as the most prevailing imaging modalities for evaluating neural disease. Likewise, genetic factors (APoE4), blood protein, cognitive score and genes are others key biomarkers of non-imaging. In Alzheimer's disease (AD), analyzing dementia structural MRI is widely and properly utilized with high quality range. Prognosis and prediction of early AD gives patients with accessible therapies which are effective in the early level of brain discord. Differentiation patient among level of cognitive impairment belongs to patient's biological, molecular genetic analysis, clinical and neuropsychological checking. Structural MRI supports also to distinguish pattern of atrophy based on diagnosis. Moreover, a variety of imaging modality such as fMRI, PET and CT demonstrate a plenty of anatomical information. Furthermore, sMRI image validates the process of brain disease for AD case and contains on exact part of brain imaging measurements for disease procedure (such as hippocampal volume of MRI measurements) [14]. Thus, fusion of sMRI with another non-imaging modalities such as cognitive score and gene, proteins offers improved accuracy and result than only magnetic resonance imaging modality [15-16]. In previous research works

variety anatomical regions of brain has shown nice accuracy but certain of ROI combination is not tested properly and more in literately. This work focuses on prognosis and diagnosis based on volume of multimodal biomarkers and sMRI imaging modality technique which is being studied in the last two decades. sMRI includes in sharp contrast in its atrophy pattern for recognizing AD to determine with applications. Thus, to modify the progress of AD and estimate the efficacy supplement for this disease, sMRI is treasured method. Moreover, to investigate the going down volume of thickness and the area of neuronal injure, metabolic deficit is examined by structural magnetic resonance imaging technique [17]. Above all work it is cleared if there are more information of atrophy pattern from sMRI image, it could be distinguished between AD versus NC and different level of MCI. While fuse of different modalities such as blood proteins and cognitive score with sMRI might increase the accuracy of performance compare to investigate with only sMRI. Therefore, this thesis work intents to assess imaging and non-imaging biomarkers modalities which is mentioned above sentence and understand to show better diagnostic accuracy by combination of multi-modality methods in AD, vulnerably it shows better factors compare to another biomarker's modality. In future we will extend and add more available biomarkers and modalities.

1.2 Methodology

This proposed research demonstrated a pipeline utilizing the obtainable neuroimaging tools for every process (skull-removing and image segmentation by MALPEM) to categorize specific subjects into three different groups (AD, MCI, and HC). The focal biomarkers to distinguish subjects in health and

abnormal are brain sMRI, and another non- imaging biomarkers (blood protein serum and Cognitive Score). Thesis objectives are the subsequent:

- ✧ To accumulate and investigate distinct cohort data are downloaded from a pre-processed Alzheimer's disease Neuroimaging Initiative (ADNI) database, which involves patients with Cognitive score, blood proteins and structural MRI.
- ✧ To categorize specific subjects into three classes utilizing diverse classifiers, features selection techniques; atrophy pattern analysis on sMRI and to obtain serum data from microarray scanners
- ✧ To estimate the outcomes of classifiers and to compare the consequences of the multimodal methods.

1.3 Contributions

The contribution of this work is in atrophy pattern investigation of structural MRI and trying to do fusion of sMRI effective with other non- imaging biomarkers such as blood protein serum and Cognitive Score to discriminate between three classes (AD, MCI, HC) which are not utilized as a statistical volume in the works: [18-20]. First of all, in this proposed work, it is segmented the anatomical statistical volume of the structural MRI brain images by utilizing Multi-Atlas Label Propagation with EM (MALPEM) This segmentation is based on a strong process approach (MAPER) extremely performant label combination (combined label fusion) and intensity-based symbol refinement using EM. This outline is modified to be useful for the brain image segmentation with gross changes in anatomy [21]. We achieved cognitive scores from ADNI dataset and blood serum autoantibodies are gathered from Nagele Lab which is uploaded in ADNI dataset [22].

The attained result is sympathetic and consistent to practice of machine learning technique and can be proposed to medical analysis and treatment system development.

1.4 Thesis Outline

This thesis work is contained within six following sections. The Section 1 is the introduction, the Section 2 is mentioned theory and background material and be explained about features which we used later in segmentation and classification for this thesis work. The Section 3 presents about reviews of related work, which single sMRI modality and multimodality evaluation method. Moreover, it shows a critical tasks valuation of this work with systems, which are linked or connected to the present work. The elaborated methods and their consequences of classification accuracy are in-state-of-the-art and about multimodal method. The Section 4 demonstrates materials and proposed method, principally it includes information about dataset, how to select features and combination process and preprocessing features for classification, feature selection, dimensional reduction and Principal Component Analysis. The Section 5 discussed about machine learning classification result and comparison with other machine learning algorithms, the kernels of SVM and discussion. The Section 6 consists of conclusion and future works.

2. Theory and Background

2.1 Brain MRI and Alzheimer's disease

Alzheimer's disease (AD) is pathophysiological heterogeneous neurodegenerative brain disease (NBD) and this disease commonly effects to aged people, who are impacted one out of nine 65 years over age millions of individuals all around world and it is expected to increase dramatically over the next decade [23]. AD shows social difficulties, memory deterioration, aphasia and other serious symptoms [24]. The understanding of properly this disease pathogenesis and the impact factors and/or situation that is important and controversial. It is known available treatment could temporarily postpone some symptoms of disease but cannot cure completely pathological progression [25]. Nowadays, it is clearly confirmed that AD disease in brain neuropathological changes could be start 20 years early symptoms evaluated for potential treatment and diagnosis [26].The postpone in symptoms emergence after the onset of pathology makes it difficult to analysis AD patients at earlier, preclinical (or pre-symptomatic) and prodromal (mild cognitive impairment MCI) disease stages. In 2010 The World Alzheimer Report announced that there would be 65.7 million patients suffering with dementia by 2030, and this rate will go up to 115.4 million by 2050. The similar research also assigned out that nearly two thirds of individual infected by dementia surviving in financially middle- and low- income countries, which are predictable to major growth in amount of exaggerated people in upcoming years as the sections are evolving speedily [27]. Alzheimer disease is becoming to be inspiring for a lot of reasons, the first reason is the dementia patients seriously count on casual attention in these countries , and it would be extremely hard work to suggest the right cure method and maintenance for

extreme large aged people of these nations and disease frequency scrambles [28]. Dementia shows a massive common price at nowadays, and is used 1.01% of the whole cost of global Gross Products of Nation [28]. It is assumed that this consuming price will get worse and worse by passing years, according to statistics it is predicted 85% worldwide general fee growth by 2030 [28], arrogating that with impossible circumstantial aspects (e.g. dementia occurrence, macroeconomic issues incidence of dementia and accessibility and effectivity of cure) revolution. Whereas roughly of its symbol could likewise demonstrate somewhat parallel to normal symbols of progressive aging, it is dynamic to message that Alzheimer's (and dementia in universal) is no extensive a normal period of aged. By passing of time, process of disease alike symptoms of disease slowly become worse. Nowadays, it is not found proper cure for Alzheimer's disease; the purpose is somewhat to go-slow the evolution of the illness, report behavioral difficulties, progress indications and expand life superiority of people. Nevertheless, existing medicine is not able to provisionally get slow the expansion of illness indicators if the sickness is perceived an earlier stage. Although these is supplementary consistent and operative dealings with eventually disease stoppage or smooth an appropriate suppository is a very vital (time consuming) purpose, even initial analysis could be relatively better cure for diseased person. It is motionless mystery about the appropriate source for Alzheimer's disease, excluding some the limited cases of measurable genetic indiscretion. Contemporary researcher says, however, AD is powerfully linked with neurofibrillary tangles and neurotic plaques in the brain [29]. The Amyloid beta protein which is constructed the neurotic plaques in the brain, is identified to become muscularly relate to the expansion of the Alzheimer's, there is still deficiency of suitable consideration whether or not it is a main aspect, as numerous

scientists accept as true it to become. This is, though, mostly the material is an indicator of the sickness. In the contemporary the tendency is eternally growing towards the correct judgement of disease and road the development former before symptom arises. Previous years' improvement in study is growth, furthermost outstandingly correct analysis of biomarkers (expressively in brain imaging modality methods) which permit sympathetic understand and analysis of AD-related fluctuation every month, years and occasionally even periods before presence of medical symptoms. The biomarkers for Alzheimer's could be characterized into primary biomarkers, which regularly calculate the quantity of amyloid statement in the brain cell (e.g. PET imaging, CSF amyloid), and far ahead biomarkers, which normally quantitated neuron deterioration (e.g. CSF tau, FDG PET, sMRI). Brain scans are commonly disregarding further reasons for disease signs, but it could be a significant symptom of whether Alzheimer's is existing [30]. In 1996 article [31] situations that "In medical training, the analysis of Alzheimer's disease is grounded on distinctive structures of the disease and elimination of other circumstances initiating dementia". The focal method to acknowledged whether person was exaggerated by the disease is medical examination the investigation of brain tissue. Nevertheless, mutually neurotic plaques and neurofibrillary tangles appears to performance a core part in the evolution of Alzheimer's disease. Though a great amount of investigations has been accomplished on Alzheimer's disease, there is still a perseverance for a former analytical scheme for the Alzheimer's disease.

2.1.1 Mild Cognitive Impairment

MCI is assumed as the initial stage of Alzheimer's disease, people who have mild symptom and still expressions ordinary behavior to the normal life

nonetheless the brain morphology jump to transformation. It illustrates a dissimilar diagnostic stage or a prodromal phase of AD. The debates are still misperception about MCI whether it is resembling to unlike analytic point or to a prodromal step of Alzheimer's disease. The people brain morphology starts to transformation in MCI-patients, brain form and shape have already been working on for fairly in some case sometimes, and syndromes are just started to seem. There is not importance in difficulty that are plain enough to inhibit distinct day to day duty, which might be recognize disease.

2.1.2 Risk Factors

Even though there are nonexistence of exact reason for dementia nevertheless convinced features are powerfully linked to the progression of Alzheimer's disease. They are clearly debated below.

2.1.2.1 Family background

Family past information and background are also related with Alzheimer's disease the people who are supplementary to progress AD whose local family participant have Alzheimer's disease. The risk aspect will rise with the quantity of patients in the people family. Whichever inherited or ecological or both reasons might have a character to diseases growth and development in families [32].

2.1.2.2 Genetic

Genetics aspects are seeing additional significant source for the progression of AD. Commonly, two type of genes are accountable for the disease growth and expansion in Alzheimer's:

- ✧ Risk genes (in control to rise likelihood)

✧ Deterministic genes (trust to become straight reason of disease)

If the marital AD demonstrates (i.e. main autosomal procedure of AD), growth of primary symptom of Alzheimer's (i.e. MCI) designate the launch of dementia. An enormous number of persons are exaggerated by early stage progression of Alzheimer's Dementia. Growth and evolution of MCI to Alzheimer's dementia in people are adjustable. Nevertheless, the research expressions that the people who have with one or two ε4 alleles in persons' apolipoprotein E (APOE) gene is powerfully connected to the growing risk influence for late-onset Alzheimer's dementia. But then again in conflicting, occurrence of ε2 allele, reduce the risk aspect in that people.

