Early Detection of Alzheimer’s Disease

Using Image Processing on MRI Scans

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Abstract—**Alzheimer‘s disease (AD) is an irreversible and progressive brain disease that gradually destroys memory and thinking skills to an extent that it starts affecting the daily life. It has become the most common cause of dementia among older people. The work presented in this paper evaluates the utility of image processing on the Magnetic Resonance Imaging (MRI) scans to estimate the possibility of an early detection of AD. The total brain atrophy and specifically the hippocampal atrophy are considered strong diagnostic tests for AD. T1 weighted MRIs have been used for the purpose of image processing to evaluate atrophy. The paper demonstrates the applications of several image processing techniques such as K-means clustering, wavelet transform, watershed algorithm and also a customized algorithm tailored for the specific case. It has been implemented on the open source platforms, OpenCV and Qt, which facilitates the implementation and utility of the developed product in the hospitals without requiring any proprietary software. The results obtained from the project could aid the analysis to detect AD along with correlation with the psychiatric results and could thus assist the doctors in detecting AD at an early stage. This could progressively help in understanding and treating AD.**

Keywords: Alzheimer’s disease; image segmentation; atrophy; hippocampus; dementia; MRI

I. INTRODUCTION

Alzheimer’s disease is an irreversible, progressive brain disease that slowly destroys memory, thinking skills and in later stages, intellectual abilities. In most people with Alzheimer’s, visible symptoms first appear after age 60. Alzheimer's disease accounts for 50 to 80 percent of dementia cases. The damage to the brain in Alzheimer’s begins a decade before the symptoms are noticeable. Early symptoms include atrophy of the hippocampus. It belongs to the limbic system and its most important functions are the consolidation of information from short-term memory to long-term memory and spatial navigation. Humans and other mammals have two hippocampi, one in each side of the brain. The hippocampus is a part of the cerebral cortex, and in primates is located in the medial temporal lobe, underneath the cortical surface.As the disease progresses, all affected areas of the brain begin to shrink.

Alzheimer’s, if diagnosed early, can facilitate timely access to diagnosis and health care. The clinical indication for an earlier diagnosis would provide critical time for medical intervention and diagnosis to be made. The interventions work better, when carried out earlier [1].

Current work in this area can be mainly divided into Neuropsychological markers and structural imaging markers. Another method is implemented using Biomarkers but this method is not particularly popular as it is considered invasive. Neuropsychological markers broadly include 1) Community based study and 2) Studies of individuals with Mild Cognitive Impairment (MCI) who are at risk of AD. In case of structural imaging, studies have shown that atrophy of the medial temporal lobe, including the hippocampus and entorhinal cortex are sensitive markers of AD [2]. Currently, automated segmentation is difficult because hippocampus is a small and tightly folded elongate structure without any clear boundaries and due to this, many researches and radiologists still use manual sketching of the hippocampal area so as to be able to detect its volume. Using the manual tracing methods a large number of experiments have been conducted thereby confirming the accuracy of using atrophy of the medial temporal lobe. One such research [3], calculated mean cerebral volume, mean hippocampal volume and the normalized volume between the control subjects (healthy subjects) and the patients. Here, results have shown that hippocampal volume in early AD patients were 13.9% lower than in control subjects.

When region segmentation and feature selection was tested on a group of people (including equal number of control subjects and AD patients) along with clinical results a high accuracy of 90% was achieved in the classification [4]. But it is to be noted that this experiment included clinical results which is usually not available in the early stages of AD. Another experiment [5], which involved manifold based learning techniques (automated), gave the following results: sensitivity-94%, and accuracy 56.1%.

Along with the above, medical history and mental status evaluation is done by the psychologists as they recommend patients of AD for further brain study based on these tests. There are many standardized sets of tests which are used specifically for this purpose. Also, sets of questionnaires are asked to the relatives of those who are affected [6].

This work explores brain atrophy and hippocampal atrophy as indicators of AD and concludes that hippocampal atrophy is a better early indicator for Alzheimer’s because overall atrophy can also occur due to other reasons like age and alcoholism. In present context, to detect atrophy in the brain, eyeballing of the MRI scan is the most popular method, but using this method it is mainly possible only to notice the atrophy at very advanced stages (if atrophy of the overall brain is being considered). In cases where the atrophy of only the medial temporal lobe is to be considered it is possible to miss the shrinkage due to human error. In confirmed cases, functional MRIs (fMRI) are also carried out along with EEGs but most of these results only confirm the presence of Alzheimer's and not detect it.