2.1.2.3 Age

Age is unique of the powerfully and obviously connected with Alzheimer's disease. People who are above age of 65 year old, have higher the risk of disease expansion compare than below that age within the five years period and correspondingly the people who are above the age 85 year old, have nearly one by two of disease growth [32].

2.1.3 Pathophysiology

The appropriate and specific reason of Alzheimer's is not identified properly because of its compound factors and pathogenesis.

2.1.3.1 Biochemistry

Alzheimer's disease (AD) is occur largely owing to the protein misfolding on brain cell by extremely gathering of amyloid beta (β-amyloid) protein. [1], [33]. The Amyloid beta which is petite peptide and produce as an irregular consequence of protein amyloid predecessor protein (APP) in brain cell whose

precise purpose is still unidentified, that is supposed to be contain in neuron progression. This kind of gluey amyloid remains completed bunch composed and produce plaques (recognized as neurotic plaques). Above plaques delay the message (i.e. signing) among brain cells, which leads to eventually basis the demise of the neurons.

Amyloid plaques are "a characteristic aspect of a uncontrolled judgement of Alzheimer's disease" [34], also which is the individual biomarker in Alzheimer's disease assistance to appropriate recognition and qualification of the gathering of amyloid protein in brain cell. The pleased of protein equal could be quantified straight over distinct plasma and cerebrospinal fluid (CSF). We might likewise utilize positron emission tomography (PET) to degree the protein. The medical standard for mild cognitive impairment because of Alzheimer's disease conditions association with the amyloid: "Contemporary mark advocates that indicators of amyloid pathology (i.e., PET and CSF) lead proposition of neuronal damage. This does not prove that Aβ is the initiating factor for the disease. Nevertheless, this is not suggested that this kind of dissimilar classes of biomarkers look like to offer diverse types of material about the development of illness inside the brain" [34]. This is recommended that irregular development of tau protein, deliberate as tauopathy, a microtubules-correlated protein shows in neurons which essentially support to steady microtubules in the cell are likewise contemplated as source of sickness. The tau protein function in the brain is to preserve microtubule conventional which assistance molecules permit go easily through it. Though, in Alzheimer's protein transformation into perverse components (i.e. ruins in tangles) which reason to impediment on transference of nourishment on brain cell and finally principal to the cell demise. The modification in

phosphorylated-tau and tau may associate with the starting of the Alzheimer's with overall impairment in synapses and neurons. The accretion of neurofibrillary tangles and β-amyloid plaques inside brain cell finally result to harm of synapses and neurons (morphological deviations of the brain's erection), which prime to the "remembrance damage and other mental difficulties" [35].

2.1.3.2 Neuropathology

The most important indicator throughout the Alzheimer's disease are occur cause of the physical and morphological deviations inside the brain (i.e. brain aberration), which is contemplate as the delicate topographies for the Alzheimer's. The symptoms habitually might be found in the hippocampus part of brain primarily in the people exaggerated by disease, the process could be announced obviously through volumetric investigation of structural MRI for Alzheimer's analysis [36]. The forfeiture of synapse and neuron in individual's brain is visibly perceptible alteration, which may be appeared through Figures. Alzheimer's disease is mostly characterized by degradation of hippocampus and cerebral cortex, which lead to cortical atrophy in parietal, frontal and temporal areas [37]. Equated with healthy control generally ventricles are enflamed in Alzheimer's disease individual, it is evidently visible in Figure 2-1. At the starting of the illness microscopic modification is occur inside the brain formerly the first indication of memory loss, one feel aggrieved study demonstrations that the media temporal lesion are existing to 5 or 6 years earlier the medical analysis of disease [38]. The similar research illustrates that there was not atrophy form detected in the frontal lobes, this specify that at the initial level of the disease it was not pure sign of atrophy but with the rounds of period at which analysis was completed its previously

exaggerated harshly. While doing the observation, authors detected the atrophy of frontal lobes only at the period nearby to finding of disease. The observation of detections likewise helps that decrease in dimensions of the posterior cingulate cortex might central to the advanced development of the disease.

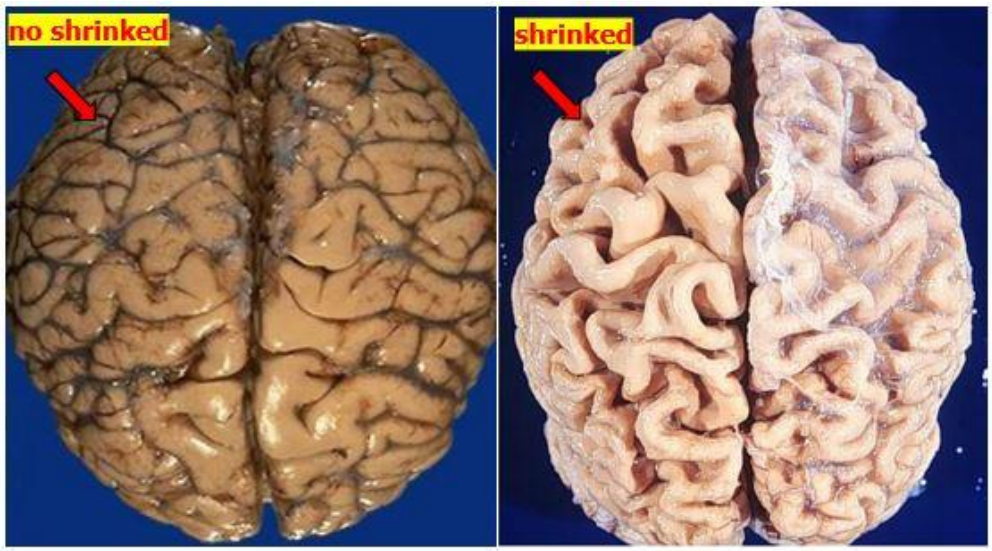

Figure 2.1. Diagram of a normal and Alzheimer's disease brain.[13]

MRI brain images simplify scientists and researchers to characterize the structural impairment in brain associated with Alzheimer's disease. Another kind of imaging modality like Pittsburgh complex B PET (PiB PET) obviously demonstrate the forms and position of beta amyloid gathering in the brain. Although the performance is extra aggressive, it requests a difference agent — likewise radioactive sugar — which is absorbable in the affected brain. Ultimately, this procedure is lately advanced and not as accessible effortlessly as similar MRI. The research in 1995 [39] was detected the component of hippocampus volume between 59 patients counting mild to moderate Alzheimer's Disease, 9 individuals with vascular dementia, 12 individuals

with idiopathic Parkinson's disease lacking dementia, 8 people with Parkinson's and dementia, 34 elderly control persons utilizing a 1.5-T magnetic resonance (MR) scanner. According to researchers, they argued the momentous reduction of hippocampal volumes (both side hemisphere) in whole individual groups as associate to control cluster and they also figure out complete volumes were unfluctuating minor in the collection of focuses with Parkinson's and dementia as relate to Alzheimer's set. It is assumed that "hippocampal atrophy does not appear to become a precise spectacle of dementia in AD nonetheless likewise happens in vascular dementia and Parkinson's unfluctuating when none dementia is present" [39]. The overall research, nevertheless, essentially mentioned the again happen of Alzheimer's disease pathology in vascular dementia and Parkinson's individuals. The base on scientist's conclusion that unique of the complex indicators in Alzheimer's disease is hippocampal atrophy, but then the specification of hippocampal atrophy looks to limit its usage in medical preparation.

2.1.3.3 Biomarkers

Alzheimer's disease (AD) gets progressive by-passing time and age, therefore the biomarkers scale gains the unusual stage order (shown in Figure 2-2). In Figure 2-2, which shows the Alzheimer's biomarkers, the bows demonstrate difference caused by ten biomarkers studied [40] (in progressive form):

- ✧ Astrocyte dysfunction are glial cells which are circulated all over the central nervous system in a preparation optimum for biological and bodily collaboration [40].
- ✧ CSF includes in three main biomarkers which are total tau(T-tau), phospho-tau (P-tau) and B-amyloid (AB42) 42 amino acid

- ✧ PET uses radioactively labelled amyloid B (AB) tracers, or the more recently investigated tau-tracers, which bind to fibrillary forms of AB and tau in the brain
- ✧ Microglia activation in the brain, concentrated around amyloid plaques, is a prominent feature Alzheimer's disease (AD). Human genetics data point to key role for microglia in the pathogenesis of AD
- ✧ ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) brain metabolism was recognized as a biomarker of neurodegeneration in the recently proposed ATN framework for Alzheimer's disease (AD) biological definition.
- ✧ Hippocampal degenerate, as determined by Magnetic Resonance Imaging (MRI), might be a indicator for hippocampal pathology in subjects with MCI and guess a extra repeated decline to medical AD.
- ✧ Plasma tau might be an available biomarker for Alzheimer's ailment (AD), nevertheless the association among cerebrospinal fluid (CSF) and plasma, tau and the value of fusing plasma tau with CSF tau and phosphor-tau (P-tau) are still uncertain.
- ✧ Magnetic resonance imaging (MRI) is a medical imaging method utilized radiology to form picture of the structure and the physiological procedures of the body. While MRI is maximum conspicuously utilized in analytical medicine and biomedical examination, it also might be utilized to procedure images of non-living substances
- ✧ The normally first known as memory damage, is a typical feature of Alzheimer's disease. Neuropathological vagaries in the cerebral

cortex and limbic system central to shortages in learning, memory, language, and visuospatial reliefs.

✧ Patients and well participants endured neuropsychological examinations assessing remembrance and language capacities.

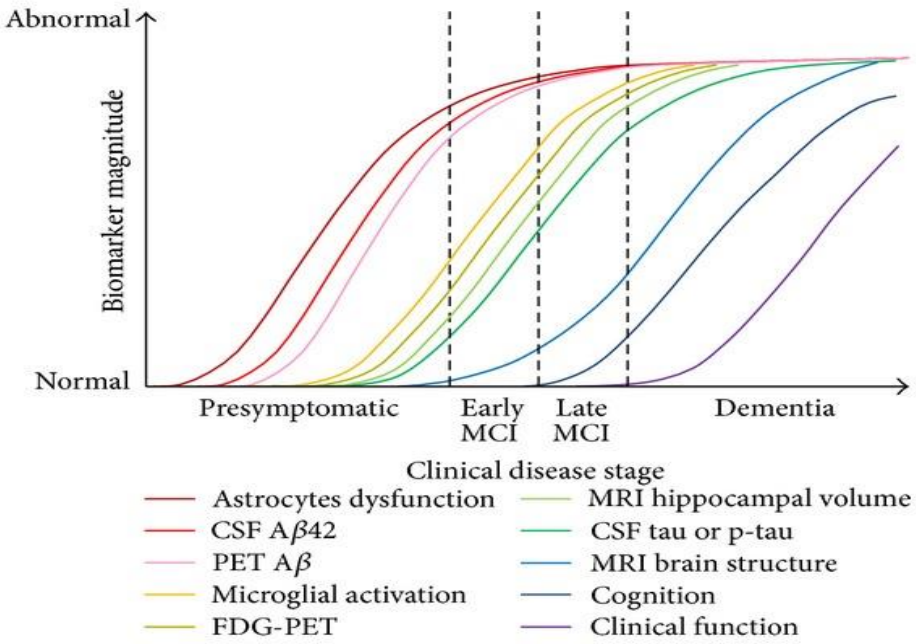

Figure 2.2. Biomarkers over the course of Alzheimer's disease [40]

In demand on progress the suitable and well-organized medicine, biomarkers play the dynamic role and we must integrate in it inside investigative context, even though biomarkers principally recommended for investigation purpose. Midst overhead reference biomarkers like tau and beta-amyloid protein (Aβ) which straight designate the pathology of Alzheimer's biomarker which have unintended or general suggestion of Alzheimer's which path the neuronal damage fairly demonstrations the detailed local pattern deviations in brain. Roughly biomarkers regularly associate to Alzheimer's disease similarly

understood in other brain syndromes. In case of both biomarkers detected in the similar patient, which central to the actual robust purpose to guess Alzheimer's disease.