The paper is organized as follows - Section 2 outlines the basic techniques used to extract the region of interest, the segmentation techniquesused to isolate the segments corresponding to the grey matter and white matterand the methodology followed to calculate the brain volume. It then presents the end tool, available to the user as open source implementation, and its user interface. Section 3 consolidates the results from the data set and the resulting analysis that is validated by the doctors.

II. PROCEDURE

A series of image processing steps were applied on the MRI scans to arrive at the volume calculations. These steps were -

A. *Boundary Detection*

One of the initial steps to analyze the MRI scans is to clean up the MRI scan so as to isolate the grey matter, white matter and Cerebrospinal Fluid (CSF).To do this the cranium has to be approximately erased from the scan. For this purpose, boundary detection algorithms were used to detect the cranium and widen the boundary edge till only the required region of interest (ROI) was visible. This method was used after testing with the sample data as mentioned below to ensure that only ROI was visible after widening the boundary.

B. *K-means*

Following the selection of ROI from the scan, the image had to be segmented so as to be able to separate the grey matter, white matter and CSF in case of Brain volume calculation and also to segment the hippocampus (grey matter) in the case of hippocampal isolation.

K-means was used as it is one of the simplest unsupervised learning algorithms that solve the well-known clustering problem. The procedure follows a simple and easy way to classify a given data set through a certain number of clusters (assume *k* clusters) fixed a priori. The main idea is to define *k* centroids, one for each cluster. These centroids should be placed carefully because of different location causes different result. So, the better choice is to place them as far away from each other. The next step is to take each point belonging to a given data set and associate it to the nearest centroid. When no point is pending, the first step is completed and an early grouping is done. At this point we need to re-calculate *k* new centroids as barycenter of the clusters resulting from the previous step. After we have these *k* new centroids, a new binding has to be done between the same data set points and the nearest new centroid.

The algorithm is composed of the following steps:

1) Place *k* points into the space represented by the objects that are being clustered. These points represent initial group centroids.
2) Assign each object to the group that has the closest centroid.
3) When all objects have been assigned, recalculate the positions of the *k* centroids.
4) Repeat Steps 2 and 3 until the centroids no longer move. This produces a separationof the objects into groups from which the metric to be minimized can be calculated

C. *Sample Set*

MRI scans of 25 volunteers referred to the Department of Radiology, Kasturba Medical College, Mangalore, by Department of Psychiatry, Department of Neurology and Department of Geriatrics were studied. Cases involving stroke, brain tumors, physical brain damage and those not willing to give consent for study were excluded from the study. The subjects included 16 men and 9 women aged between 16 to 83 years (Mean - 48.32 years; Standard deviation - 16.27 years). They were neurologically intact and had no systemic disease. MRI imaging was performed using a 1.5-T MRI machine. T2 tirm flair MRI images were acquired for each subject along the axial plane. The MRI scans are captured at regular intervals known as slice thickness which is dependent on the MRI machine being used. Smaller slice thickness gives greater accuracy and greater details for image processing. Each set of axial scans used here contained 22- 26 slices of 6.5mm slice thickness. On these scans, clustering and segmentation algorithms were used with *k*=8 and *k*=10 to calculate grey and white matter volume of the brain and to isolate the hippocampus in particular slices of the MRI respectively.

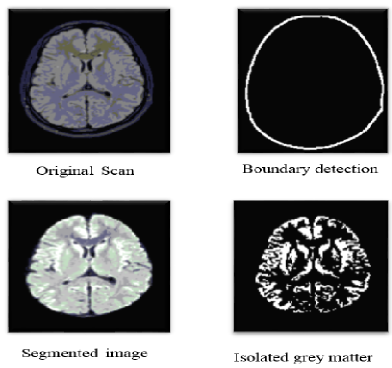


Fig.1 Steps in brain volume calculation

D. *Image processing algorithms*

1) Brain Volume Calculation

Slice Area calculation - using k-means segmentation: To calculate the brain volume (grey matter + white matter), the main concept used is 1) Boundary detection (to select ROI) and 2) K means segmentation (to isolate the grey and white matter). This is done by segmenting the brain into n parts and selecting the relevant clusters. Fig. 1 shows the results of applying boundary detection, segmentation and isolation on a single MRI slice. This procedure is iterated over all the slices and area is calculated taking into account the pixel:image resolution ratio.

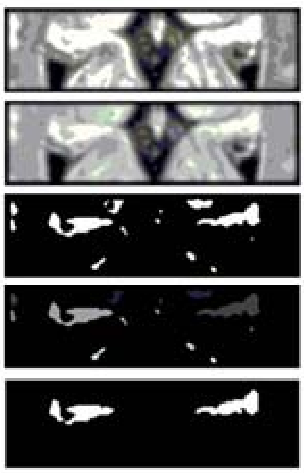
Volume calculation: The grey matter and white matter in each slice are isolated using the segmentation techniques. The volume of grey matter and white matter is calculated using the slice thickness by applying the trapezoidal rule. Slice thickness is the attribute of the MRI scans dataset which refers to the gap between consecutive scans (the tested data uses slice thickness of 6.5mm).

Separation into grey and white matter: Once again, to separate the brain volume into grey and white matter, clustering is done through K-means segmentation and the relevant clusters are selected for each following which the volume is calculated in the above described manner.

2. Hippocampal Volume using Interactive regionselection

Selection of ROI: Interactive region selection is a concept used to let the user determine the ROI as per their requirement. In this case, it was used to determine the approximate region of the hippocampus so as to further isolate it. Here the ROI selection was done with the help of OpenCV [7] tools and libraries. Once the ROI was selected, the algorithm was run on the selected region. This was done for 3- 4 slices where the hippocampus is predominantly visible. Once the hippocampus was isolated for each slice, the area for that slice was calculated and multiplied by the slice thickness so as to obtain the volume.

Hippocampal selection in a defined ROI: Once the ROI is selected, the following steps select and calculate the area of the hippocampus in a given slice. The results obtained at each step are shown in Fig. 2.



a) Region of interest isolation

b) Segmentation

c) Binary Image

d) Bounded regions separation

e) Hippocampal isolation

Fig. 2 Steps of hippocampal isolation

a) The ROI was established in a particular slice and cropped out. The noise was then removed on the image using averaging filters.(Fig. 2a)
b) Considering the knowledge that the hippocampus is made of grey matter and that grey matter appears lighter in T2 axial images, histogram equalization was carried out on the image so as to increase the contrast.Following this, K-means segmentation was applied on the ROI. (Fig. 2b)
c) The segment indicating the grey matter content was masked and isolated. (Fig. 2c)
d) Following this, all the pixels were scanned from left to right, top to down so as to isolate all connected regions into a label, thereby separating regions of the same image according to boundary, similar to watershed algorithm. (Fig. 2d)
e) Finally, knowing that the hippocampii would be the largest grey matter content in the selected ROI, the area of each labeled region was found and the 2 regions with maximum area were retained and selected as the hippocampii. (Fig. 2e)
f) The area is now calculated by using the pixel: image ratio.

Hippocampal Volume calculation: The final volume of the hippocampus is calculated similar to the brain volume calculation. The area of the hippocampus is taken from each slice and multiplied with the slice thickness. But this method has certaininaccuracy in the case of hippocampal volume as the hippocampal is a very small and tightly folded structure, and is visible in very few slices (2-5). Thus the volume calculated is highly approximated. But the accuracy of the volumeincreases as the number of slices of the brain increases in the scans.

E. OpenCV Implementation

This project was initially designed and tested on the MATLAB platform. However, MATLAB is a proprietary platform and it is very unlikely that the hospital laboratories would be equipped with MATLAB. Owing to the growing demand for open source implementations and the associated benefits, the image processing algorithms mentioned above were ported from MATLAB to OpenCV 2.2. Moving in the same direction, another open source platform namely the Qt was selected to provide an attractive end user interface so that the entire software could be used by a non-technical personnel.