2.2 Microarray scanner

Microarray knowledge is an operative skill to investigate investigational variances in people of biomolecules in a high-throughput setup. In furthermost, microarray scanners practice lasers to lighten one pixel at a period till all the spots on a range mark have been scanned and noted as a high-resolution image case. The scanned pictures are examined in an information abstraction procedure that dealings the qualified fluorescence of two fluorophore markers of the examination and regulator ingredients in each spot are mined. This includes measurable dispensation to compute numerous relations of the fluorescence concentration at two dissimilar wavelengths, which frequently makes a marvelous quantity of numerical data that needs additional clarification.

2.2.1 Ratio images' generation and preparation

Intended for a measurable judgement training, the ratio images characteristically signify the modification in movement of a test example relation to a location (control) model. The settlement utilized in analyzing blood serum protein adopts that the reference example is considered with Cy3 (532nm), and the test model is considered with Cy5(635nm). The considered microarray slide is scanned, engendering images comprising the fluorescence (F) intensity capacities of the Cy3 and Cy5 fluorophores. A ratio images is calculated and displayed as the scan occurs. The GenePix 4000 scanner makes and produces a 16-bit unidentified digit image, meaning that the active variety

for the pixel intensity standards for the Cy3 and Cy5 stations variety between from 0 to 65535 gray points. The 16-bit intensity values are used for all the controls listed in the result tab. In the displayed ratio image, a red spot indicates that the test sample for this feature is expressed at a level lower than the reference sample; a yellow spot means that there is similar activity for the two populations. A ratio image therefore provides a visual summary of the whole microarray. GenePix pro computes five different ratio quantities, which are classified into three groups. The first ratio calculation method uses median or mean values derived from the whole feature (ratio of medians, ratio of means), whereas the second method calculates ratios pixel-by-pixel (median of ratio, mean of ratio). A third method extrapolates the ratio value by regression analysis (regression ratio).

2.3 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a clinical imaging modality, which is utilized in radiology to illustrate an image of the anatomy and it also physiologically procedures the body in both health and disease complaint [41].

By utilizing strong magnetic fields, magnetic field inclines, and radio waves to yield the images of organs body. Structural MRI is a non-invasive imaging method that produces three high-dimensional whole anatomical scans deprived of harming the radiation. The sMRI is employed for treatment observing, diagnosis, and abnormality recognition.

2.3.1 Technology

As I mentioned above, MRIs create a strong magnet, which produce a powerful magnetic field signal that move forward the proton into the body to affiliated with that of field. When a radiofrequency pulse conceded through the patient body, the proton jumps to simulate, and it turn out of an equilibrium,

which is draining beside the pull of the magnetic field. Furthermore, when the radiofrequency pulsation is twisted off, the sMRI devices are now able to sense the energy unrestricted by the rearrange protons within the magnetic field. Time which incomes the protons to straighten with the magnetic field completely be contingent on the location of the chemical molecules. Physicians are proficient to express the modification between numerous kinds of matters based on these design of magnetic possessions [42]. Moreover, to attain a sMRI scans, a patient is placed inside a huge magnet and they must keep on motionless through the imaging procedure, so that image is not get blur. The contrast managers chemical (containing the element Gadolinium) might be assumed to a subject intravenously before or during the sMRI progression to grow the speed of proton readapt with magnetic field. The faster the protons settle in, the brighter the scans will be.

2.3.2 Imaging

The result images demonstrate various shades of gray color that reproduces dissimilar thicknesses, grounded on the detail that these parts are with little water, which satisfied fewer hydrogen protons that announce signals back to the radioactive loops. The different machines illustrate these differently (according to the signal weighting), T1-weighting will yield images of thick bone, air, and other material comprising fewer hydrogen protons, which will stand impartially dark, and fat will become bright and so on. The number of pixels could be from one of 255 shades of gray depend on signal strength, which 0 tell black and 255 illustrates white.

2.3.3 The Alzheimer's Disease Neuroimaging Initiative

The ADNI dataset is enduring, longitudinal cooperative research database that objects to "progress medical imaging, genetic, and biochemical biomarkers for the initial discovery and pursuing of AD". The six-year

"ADNI-1" study launched in 2004 ageing control patients. But far along, this investigation was prolonged with "ADNI-GO" from 2009 to 2011, accumulating more 200 subjects that were known as having early MCI in order to exam biomarkers in an early stage of disease. The purpose of the coordinator is to comprehend well the pathology of AD utilizing by known biomarkers, to empower initial analysis of AD; which deliver medical exam information in order to sustenance new training methods relating to interposition, and to endure and advance the dispersal of their dataset. The initiative developed effectively early stage detection techniques for an Alzheimer's (which includes CSF biomarkers, amyloid-42 and total-tau, p-tau, AV45) and standardized techniques for clinical trials (which includes sMRI, FDG-PET, fMRI and CSF biomarkers), and they also established their open access dataset, which contains large amount of brain images.

In an evaluation [43] of the ADNI development, review the consequence of all paper issued as in February 2011. Weiner et al. [44] make a list the bellowing focal activities in the later years.

- ✧ The development of medical examination effectiveness over distinguishing the patient's behavior, is greatest probable to experience unclear in the future medical deterioration and the usage of more complex consequence procedures to decrease model sizes
- ✧ For the expansion of prominent methods for the primary estimation of an AD. The total p tau and CSF and as well as amyloid-PET biomarkers has imitated the initial phases in the AD pathology, in steady or uniform non-stable subjects and these biomarkers are the important candidates for the guess of an AD in its preclinical stage.
- ✧ The valuation of alternate styles of analytical classification. Presently, the best classifiers connection optimal features from all numerous modalities

of biomarkers including (sMRI, FDG-PET, CSF) and clinical investigation.

2.4 Machine Learning

Machine learning unique of the prevalent divisions of artificial intelligence which contain algorithm strategy and study outline automatically over facts. Machine learning (ML) algorithm could study to make smart choices completely grounded on their capacity of multifaceted patterns recognition, which might be appropriate to identify handwritten pattern, stock market investigation, image study and medical judgement. This thesis mainly focuses on medical imaging and medical diagnosis. This is fundamentally a classification duty in which the purpose ought to be, for instance, to use neuroimaging information to classify whether it is given briefly information about patient who has Alzheimer's disease.

Machine learning is normally a multidisciplinary ground, diagram on the investigation from a various of research area, such as figures, attitude, and neurobiology or it might be also cleared as the knowledge of achievement computers to acquire and accomplish duty alike a humans do, and improve their knowledge procedure in independent style, by providing them a practical information with their explanations. For instant, a database that trainings in what way to show checkers may well improve its concert by its volume to success with the admiration to the session of errands elaborated with playing checkers over the understanding attained while playing checkers competitions contrary to itself. A machine learning technique normally contain three main fragments which are training, training procedure and model. The education process might be clarified if the dataset is accomplished well. Furthermore, according to compute the skilled model's actual routine, I have provided a

hidden test data, which is beforehand disconnected dataset. The purpose of the learning procedure is to discovery how the training method is achieved on invisible test dataset.

Machine learning could be separated into three learning paradigms, namely supervised and unsupervised learning, and reinforcement learning. Supervised learning arrangements with considered sample data, where inputs are involved with chosen output values. This could be detected as a similar in the psychological idea of perception learning. Although in supervised learning, examples are unlabeled, and their consequences are not existence of any mistake to analyze a possible explanation. Supplementary, Reinforcement learning agreements with trying to influence a detailed purpose by performing an achievement in an energetic situation in command to adventure a recompence, deprived of being obviously expressed if the learner is impending its purpose. There are numerous of machine learning recreations, among of all that make different prior assumptions about the likely input-output mappings or data sharing, in supervised and unsupervised learning correspondingly. The models make these different assumptions by the requirement, since the problem they are dealing is ill-posed, and the training data is insufficient for the models to find the right solution by themselves. For instant, a mapping might not occur, or there may not be enough data to rebuild it or there ought to be an unavoidable existence of noise that makes a perfect fit model, which is useless in real world. These sets of expectations that the learning procedures makes in order to make learning achievable is called inductive bias. The inductive bias (also called as learning bias) of learning procedure is the set of expectations that the learner uses to guess the outputs of a given inputs that is has not seen yet. Inductive bias is therefore important because it defines how

the learner generalizes outside the observed training samples. The learning process attempts to minimize some amount of error, such as least mean square or mean squared error. They do this by choosing the best weight that fit the set of training samples, i.e. and, which also helps to minimizing the loss between the observed training instances (and other prior are kept constraints) and the guessed values.

In this thesis, I will mainly concentrate on supervised learning techniques such as SoftMax classifier. Additionally, I will also cover some unsupervised learning methods for preprocessing purpose, like PCA.

2.4.1 K-Nearest Neighbor classification

KNN is a typical example of a lazy learner. It is called lazy not because of its apparent simplicity, but because it does not learn a discriminative function from the training data but memorizes the training dataset instead. KNN belongs to a subcategory of nonparametric models that is described as instance-based learning. Models based on instance-based learning are characterized by memorizing the training dataset, and lazy learning is a special case of instance-based learning that is associated with no(zero) cost during the learning process. The KNN algorithm itself is straightforward and can be summarized by the following things:

- ✧ Choose the number of k and a distance metric.
- ✧ Find the k nearest neighbors of the sample that we want to classify.
- ✧ Assign the class label by majority vote.

Based on the chosen distance metric, the KNN algorithm finds the *k* samples in the training dataset that are closest (most similar) to the point that we want

to classify. The class label of the new data point is then determined by a majority vote among its *k* nearest neighbors.

2.4.2 Random Forest classification

The idea is largely that if one tree is good, then many trees (a forest) should be better, if there is enough variety between them. The most interesting thing about a random forest is the ways that it creates randomness from a standard dataset. As well as increasing the randomness in the training of each tree, it also speeds up the training, since there are fewer features to search over at each stage. Another benefit of this is that there is no need to prune the trees. Once the set of trees are trained, the output of the forest is the majority vote for classification, as with the other committee methods that we have seen, or the mean response for regression. And those are pretty much the main features needed for creating a random forest. The basic Random Forest Training algorithm is given below.