There are two solutions the program offers; the first being to calculate the overall brain (gray and white matter) volume and the second, to calculate the volume of the hippocampii. The K-means code was successfully implemented and tested using OpenCV and C/C++ libraries and the segmentation results obtained matched with the MATLAB results.Many other functions such as convolution, erode, dilate, RGB to grayscale, region extraction, area calculation etc. were required for the OpenCV implementation, most of which, were composed explicitly with customized attributes to fit our requirements and more importantly to be on par with the library functions.

Brain volume calculation is implemented in OpenCV with K-means as the basic segmentation technique and other functions to aid the process. The program segments the MRI scan into gray matter and white matter and calculates the area of each segment. The challenge in the process is the associated noise and the cranium which hampers the segmentation.

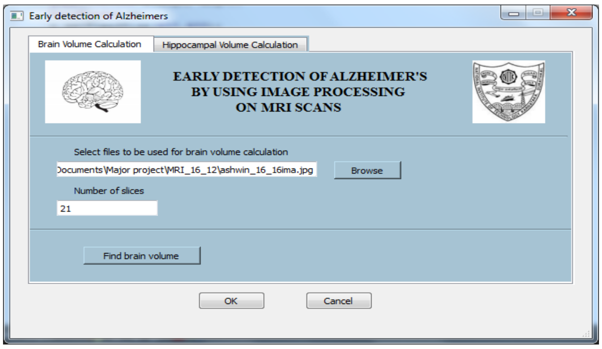


Fig. 3 Screenshot of the application user interface created

Filtering and eroding techniques to overcome these challenges and to improve the accuracy. The process is iterated for all the MRI scans (usually 22) and the volume of the gray, white matter and overall brain volume are calculated. The end solution is available as a Win32 executable file which can be run on any system without any software requirement. The output indicates the gray matter, white matter and the total volume of the brain. The hippocampal isolation and volume calculation process works on similar lines but with some challenges and differences. The hippocampii present in the brain constitute a small part of the brain but the hippocampal volume is a vital indicator in the detection of Alzheimer's disease. Owing to the small size of the hippocampii and the noise present in the MRI it is difficult to isolate the hippocampii. Filtering techniques are utilized to reduce the noise and the image is cropped interactively to further reduce the error probability. The user is expected to mark the smallest rectangular region containing the hippocampii using the selection tool. This further enhances the accuracy of the algorithm. Finally the 2 parts of the hippocampii are isolated and the area of the same are calculated. The process is repeated for a series of MRI scans containing the hippocampii and the volume of the hippocampii is estimated. The output of the program is the volume of the hippocampii. These volumes calculated can be considered approximate as there are errors introduced due to data loss when DICOM images provided by the MRI machine is converted to bitmap format and when the trapezoidal rule is applied for volume calculation.

The figures corresponding to the brain (grey and white) and hippocampal volume in comparison with the standard statistical data help in understanding the condition of the patient and if he/she is prone to Alzheimer's disease.

F. Qt Implementation

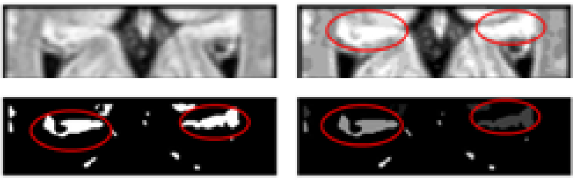
Since the end users of this application are doctors, a user interface has to be provided to abstract theimplementation details from the user. Qt is a cross platform application framework which is widely used to develop application software with graphical user interface. A simple user interface was developed for the brain volume calculation and hippocampal isolation through which the user could select the slices of interest and feed it to the application. Separate application tabs were provided for hippocampal and brain volume calculations. Fig. 3 shows the end application for use by the doctors.