For each of *N* trees:

- ✧ Create a new bootstrap sample of the training set.
- ✧ Use this bootstrap sample to train a decision tree.
- ✧ At each node of the decision tree, randomly select *m* features, and compute the information gain only on that set of features, selecting the optimal one
- ✧ Repeat until the tree is complete

2.4.3 Support Vector Machine classification

In this section we introduce some basic concepts of SVM, different kernel function and kernel selection of SVM. The SVMs are set of associated supervised learning approaches utilized for classification and deterioration [45]. They linked to a family of general linear classification. A superior

possession of SVM is, SVM instantaneously diminish the experiential classification mistake and exploit the geometric boundary. So SVM named Maximum Margin Classifiers. SVM is founded on the Structural risk Minimization (SRM). SVM chart input vector to an advanced dimensional interplanetary where a best untying hyperplane is constructed. Two equivalent hyperplanes are created on each side of the hyperplane that distinct the statistics. The unravelling hyperplane is the hyperplane that take full advantage of the distance between the two equivalent hyperplanes. A supposition is completed that the greater the boundary or distance between these equivalent hyperplanes the improved the simplification mistake of the classifier will be [45] deliberated data opinions of the procedure:

$$\{(m_1, k_1), (m_2, k_2), (m_3, k_3), (m_4, k_4) \ldots . (m_n, k_n)\} \quad (1)$$

where k_n=1/-1, a persistent signifying the class to which that argument m_n fits *n*= number of samples. Each m_n is p-dimensional is actual vector. The scaling is significant to protector in contradiction of variable (attributes) with greater variance. We could assessment this training data, by means of the summersaulting (or separating) hyperplane, which takes:

$$w.m + b = 0 \quad (2)$$

where *b* is scalar, and *w* is p-dimensional vector. The vector *w* points perpendicular to the unraveling hyperplane. Addition the counterbalance parameter *b* permits us to rise the margin. Inattentive of *b* the hyperplane is compulsory to pass through the derivation, limiting the resolution. As we are concerned in the supreme margin, we are concerned in SVM and the equivalent hyperplanes. Corresponding hyperplanes could be designated by equation:

$$w.m + b = 1 \ \ and \ \ w.m + b = -1 \quad (3)$$

If the training statistics are linearly distinguishable, we can choice these hyperplanes so that there are no arguments among them and then effort to exploit their detachment. By geometry, we discovery the detachment between the hyperplane is $2 / |w|$. So, we need to diminish $|w|$ and to stimulate statistics arguments, we need to guarantee that for all either:

$$w.m_i - b \geq 1 \quad or \quad w.m_i + b \leq -1 \tag{4}$$

This could be inscribed as

$$k_i\ (w.m_i - b) \geq 1\ ,\quad 1 \leq \mathrm{i} \leq \mathrm{n} \tag{5}$$

2.4.3.1 Kernel selection

The training directions m_i are plotted into an advanced (might be infinite) dimensional interplanetary by the function Ψ. Then SVM discoveries a linear extrication hyperplane with the highest margin in this sophisticated dimensional interplanetary. The C>0 is the penalty limitation of the fault term. Furthermore, F (m_i , m_j)= $\Psi(m_i)^T\ \Psi(m_j)$ is called kernel function [45]. There are numerous kernel functions is also a study issue. However, for overall determinations there are some general kernel function. [45-46]

Linear Kernel:

$$\mathrm{F}\ (m_i , m_j)\ = {m_i}^T m_j \tag{6}$$

Polynomial Kernel:

$$\mathrm{F}\ \left(m_i , m_j\right) =\ (\gamma {m_i}^T m_j + r)^d\ ,\quad \gamma >\ 0 \tag{7}$$

RBF kernel:

$$\mathrm{F}\ \left(m_i , m_j\right) =\ \exp\ \left(-\gamma\ |\ m_i - m_j\ |^{\,2}\right),\quad \gamma >\ 0 \tag{8}$$

Sigmoid kernel:

$$\mathrm{F}\left(m_i, m_j\right) = \tanh\left(\gamma {m_i}^T m_j + r\right) \quad (9)$$

Here is γ, r, and d are kernel constraints. In these general kernel functions, RBF is the key kernel function because of subsequent reasons. [45]

- ✧ The RBF kernel nonlinearly plots examples obsessed by an advanced dimensional space unlike to linear kernel
- ✧ The RBF kernel includes fewer hyperparameters than the polynomial kernel
- ✧ The RBF kernel has less arithmetical complications.

3. Reviews of related works

3.1 Classification of structural MRI

Recently, a numerous classification architecture has been utilized obviously to examine compound imaging patterns in neuroimaging examples with an assessment to categorize the AD or MCI subjects with further diagnosis groups based structural MRI. According to classification outline, feature abstraction and classification procedure are the required mechanisms for every machine learning method. In this part, I will represent somehow earlier related works which are done on AD employing machine learning techniques.

Structural MRI has the capability to imagine precise atrophy designs in the brain; hence, it is significant for the difference analysis of AD [47]. From the sMRI point of view, brain degeneration and neuronal damage, as communal MRI biomarkers in some singular parts of the brain, are key standards for the analysis of AD. Atrophy begins from the entorhinal part and endures in the hippocampus, amygdala, and Para hippocampus lengthways with ailment development [48-49]. The other brain areas, such as the posterior temporal, parietal cortex, and mesial temporal lobe, are affected by development of AD [50]. When deviations in dissimilar independent brain regions happen, it is probable to measure the gradation of atrophy visually. The volumetric quantity is the most communal measurable metric utilized in AD [49]. The voxel-based morphometry (VBM) is a authenticated technique to measure atrophy over the whole 3D sMRI scan [51]. Furthermore, VBM gives an alternate, one of which is guide separation of ROIs instead of the voxel-based method. The research [52] planned a completely data- determined method to discovery the anatomical structural designs in 3D images by using feature-based morphometry (FBM). To categorize the themes founded on their image, FBM

could endorse an image model which is further connected to the greatest possible group. The researchers used this method to acquire high accurateness of manifold kernel increasing, which is about 95% correctness of classification between AD and HC, and about the accuracy of 72% between MCI changeable and MCI non-convertible. The research work [53] represented an automatic classification method for AD analysis in structural MRI. The hippocampal part is the ROI in this approached work. Their planned technique abstracts the visible structures through structural MRI utilizing the image signal estimation by Circular Harmonic Functions. In this process the probabilistic outcome gained from categorizes on both the volume of CSF and local features were combined, a next stage combination arrangement can achieve the classification duty of the MRI scans. The research work [54] is applied Sparse Logistic Regression (SLR) to categorize 69 AD and 60 HC subjects grounded on voxel-wise grey matter capacities consequent from structural MRI. Reprimanded Logistic Regression (PLR) and Spatially Regularized Sparse Logistic Regression (SPSLR) are two different designs of SLR which applied to solve the problematic of taking large number of voxels in assessment to the quantity of training subjects. The contribution features in the classifiers for this work were the consistent grey matter voxel intensities. Their consequences represent about 85 % of general classification accuracy for AD and HC [54]. In 2013 Gupta, Ayhan and Maida et al. [55] “used a sparse auto-encoder to learn a set of centers from normal images and then implemented convolution to excerpt structures from the Alzheimer’s disease Neuroimaging Initiative (ADNI) dataset”. They then separated sMRI examples into three collections (AD, MCI, and HC). Their method attained high analytical accuracies, and their technique was also very modest with other approaches, notwithstanding “existence very humble”, and without integrating previous domain-knowledge in the

information dispensation expression. Grounded on a vast sub-group of ADNI data, Cuingnet et al. [56] presented a contrast of ten sMRI-based feature mining methods and their aptitude to differentiate between clinically pertinent issue collections. The ten approaches assessed cover five voxel-based procedures, three approaches cantered on cortical thickness and two methods based on the hippocampus. The optimum compassion and specificity values are (81%, 95%) related to AD vs HC, (70%, 61%) related to S-MCI vs P-MCI and based on 73%/ 85% for HC vs P-MCI.

Recently, Zhang et al. [57] projected a multimodal classification method by using multiple-kernel SVM built on the biomarkers counting sMRI, PET, and cerebrospinal fluid (CSF) to differentiate AD (or MCI) and standard control (NC) subjects. For the binary classification (AD vs NC and MCI vs NC) consequences, their recommended approach gains a respectable accuracy for AD classification while MCI classification they achieve an inspiring accuracy. In latest year, Cho et al. [58] achieved experimentation on 72 MCI-C and 131 MCI-NC subjects. Utilizing the incremental learning method founded on longitudinal frequency, which demonstrations the illustration of cortical thickness data. In addition, their planned technique gives better consequence than the ten-benchmark approaches for MCI-C vs. MCI-NC classification as described in [56] and gain sensitivity as 63% and specificity as 76%. Wolz et al. [59] utilized four dissimilar automatic feature mining methods (explicitly hippocampal volume, cortical thickness, TBM, and complex-based learning) to examine structural MRI data of 834 subjects from ADNI dataset, which are AD, MCI, and Healthy Control (HC). The mined features were employed to equate the presentation of two classification methods such as, LDA and SVM, for AD cataloging and MCI estimation. The best accuracy for AD versus HC

classification was gained by uniting all extracted features and using LDA classification technique; 89% of accuracy (sensitivity of 93% and specificity of 85%). Likewise, utilizing fusion features and the LDA classifier consequence in the maximum accuracy of 68% (sensitivity of 67% and specificity of 69%) for classification of MCI-converter and MCI-stable subjects. Once dissimilar feature categories were considered separately, the TBM features presented the greatest consequence. The researchers also achieved feature assortment utilizing a stepwise deterioration technique. Besides, age and gender alteration utilizing a linear reversion method was implemented to eliminate disease-related belongings of age and gender on the classification. Beheshti and Demirel et al. [60] presented a technique which decrease the sizes of GM area in an administered style. They have employed intensity dispersal voxels of a GM maps, somewhat than utilizing assets of all the voxels of a GM charts, as a feature. The optimum hyper amount of a bins in the intensity circulation was then designated founded on the Fisher standard of enlargement between the AD and HC subjects, and the subsequent intensity dispersal grounded features were advanced employed for SVM-based AD classifications. In 2015, Salvatore et.al [61], employed sMRI images as a biomarker for initial classification of AD with other groups. They have utilized PCA purpose for feature extraction determination and SVM as a classifier for classification intention. They originated that hippocampus, entorhinal cortex, basal ganglia, gyrus rectus, precuneus, and cerebellum, are the critical areas recognized to be powerfully complicated in the pathophysiological mechanisms of AD. There classifier attained classification accuracy as the 76% of AD vs. CN, the 72% of MCIc vs. CN, and the 66% of MCIc vs. MCInc utilizing nested 20-fold cross validation procedure.

Above, I have discussed some previous published and related journal papers to AD using machine learning techniques. Upcoming chapter, I am going to clarify our approached method using this ideas and models

3.2 Multi-Modal method

Current researches have been verified that multi-modal comprises matching information for analysis of AD and its classification into dissimilar phases with the best accuracy.

Nevertheless, to accomplish more dependable classification consequences, these manifold biomarkers ought to be joint to deliver a precise judgement. In earlier chapters, we studied some modalities, for instance sMRI, FDG-PET, P-tau which produced reasonable consequences. In this chapter, we considered some investigation that utilized multi-modality to attain better outcomes. Some of the journals above got additional experimentations to demonstrate the consequences of fusion two multi-modal or fusing more medical and genetic biomarkers. Dissimilar biomarkers could be described diverse features of pathological deviations related with AD. Roughly, most of biological biomarkers have been advanced for judgement of AD. Three CSF biomarkers are communal in recent new research field: total τ (T-τ), hyper-phosphorylated τ (P-τ) and the 42 amino acid isoforms of Aβ (Aβ42) [62]. In this chapter, we revised the journals in alike fields, and we designated some applicable investigation to represent in this paragraph. In these researches, dissimilar methods were implemented to make the images, to excerpt the features, to choose the classifiers, and to utilize some additional biomarkers. The consequences were attained in numerous comportments, which are considered. Amongst all considered labor, there are a rare revision that piercing to the dissimilar phases of MCI (EMCI and LMCI). The revisions that utilized sMRI

images only provided us a respectable past evaluation on approaches for discovery ROIs and dissimilar classifiers.

4. Proposed method and Materials

4.1 Our proposed method

This section demonstrates the workflow of our proposed experiment and find out how our modeled classifier could be trained to distinguish AD from other diagnosis groups. In this thesis, I have approached a multimodal model utilizing machine learning methods to differentiate AD from other prognosis groups.

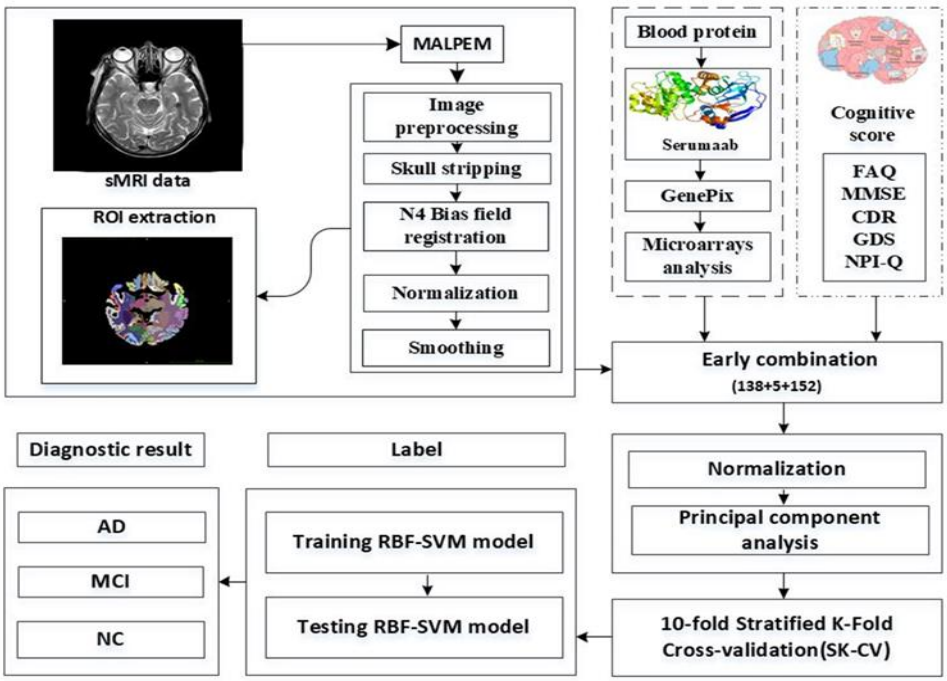

Figure 4.1. Block diagram of proposed machine learning methods

4.1.1 The sMRI dataset from ADNI

I have downloaded ADNI dataset from ADNI homepage. In total 187 three dimensional T1-weighted images were downloaded. Among 187, 46 patients belong to AD subjects (21 females, 25 males, age ± SD = 76.3±7.8 years,

FAQ = 14.1 ± 3.2, MMSE = 23.5±1.8, CDR=1.52 ± 1.2,GDS = 1.76±1.56, NPI-Q= 4.6 ± 2.21), 70 patients belong to MCI (30 females, 40 males, age ± SD = 74.7±7.2 years, FAQ = 15.7 ± 2.9, MMSE = 26.9±1.8, CDR=1.61 ± 1.6, GDS = 1.96±2.7, NPI-Q= 3.6 ± 1.26), 71 patients belong to HC (33 females, 38 males, age ± SD = 77.3±5.2 years, FAQ = 15.9 ± 2.8, MMSE = 29.1±0.9, CDR=1.72 ± 1.9,GDS = 2.21±1.7, NPI-Q= 0.95 ± 2.11).

Above, all sMRI scans were early revised for excellence and Gradient inhomogeneity improvement (grad warp), B1 non-uniformity modification, and N3 bias field processing (to decrease remaining intensity non-uniformity) were implemented [63-64].

Table 4.1. Demographics information about ADNI dataset (Mean/Standard deviation) values

Group	AD	MCI	NC
Female/male	21/25	30/40	33/38
Age	76.3±.7.8	74.7±.7.2	77.3±.5.2
FAQ	14.1±.3.2	15.7±.2.9	15.9±.2.8
MMSE	23.5±.1.8	26.9±.1.8	29.1±.0.9
CDR	1.52±.1.2	1.61±.1.6	1.72±.1.9
GDS	1.66±.2.2	1.96±.2.7	2.21±.1.7
NPI-Q	4.6±.2.21	3.6±.1.26	0.95±.2.11

4.2 Feature extraction by utilizing MALPEM

In this thesis, we segmented features which are cortical thickness, and subcortical volume by using Multi-Atlas Label propagation with EM (MALPEM) with Neuromorphometrics atlas. It is sown in Figure 4.2.

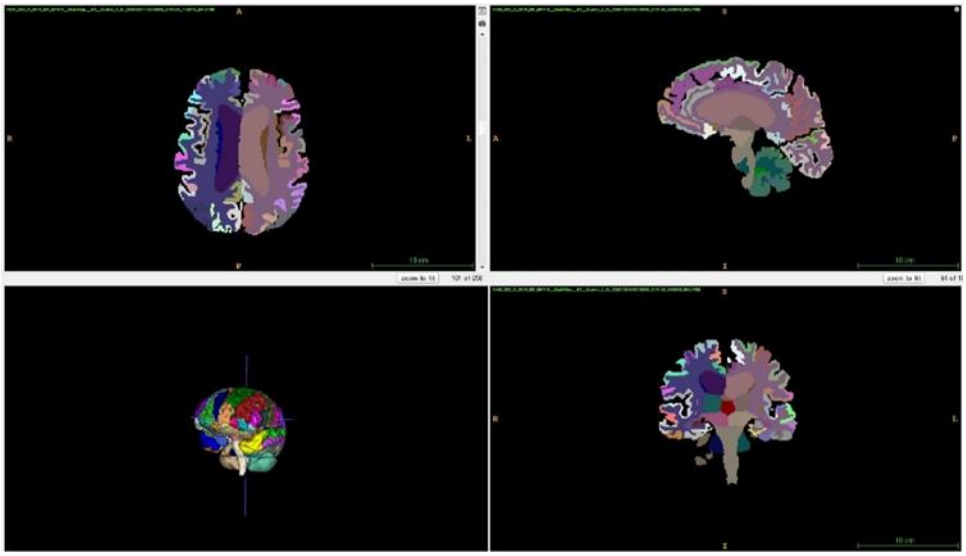

Figure 4.2. The segmented sMRI brain's cortical and subcortical region

The MALPEM was constructed automatic workflow which consists of several standard image processing and finally divides 138 ROI (region of interest). In recent years, multi-atlas segmentation has developed like the most accurate methods for the segmentation of T1-weighted images, mostly focused on graph-cut or expectation-maximization (EM) optimization. The MALPEM was evaluated as a Top 3 method in a Grand Challenge on whole-brain segmentation at MICCAI 2012 [65]. All 187 subjects' sMRI images were segmented individually utilizing MALPEM as designated in [66]. It consumes between 8 to 10 hours for each subject. For this segmentation we used the automatically explained Neuro-morphometrics (NMM) brain atlas (n=30; provided by Neuro-morphometrics, Inc. under academic subscription [67] last accessed 15 March 2018). This atlas automatically distinguishes the whole brain images into 40 non-cortical and 98 cortical parts. We utilized MALP (Multi-Atlas Label propagation) to acquire the specific probabilistic of a brain atlas for sMRI brain image as K which should be segmented [66]. This

probabilistic is integrated into the EM framework as a spatial anatomical task. The *n* is indicated as voxel of *K* by j=1, …n, therefore the intensities of voxel $Z_i \in D$, image should be described $K = \{Z_1, Z_2 \ldots\ldots Z_n\}$. The probabilistic priors are produced through the transformation of manually generated *L* atlases into the unseen image's coordinate space. For the propagation of the tag, we measure the *L* transformations using a non-rigid registering technique based on free-form deformations (FFD), which follows a previous rigid and some alignment. By using a locally weighted multi-atlas fusion strategy, the probabilistic atlas was designed for image intensity normalization and rescaling by the Gaussian weighted the sum of squared differentiation. The estimated hidden segmentation employing the observed intensities *j* is followed by the approach of Leemput [68]. We consider which observed log-transformed intensities of voxels refer to a spatial class *N* are dispensed with mean φ_N and standard deviation ρ_N returns method parameters;

$$\psi = \{(\varphi_1, \rho_1), (\varphi_2, \rho_2), \ldots\ldots, (\varphi_N, \rho_N)\} \quad (10)$$

We used the approach of global Markov Random Fields (MRF) for applying the regularization of the resulting segmentation. The EM algorithm disposes to make segmentations with very low-intensity variance with the region (intra-class variance) compared to the Gold standard segmentations. Therefore, we determined normalized intra-class variance for each region ($\rho_{NGold,k}$) by averaging the normalized standard deviations $\frac{\rho N}{\varphi N}$ of every group over the training subjects. Moreover, we measured the averaged (averaged over all training subjects segmented with a leave-one-out strategy) distributed standard deviation within every region assembled by the EM algorithm ($\rho_{EM,k}$). By determining $\Delta_N = (p_{NGold,k} - p_{EM,k})^2$, we evaluated by which value the intra-class variance of the spatial group might be enhanced on average to better

match the gold-standard innates [69]. Final segmentation is created by fusing the refined labels for this subset with the labels from the MALP approach for enduring parts.

4.2.1 Volumetric features

Volumetric feature discusses to the feature dimensions of the volume of designated brain areas and is supported to figure out by accumulating whole voxels inside the outlined region of interest (ROI). In this research, we have utilized MALPEM automatic toolbox, the whole cortical, subcortical area were extracted from every subject's brain. Totally, 138 volumetric features (40 belong to subcortical volumes and 98 belong to cortical thickness) were extracted from the brain of every subjects.

4.3 Serum samples and human protein microarrays

Serum from the following subject groups were used to probe custom human protein microarrays described above: 100 MCI paired with 100 age- and sex-matched controls; 50 AD subjects; 83 initially healthy controls that later converted to MCI paired with 73 age- and sex-matched controls. All were obtained from the ADNI. To identify autoantibodies in human sera, we used custom human protein microarrays, each containing 50 selected human protein antigens, 33 consistent with a diagnosis of prodromal AD at the MCI stage, and 17 consistent with a diagnosis of AD (Nagele et al., 2011; DeMarshall et al., 2016). All proteins were given an expression as GST combined proteins in insect cells, sanitized under native circumstances, and marked in replacement onto nitrocellulose-coated glass slides. All arrays were probed and scanned as described previously (DeMarshall et al. 2016) Microarray slides were blocked (Blocking Buffer, Cat. No. PA055, Invitrogen) and at that time incubated with serum samples, thinned 1:500 in washed buffer. After washed, arrays were

investigated with anti-human IgG (H+L) get a conjugated to Alexa Fluor 647 (Cat. No. A-21445, Invitrogen), washed and then dried [71].