TABLE 1.GREY AND WHITE MATTER VOLUMES

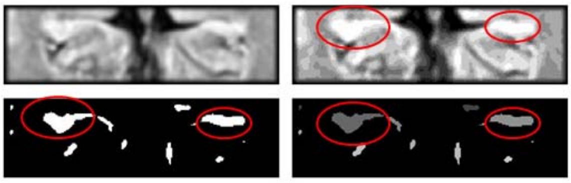
Sample No.	Sex	Age	Brain Volume	Grey Matter Volume	White Matter Volume	Comments
1	M	16	872	433	439	Healthy
2	M	20	1063	634	429	Healthy
3	F	34	1027	495	532	Healthy
4	F	35	1062	543	519	Healthy
5	M	35	1158	521	637	Healthy
6	M	35	1152	560	592	Healthy
7	F	43	1088	537	551	Healthy
8	F	43	985	451	534	Healthy
9	M	45	1050	481	569	Healthy
10	M	47	1021	413	608	Healthy
11	M	48	1040	485	555	Healthy
12	M	49	1076	398	678	Atrophy possible AD
13	F	52	1035	519	506	Healthy
14	M	54	1032	454	578	Healthy
15	M	55	921	433	488	Atrophy
16	F	63	1031	495	536	Healthy
17	M	65	962	435	527	Atrophy
18	M	66	1026	511	515	Healthy
19	M	68	980	447	533	Atrophy
20	M	70	920	354	566	Atrophy, possible AD
21	F	78	810	312	498	AD
22	F	83	821	258	563	Atrophy, Possible AD

III. RESULTS

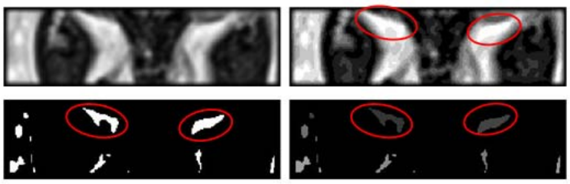
The two targeted processes namely the brain volume and the hippocampal volumecalculation have been implemented successfully. The results for brain volume calculation are as shown in Table 1. The comparison of the grey and white matter in each case helps us conclude as to whether the patient is healthy, going through atrophy due to age or AD. In case of healthy patient the brain volume corresponds to that of a healthy brain i.e. without atrophy. In case ofatrophy due to age, the difference between the gray matter and white matter volume is not significant and so it is possible to distinguish between atrophy due to age and atrophy due to Alzheimer's. In case both the overall brain volume is less and the difference between the gray matter and white matter volume is higher, then it is most likely a case of Alzheimer's. For instance, Patient no. 18 – Atrophy; Patient no. 19 – atrophy and possible AD; Patient no. 20 – huge difference in gray to white matter ratio and hence confirmed AD. In the case of hippocampal isolation, the devised algorithm, which uses watershed and filtering, is seen to isolate the hippocampus. These results validated by the doctors. This algorithm takes into consideration the ROI where the hippocampus is present thereby ensuring that it is generalized and applicable to all cases and interactive segmentation is used to improve the accuracy. Hippocampal volume is a vital parameter in the detection of Alzheimer's and the comparison of its volume along with the overall volume of brain provides a very strong ground for the detection of Alzheimer's disease. The methods have been tested on several data sets obtained from the hospital and the resultshave proved the efficiency of the algorithms. The vital step of the hippocampal isolation at every slice has been demonstrated in Fig. 4. Overall these techniques create a tool which serves as an aid to the doctors in their diagnosis.



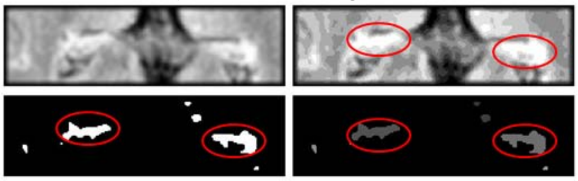
a) Patient 7, F, Age:43



b) Patient 8, F, Age:43



c) Patient 22, F, Age:83



d) Patient 12, M, Age:49

Fig. 4 Hippocampal Isolation

IV. CONCLUSION

The paper has demonstrated the novel application of image processing to derive a useful effective end product that can assist the doctors in their diagnosis. All the tool features described in this paper have been crafted on consultation with the doctors and have also been experimentally verified. This tool can also serve as a teaching aid for the medical students to validate their understandings. The open source feature of the work encourages other engineers to build on this and create better technologies for medical science. The use of image processing for medicinal diagnosis and research is extensively growing and thus improving the lives of people. We believe that our work has contributed in this direction and hope that it will be helpful to both the technical and the medical community.

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