4.3.1 Protein microarrays analysis

Microarrays were gained with a GenePix 4000B Fluorescence Scanner (the Molecular Devices, Sunnyvale, CA, The USA). Data were acquired using a GenePix Pro 7, saved as Genepix Results (GPR) files and analyzed using ProtoArray® Prospector v5.2.3 software modified for use with our custom microarrays. Prospector is a non-charged, user-friendly data analysis tool provided by Invitrogen [70]. Resulting GPR files for each of the microarrays representing each of the 400 ADNI sera tested were uploaded into the ADNI's LONI database [71].

4.4 Cognitive scores

The mental score [72-73] is a collective quantity of the present intellectual asset of dissimilar mental skills. The intellectual score offers a fast method to determine wherever you presently attitude cognitively and assistance you measure your development by passing time. Intellectual capability inspections evaluate the capabilities complex in thoughtful (e.g., memory, awareness, cognitive, spoken and mathematical ability, and a problematic resolving). Like calculations process requests proposed to guess subject's possible to utilize mental procedures to response work-related queries or to acquire new occupation information. In this thesis, all subjects have been tested through Mini-Mental State Examination test (MMSE), Global Deterioration Scale (GDS), Functional Activities Questionnaire (FQA), and Neuropsychiatric Inventory Questionnaire (NPI-Q). I attained these scores from the ADNI homepage.

4.5 Feature selection

The next step after extracting features, the process of normalization is employed. After completion of segmentation, all the segmented data were normalized to zero mean and component variance for every feature, as demonstrated in Figure.4.1 utilizing ordinary scalar function of Scikit-learn library. According to normalization, ξ is given data matrix where the subjects are in rows, and the features of subjects are in columns. The elements of normalized matrix illustrate like ξ (*m, n*) and equation is given by:

$$\xi_{\text{norm},(m,n)} = \frac{\xi_{(m,n)} - \text{mean}(\xi_n)}{\text{std}(\xi_n)} \tag{11}$$

4.5.1 Dimensionality reduction

This method is a kind of training procedure, wherever I gain higher-dimensional example or features, similar images in medium procedure, and advanced I alter it into a lower-dimensional interplanetary utilizing some methods. By using this process, I could diminish somewhat dimensional features into 2D or 1D horizontal. Besides, in our situation I will use this technique to decrease features of the multimodal procedure, which I have gained by utilizing MALPEM toolbox. In our situation, I have employed Principal component analysis (PCA) [70] as a dimensionality decreasing procedure.

4.5.2 Principle Component Analysis (PCA)

Principal component analysis (PCA) [74] is a numerical procedure that usage of orthogonal alteration technique to renovate a usual of comments of which are probably a connected mutable into a usual of linearly uncorrelated aspects, which is named as principal components. The constant attained from a MALPEM toolbox, has expands the dimensionality of the variables

interplanetary that styles the classifier task more compound. Furthermore, it likewise principals to utilize extreme computational control and enormous reminiscence packing. Therefore, it is significant to inferior the measurement of the variables makes and become imperative features to grow the classification consequences. PCA is employed to discovery a linear low dimensional decrease interplanetary in the database. For instance, the modification of the constructed data is fine conserved. The core concept behind employing PCA is to decrease the dimensionality of the example features, which consequences in more drivable and precise classification.

Far along, acquire PC are passed through to the classifier for the classification determination. Additionally, these input mediums only own PCs. PCA is an unconfirmed learning technique and a very influential and dependable instrument for database examination. As mentioned above, once the definite design in the statistics is originate, then they could be trampled into lower sizes. Finally, the number of components was resolute by keeping the alteration bigger than 96%.

4.6 Cross-Validation

The limitations of classifier are enhanced executing to the training dataset. Therefore, independent test database is compulsory for developing a suitable intention of the applicability proposed for the classifier on original dataset. The Cross-validation distributes a better-quality technique to evaluate this interpretation performance quantity when there is not availability of such dataset. On the extreme, cross-validation technique is usually used k-fold, which the dataset is split casually into k number of subcategories. The determination of training, a solitary cross-validation fold ($k - 1$) subfields are difficult to make a classifier, and the enduring of data subgroups are cover for

testing drive. The process is repeated till k periods, such that for testing every of the subdivisions are used once time, and the standard of the folds are available as a conclusion result. Additionally, alternative for cross-validation method is random assortment with imitation, in which the dataset is divided uselessly into steady sizes training and testing stages. For example, 60/40 splitting mean that the 60% of the dataset was selected on a single round for training, with the remaining 40% data for testing purpose. Therefore, this process should be repeated, and the becoming a middling of importance over the reappearance illustrate the last moment. Reappearance of unintended assortment has the advantage due to its independent ability on the sizes of the training and testing sample on the repetition quantity. However, around overlap between test sets may happen, and the Monte Carlo variance is also demonstrated by the method. The main concept that recurring procedure of different partitions of the database in inspection will create the alteration on significances. In case of two modules M1 and M2 are different scopes, the training and testing circles should to be selected grounded on such that composed of them concealment instances from the correspondingly trainings in moderately equal extents to the whole database. That is recognized as stratified cross-validation, and it has been visible to make performance with a temperately inconsequential modification than uniform cross-validation method [48]. Equally the recurrent arbitrary selection and k-fold cross-validation produce circulation of a normal presentation standards crossways the recurrences or folds. The numerical significance of outcome alterations gained from two classifiers could be quantity by accomplishment unpaired t-tests between these disseminations. Likewise, variation test might be beneficial to measure whether the classifiers consequences are meaningfully assorted from casual. Variation test contains cross-validation presentation on

database for which the analytical collection has been done arbitrarily. Below the worthless suggestion, the outcome which include in a circulation of classification consequences that the classifier could not correctly guess the medical group from the database. Variation test among the circulation of attained consequences and unpaired t-tests characterizes whether the gained outcomes are variable meaningfully from casual.

4.7 The performance of classification and statistical analysis

The presentation of dimensional classification is important to measure the propriety and reliability of an accomplished procedure with self-determining test statistics and significant for the optimization of constraints during training procedure. The easiest and extensively utilize presentation metric are AUC, accuracy, sensitivity, specification, precision and F1-score. The accuracy gives the proportion of dataset which are properly identified by the classifier. Nevertheless, this dimension method does not always illustrate a suitable assessment of performance, and alongside that other appropriate metrics are labeled with detailed in Section 4.7.1. The technique of cross- validation might be applied to measure the classifier's simplification performance, likewise there is insufficient of plentiful and proper autonomous database available for testing. According to solitary round of cross-validation dataset are divided in to two subsections, so that it might be trained and tested employing the dissimilar subdivision of dataset. Commonly, the outcome is informed as the middling over manifold recurrence in which diverse partitions of the database are employed. The proper of most commonly utilized cross-validation methods are explained in Section 4.6.

4.7.1 Performance metrics

The performance assessment of a binary classifier could be comprehended over a confusion matrix, as illustrated in Table. The assessment of the system was assessed using the RBF-SVM classifier for every precise test including binary classification tasks. The amount of dataset sample correctly labelled by the classifier are presented along the diagonal. These may be characterized into true positives TP, which characterizes appropriately perceived abnormal, and true negatives TN, which signify properly spotted healthy normal. The amount of inaccurately categorized dataset by classifier might be characterized into false negative FN, which demonstrate the abnormal imperfectly recognized and classified as normal, and false positives FP, presenting normal individual misleadingly classified as abnormal. The accuracy measures the quantity of samples that were properly categorized by classifier, which is,

$$Acc = \frac{TP + TN}{TP + TN + FP + FN}. \tag{10}$$

Though, the unbalanced class distribution, the calculation of accuracy might result in a misleading the performance of estimation for a testing dataset. Hence, additionally the performance of four metrics ought to estimate, namely, sensitivity, specification, precision, and F1-score. They are illustrated as below equations:

$$Sen = \frac{TP}{TP + FN}. \tag{11}$$

$$Spec = \frac{TN}{TN + FP}. \tag{12}$$

$$PPV = \frac{TP}{TP + FP}. \tag{13}$$

$$F1\ score = \frac{2TP}{2TP + FP + FN}. \quad (14)$$

The sensitivity (11) illustrates the predicted group's accuracy, specificity (12) illustrates the predicted absence group's accuracy. Sensitivity, which is called also recall or probability of detection, analysis the proportion of actual positives that are correctly determined. Similarly, specificity investigates the proportion of actual negative that is not included in the class. Precision (13) (positive predictive value (PPV)) is the element of appropriate incidences between the repossessed incidences, and F1 score (14) (which is also named F-score or F-measure) determination of a test's accuracy.

Table 4.2 Confusion metrics representing binary classifier

True Class	**Predict class**	
	S1 (abnormal)	**S2 (normal)**
S1 (abnormal)	TP	FN
S2 (normal)	FP	TN

5. Experimental Results and Discussion

5.1 Data labeling

In this chapter, it is demonstrated the results of the researcher approach which is mentioned the above chapters. Our proposed method is run with a 70/20/10 dataset divided (training/testing/validation) parts. I have gained unbiased estimations of the performance for every classification problem, and to confirm that, it had enough test/validation sample available with the dataset variances with less examples. The performance of the three chosen features (volumetric features, Seruma protein, and cognitive score) was confirmed and tested using RBF-SVM classifier on normal and abnormal subjects with three binary classifications:

- ✧ AD vs HC
- ✧ AD vs MCI
- ✧ MCI vs HC

5.2 Machine Learning classification results

There was not any the problem of overfitting in this RBF-SVM classifier. When I operated this classification technique, I followed below parameters as a constant for all classification groups.

- ✧ Cross-validation: stratified K-fold (10-fold)
- ✧ Activation function: Adam
- ✧ Batch size: 16
- ✧ Learning rate: 0.001
- ✧ Epochs: 1000

The achieved classification results for our ML model are given from Table 5.1-5.5 related to AD vs CN, AD vs MCI, and MCI vs CN. Moreover, the report of classification for all groups are shown in Figure 5.1, to 5.5, respectively. All works were executed in 64-bit Python 3.6.5 environment on Intel(R) Core (TM) i7-8700 at 3.20 Hz and 32 GB of RAM by running an Ubuntu 16.04 LTS. The approached method might be implemented on any computer in which Python 3.6.5 is available.

5.2.1 RBF-SVM result

In the below tables, it is illustrated the result of groups by using RBF-SVM classifier. Moreover, I compared my result with other SVM kernels and Machine learning classification methods. As we can see below table in this kernel the combined biomarkers achieved higher accuracy compare to single modality. Especially MCI vs NC gained the highest accuracy as 97.62% among other groups. This kernel is used in non-linear classification and it has gamma and C parameters.

Table 5.1. Classification result of RBF-SVM classifier

RBF-SVM classifier						
Confusion metrics		**ACC**	**SEN**	**SPE**	**PRE**	**F1**
AD vs NC	**Serum**	85.71%	90.48%	78.57%	86.36%	88.37%
	Cognitive	95.24%	95.83%	94.44%	95.83%	95.83%
	sMRI	85.71%	94.74%	75%	81.82%	87.80%
	Combined	**91.43%**	**90.48%**	**92.86%**	**95%**	**92.68%**
AD vs MCI	**Serum**	68.57%	86.67%	55%	59.09%	70.27%
	Cognitive	85%	86%	84%	87%	89%
	sMRI	85.71%	86.96%	83.33%	90.91%	88.89%
	Combined	**88.57%**	**90.00%**	**86.67%**	**90%**	**90%**
MCI vs NC	**Serum**	85.71%	84.62%	87.50%	91.67%	88%
	Cognitive	86%	87.35%	88.80%	88.96%	89%
	sMRI	95.24%	95.83%	94.44%	95.83%	95.83%
	Combined	**97.62%**	**100%**	**95.65%**	**95%**	**97.44%**

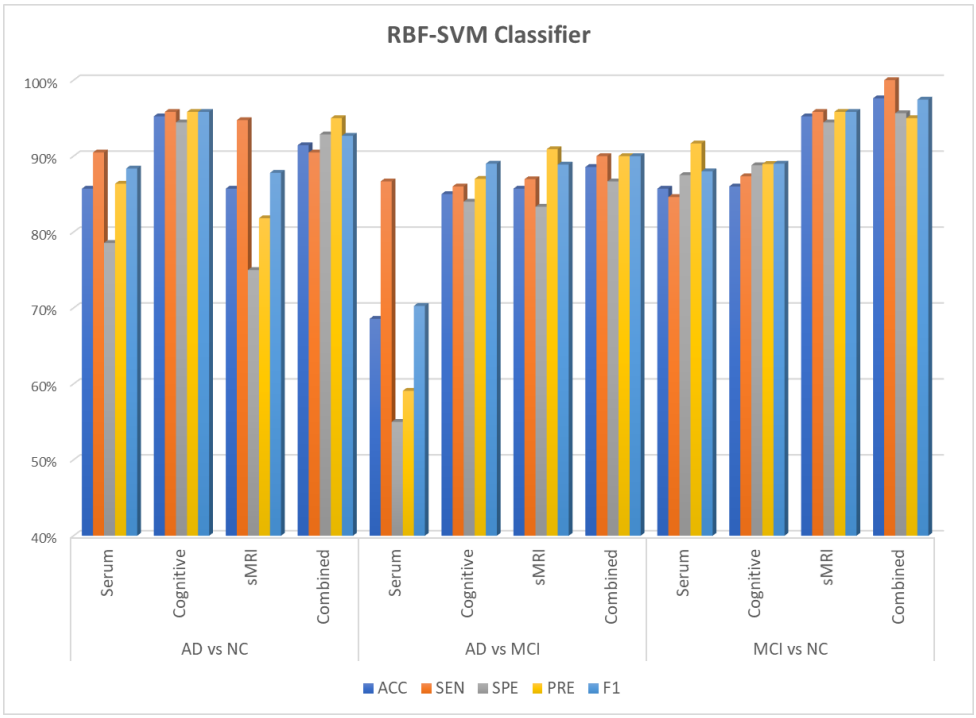

Figure 5.1. Classification result with RBF-SVM Classifier

5.2.2 Polynomial-SVM result.

The Polynomial-SVM is less popular as kernel in SVM and it is used usually and popular in natural language processing (NLP). The most common degree is d=2(quadratic), since larger degree tends to overfit on NLP. We can see result it is the lowest accuracy among kernels. Therefore, it is not recommendable to use this kernel in our model.

Table 5.2. Classification result of Polynomial-SVM classifier

Polynomial-SVM classifier						
Confusion metrics		**ACC**	**SEN**	**SPE**	**PRE**	**F1**
AD vs NC	**Serum**	64.15%	45%	65.12%	56%	61%
	Cognitive	65%	66.12%	50.15%	58.16%	59.35%
	sMRI	53.96%	65.12%	53.98%	68.12%	66.51%
	Combined	65.32%	56.36%	66.01%	68.52%	56.86%
AD vs MCI	**Serum**	55.63%	67.12%	65.01%	68.23%	62%
	Cognitive	65%	66%	64%	67%	69%
	sMRI	59%	61.21%	55.32%	65.65%	59%
	Combined	56%	66%	57.12%	59.23%	46.12%
MCI vs NC	**Serum**	65%	68%	69%	69%	73%
	Cognitive	66%	67.35%	58.80%	58.96%	69%
	sMRI	65%	55%	50%	74%	62%
	Combined	60%	62.12%	71.12%	61.56%	66.89%

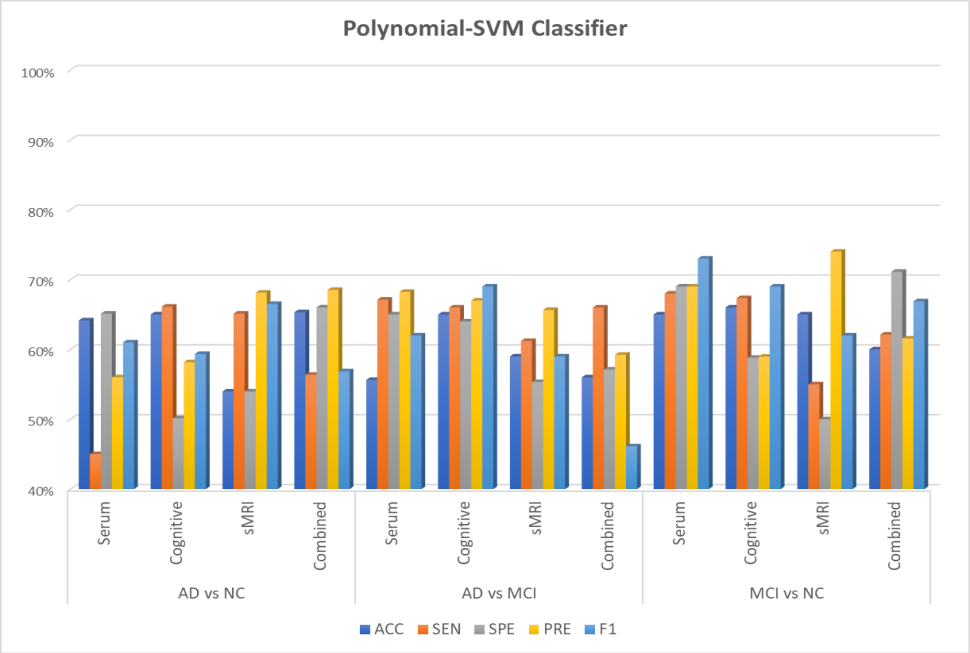

Figure 5.2. Classification result with Polynomial-SVM classifier

5.2.3 Linear-SVM result

Linear kernel SVM is used when the data is linearly, that is, it can be separated using single line. It is one of the most common kernels to be used. It is mostly used when there are many features in a dataset. One of the examples where there are a lot of features is text classification, as each alphabet is new feature. So, mostly Linear kernel SVM is utilized in Text classification. In this kernel mostly cognitive score classified well.

Table 5.3. Classification result of Linear-SVM classifier

Linear-SVM classifier						
Confusion metrics		**ACC**	**SEN**	**SPE**	**PRE**	**F1**
AD vs NC	**Serum**	60%	60%	80%	100%	74.99%
	Cognitive	91.42%	100%	82.35%	85.71%	92.30%
	sMRI	68.57%	75%	60%	71.42%	73.17%
	Combined	77.14%	72.41%	100%	100%	84%
AD vs MCI	**Serum**	60%	60%	80%	100%	74.99%
	Cognitive	93%	84.23%	95.12%	92.11%	96%
	sMRI	60%	60%	85%	100%	76%
	Combined	60%	60%	81%	100%	75%
MCI vs NC	**Serum**	47.61%	45%	50%	45%	45%
	Cognitive	80.12%	86%	89%	90%	88%
	sMRI	76.19%	75%	77.27%	75%	75%
	Combined	61.90%	60%	63.63%	60%	60%

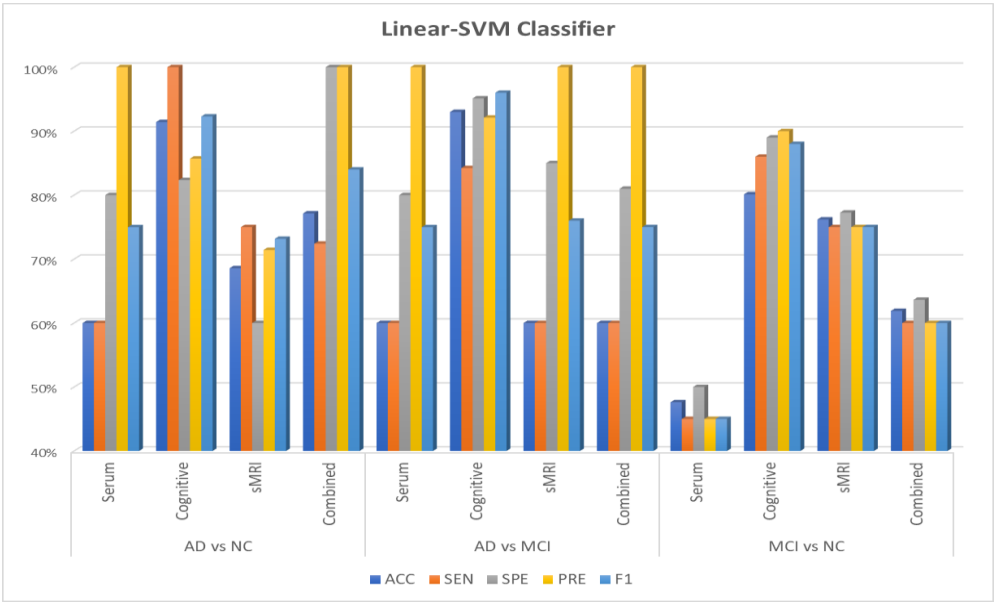

Figure 5.3. Classification result with Linear-SVM classifier

5.2.4 K-Nearest Neighbor result.

Table 5.4. Classification result of KNN classifier

KNN classifier						
Confusion metrics		**ACC**	**SEN**	**SPE**	**PRE**	**F1**
AD vs NC	**Serum**	65.71%	68.18%	61.53%	75%	71.42%
	Cognitive	97.14%	95.23%	100%	100%	97.5%
	sMRI	74.28%	70.37%	87.5%	95%	80.85%
	Combined	65.71%	68.18%	61.53%	75%	71.42%
AD vs MCI	**Serum**	68.57%	68%	70%	85%	75.55%
	Cognitive	96.24%	94.12%	99%	99%	98.02%
	sMRI	62.85%	61.29%	75%	95%	74.50%
	Combined	71.42%	70.83%	72.72%	85%	73.27%
MCI vs NC	**Serum**	57.14%	54.54%	60%	60%	57.14%
	Cognitive	80.36%	89.12%	95%	96%	97.68%
	sMRI	80.95%	73.07%	93.75%	95%	82.60%
	Combined	66.66%	60.71%	78.57%	85%	70.83%

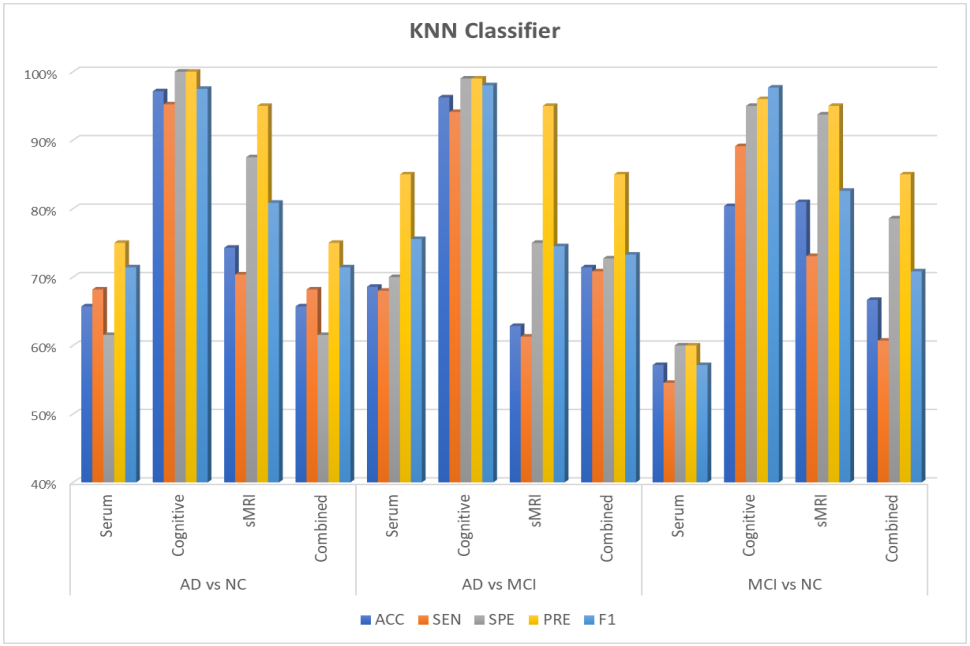

Figure 5.4. Classification result with KNN classifier

In this machine learning classification shows also better result for cognitive score with almost all groups. According to AD vs NC cognitive score shows the best accuracy among other groups like 97.14%.

5.2.5 Random Forest result.

The Random Forest classifier consists of several a bunch trees, with each tree grown utilizing some shape of randomization. Every internal node covers a test that best splits the space of data to be classified. An image is distinguished by sending it down every tree and combining the reached leaf disseminations. Randomness could be inserted at two points during training: in subsampling the training data so that each tree is rising using a dissimilar subset and in choosing the node tests. In case of this classifier the cognitive score is classified better than other groups but still it not as well as RBF-SVM. The highest accuracy gained 91.67% for AD vs NC based on cognitive score.

Table 5.5. Classification result of Random Forest classifier

Random Forest classifier						
Confusion metrics		**ACC**	**SEN**	**SPE**	**PRE**	**F1**
AD vs NC	**Serum**	70.83%	68.42%	80%	92%	78.79%
	Cognitive	91.67%	100%	83.33%	85.71%	92.31%
	sMRI	75%	72.22%	83.33%	92.86%	81.25%
	Combined	54.17%	56.52%	68.25%	92.86%	70.27%
AD vs MCI	**Serum**	52.17%	55.56%	40%	76.92%	64.52%
	Cognitive	73.91%	73.33%	75%	84.62%	78.57%
	sMRI	43.48%	50%	48%	69.23%	58.06%
	Combined	52.17%	55%	33.33%	84.62%	66.67%
MCI vs NC	**Serum**	53.57%	53.33%	53.85%	57.14%	55.17%
	Cognitive	85.71%	85.71%	85.71%	85.71%	85.71%
	sMRI	67.86%	63.16%	77.78%	85.71%	72.73%
	Combined	78.57%	72.22%	90%	92.86%	81.25%

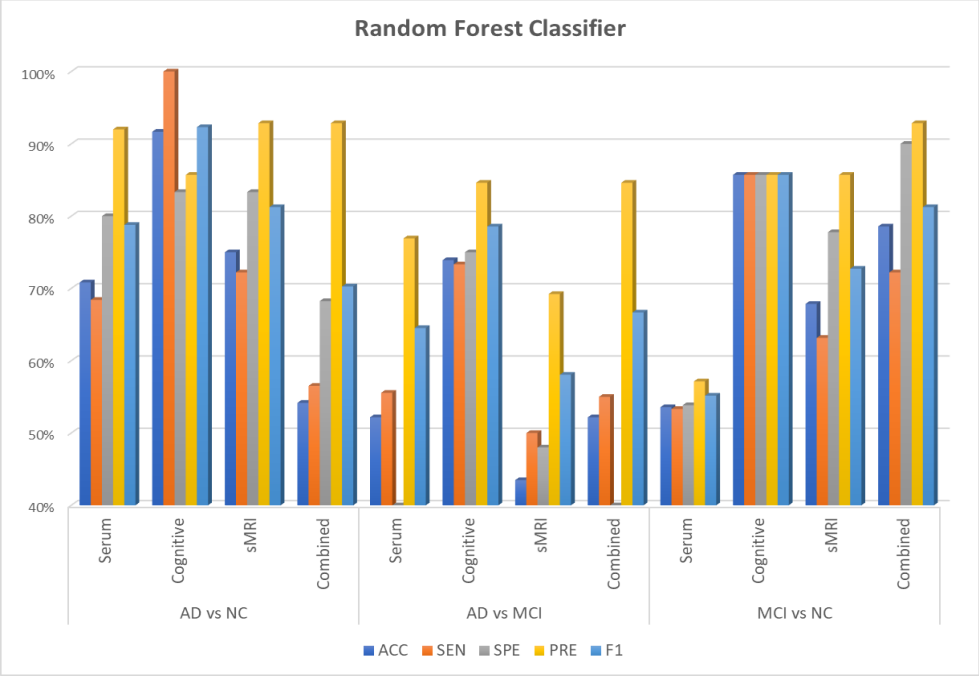

Figure 5.5. Classification result with RF classifier

5.3 Discussion

In this proposed method, we demonstrated the statistical analysis and form classification to distinguish and recognized atrophy pattern for three groups (AD, HC, MCI). The separated sMRI were preprocessed utilizing MALPEM toolbox. After completing preprocessing process then we fused with serum autoantibody blood-borne biomarker and cognitive score and finally we did classification by using RBF-SVM classifier.

In previous related works there has been a great agreement of investigation importance on the examination for blood-borne biomarkers suggestive of AD pathology, but most efforts have found only limited success.[74] The some studies have exposed that autoantibodies are astonishingly many in human sera irrespective of age or disease. Disbelieving that these autoantibodies might show a role in neurodegenerative ailments, we required to regulate if the attendance of continuing pathology reasons variations in the spectrum of autoantibodies current in the serum. If so, then maybe these deviations could be utilized to classify exact autoantibodies that are valuable as analytic indicators or biomarkers. [75-76] DeMarshall C. el.at [77] researcher used human protein microarrays to describe the difference appearance of serum autoantibodies in AD and non-demented control (NDC) groups and they recognized possible analytical biomarkers for AD. In the subsequent they designated individual 10 autoantibody biomarkers that could successfully distinguish AD sera from NDC sera with 96.0% of sensitivity and 92.5% of specificity. Lei Xu. el.at [78] researcher utilized the prediction of AD by using of support vector machine method founded on gene-coding protein order material. According to their method, the regularity of two successive amino acids is utilized to label the categorization data. The accuracy of the planned

technique for recognizing AD was 85.65% and AUC was 85.7%. Fang Yao.el.at [79] they composed tissue-based gene expression information of AD patients and healthy controls from GEO database. Then it is examined, recognized, and applied a blood-secretory protein estimation program on these genes and foretold AD-related proteins in blood. Finally, they composed blood examples of AD patients and healthy controls to confirm the potential AD biomarkers by using ELISA researches and Western blot examination. They achieved 93.2% of AUC. In our case, we did classification each of biomarkers and final stage we combined all in one used RBF-SVM classifier. Except RBF-SVM kernel for comparison we implemented our work with other kernels such as Linear and Polynomial. Moreover, we compared our work with some machine learning algorithms and among all our model achieved the highest accuracy for MCI vs NC. The RBF-SVM achieved for MCI vs NC with combined method 97.62% accuracy and 100% sensitivity,97.44% F1 score compare to single modality sMRI, seruma protein and cognitive score. Polynomial-SVM gained for MCI vs NC with combined method 60% accuracy, 62.12% sensitivity and 66.89% F1 score. Furthermore, Linear-SVM achieved for AD vs NC with combined method 77.14% accuracy, 100% specification, 100% precision. In another machine learning case, KNN showed low result in multimodality compare to single modality. For instance, AD vs NC with cognitive score 97.14% accuracy, 100% specification and 100% precision. Moreover, in Random Forest illustrated AD vs NC with cognitive score 91.67% accuracy, 100% sensitivity 92.31% F1 score in single modality compare to multimodality.

6. Conclusion

In this approached method, I have implemented machine learning model like RBF-SVM for classification of AD with other diagnostic groups. In this experiment, I have proposed three binary classification problems such as: AD vs HC, AD vs MCI, MCI vs HC and I have utilized ADNI dataset. According to experiment result, it is illustrated that the fusion of three imaging and non-imaging biomarkers which are (sMRI, SerumaAab protein, Cognitive score) increases AD prognosis. Moreover, it is given result that excessive probable to predict early of the mild cognitive impairment (prodromal stage of the Alzheimer's disease). In this approach, we proposed the PCA feature selection technique for combined features and used RBF-SVM classifier that increase significantly the performance of classifier. For machine learning approach, I have utilized three kinds of features (Cognitive score, SerumaAab protein, and volumetric volume). I did classification with Radial Basis Function based Support Vector Machine classification technique with help of 10-fold Stratified cross-validation model and attained good result for MCI vs NC group compare to other groups.

In conclusion, the consequences verified that the fusion of three measures form sMRI, cortical thickness, subcortical volumes, SerumaAab blood protein and cognitive scores (MMSE, FAQ, CDR, GDS, and NPI-Q) improve AD diagnosis, also it is shown that excessive probable to early clarification of the mild cognitive impairment (prodromal stage of the Alzheimer's disease). In this approach it is projected the PCA features selection with RBF-SVM classifier for the manifold biomarkers-based AD analysis which meaningfully advance the classifier's performance. Furthermore, the results were illustrated became better or satisfactory compare to the earlier literatures, epically for the

greatest inspiring classification task for instance AD versus MCI and HC. The extra value of merging dissimilar anatomical MRI measures ought to be measured in AD scanning protocols. There is commonly repetition to solitary utilize the precise portion or a sole measure of entire brain atrophy for AD prediction. The attained results demonstrate that medical AD judgement could advantage from manipulative manifold measures from an anatomical sMRI scan with non-imaging biomarkers and integrate these altogether in an automatic machine learning classification. The recommended technique in this thesis successfully encourages the analysis accuracy of AD and MCI, nevertheless this process has some disadvantages. In the future, this disadvantage will be contained the development from below parts: Firstly, we will try to enhance parameter for gaining better procedure for prognosis of Alzheimer's disease. Secondly, in order to increase the efficiency of the recommended technique the database will be enlarged which we will extend the longitudinal database for the well understanding of evolution of Alzheimer's (AD), covering the different kind of imaging and non-imaging modality and to use the specific parts of brain which affect easily such as Hippocampus, amygdala and cortex from sMRI and fMRI anatomical images that may give the dissimilar distinguishing statistics of the brain abnormality.

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