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A Study & Review on Exploration of Multiple Sclerosis : Automatic vs. Conventional MRI modalities approach

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ABSTRACT :

Among various neurological disorders, Multiple sclerosis (MS) is an auto-immune, demyelinating disease in which the myelin sheath or the insulating covers of nerve cells in the brain and the spinal cord are damaged by the self immune system. Due to this damage the ability of various parts of the nervous system disrupts, that includes physical, mental, and sometimes psychiatric problems. In this disease, the body's immune system attacks the protective covering surrounding the nerves of the central nervous system (CNS).Due to these attacks, various damages occur to the tissues, which are also known as Lesions, sometimes called scars or plaques, are the hallmarks of multiple sclerosis. Until and unless any symptom of this disease occurs, there is no significant tool to diagnose it, except MRI. Scars or Lesions detected by MR(Magnetic Resonance) sequences confirms the diagnosis of the disease as well as helps to monitor the evaluation of the disease along with the efficiency of the therapies being used to treat it.

To monitor the progression of the disease, the change in the lesion load is necessary to be determined on the criteria of volume, shape, location and size. Thus, to study the change in the behavior of lesions, it is necessary to divide them in segments. Analysing the results of Magnetic Resonance, there have been conventional, semi-automatic and automatic segmentation methods. Also few latest methods have been proposed to reduce the complexities that occur due to manual segmentations.

This research work studies various methods of Lesion segmentation and reviews the various proposed methods in the literature.

Keywords - Multiple sclerosis; Lesions segmentation, MRI, Automatic segmentation, Electromyography, Isometric Contraction, White Matter, Grey Matter, Cerebrospinal Fluid.

INTRODUCTION :

Multiple sclerosis (MS) is a disease in which the body's immune system attacks the protective covering surrounding the nerves of the central nervous system (CNS).According to recent surveys, it is one of the common disease, affecting young and adults, causing disability and more than 2.5 million in the world are suffering from the same and this number is rapidly increasing. MS appears with symptoms such as lack of vision, abnormal gait, squint, and neurological disorder. However in the acute phase, the organ paralysis and even blindness is expected. Early detection of MS and estimation of its progression are critical for optimal treatment of the disease. There's no single definitive test that can diagnose MS. Diagnosis is based on symptoms, clinical evaluation, and a series of diagnostic tests to rule out other conditions. But out of all, Magnetic resonance imaging (MRI) is an important tool in diagnosing MS. It can reveal about the scars, also called lesions, on the brain or spinal cord. MRI is also used to monitor disease activity and progression. In todays technological era, the technique of magnetic resonance in

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medical diagnosis has also improved. Earlier, manual segmenting of the lesions was possible through MR, but since a huge amount of data is required to be analyzed , the manual method becomes time consuming. Hence, the automatic segmentation of MS lesions in brain and spinal cord comes out as a positive solution.

Recently, a number of segmentation methods have been presented. The suggested method by Souplet et al. is one of the most significant ones. They used brain atlas to register the T1-weighted (T1-w) and T2-w images. They computed the belonging value of each voxel to the three different tissues; gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Resulted values were used to initiate Gaussian mixture model (GMM) parameters to segment all the three (T1-w, T2-w, T2-fluid attenuation inversion recovery [T2-FLAIR]) image sequences. Then Mahala Nobis distance between voxel intensity and average intensity in each class was computed and in comparison to a constant threshold, lesions were detected. Although this approach was robust against noise and in homogeneity, it fails when there are several lesions and also it does not show satisfying performance in brain atrophy cases. Complexity and time-consuming registration task are other drawbacks of this method.

For example Subbanna et al. presented a fully automated framework to identify the MS lesions in multi-channel MRIs. Manual segmented images were used to extract intensity histograms of both tissue and lesions. Then multivariate Gaussian distributions were estimated from the histograms and by using Markov random fields (MRFs) the classification of brain tissue and lesions was done. This method relies on manual segmentation, which may carry human error and also it needs to be trained for new image sequences.

Khayati et al. combined an adaptive mixtures method means, MRF and a Bayesian classifier to simultaneously classify the three main brain tissues and the MS lesions using only FLAIR images. In particular, they first proposed to segment the brain into four classes, means: WM, GM, CSF and "others". Afterward, inside the "others" class, lesions were detected as outliers, which have not correctly explained by the model. They used only FLAIR image while MS lesions may appear independently in different images.

His clinical symptoms result of demyelination of nerve fibers in the brain, spinal cord and optic nerve. It is characterized by both multifocal lesions in the white matter (WM) and gray matter (GM), and can diffuse more in the parenchyma. The most classic symptoms are physical manifestations: eye signs (loss of vision in one eye, orbital pain, and double vision), motor disorders (balance problems, paralysis etc.), sensory disturbances (tingling, neuralgia, hyperpathia).

The lesions have different localizations and various manifestations from a patient to another and even in the same clinical case from one developmental stage to another. Until today, there is no typical diagnosis of MS. Doctors rely on a set of clinical and biological details and MRI images. The foundations of the diagnosis of MS are based on proving the existence of focal lesions on MRI (dissemination in space) and the arrival of new ones (dissemination in time).

The identification and the segmentation of MS lesions constitute an essential step in illustrating the MS disease burden and in calculating, evaluating and deducing more specific processes of loss. The arrival of computer and the incorporation of new digital techniques of medical imaging facilitate the

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localization, the segmentation and the counting of lesions. First of all, the procedure was totally manual. This makes more time consuming and lets a huge intra- and inter- expert variability. Then many semi-automatic segmentation methods have been proposed in order to reduce both of these factors. Eventually, the purpose is to make automatic techniques that can treat big number of images effectively. In these 15 years, many methods were proposed but no one was extensively used.

The remaining of this paper is organized as follows: in section II we present the localization of MS Lesions. Then, in section III, we revise their aspects in MRI sequences. After that, in section IV, we remind the general principle of lesion segmentation. Hereafter, we review several MS lesion segmentation methods. Finally, we would end up with a conclusion and suggest some perspectives.

LOCALIZATION OF MS LESIONS ON CONVENTIONAL MRI

Typically, the lesions are characterized by a more or less intense contrast, and the appearance of necrotic area in the center surrounded by edema.

A. Periventricular lesions

These are typical lesions of MS. They are usually large, spreading over a diameter of 5 to 10 mm, frequently having a corona structure but with different shapes. Their detection is often easy when they are well contrasted in their central areas. However, their contouring is difficult since they endow complex shapes.

B. The juxtacortical lesions

They are usually small, low contrasted and having spherical or ellipsoidal shape. Their appearance is a discriminative criterion asserting the existence of the disease. Their detection is often difficult, particularly in T2-FLAIR sequences, when the lesion size is smaller than the slice thickness and reproducing consequently a low contrast.

C. Cortical lesions

They include juxtacortical lesions diffusing into the adjacent GM, and lesions occurred in the cortex. They are well detected by diffusion MRI.

D. Necrotic lesions

These are old lesions having a central necrotic area similar to liquid and returning a signal similar to CSF. For periventricular lesions, necrotic area is often ignored because it is confused with the ventricles.

ASPECTS OF MS LESIONS IN MRI SEQUENCES

Different MRI imaging modalities provide a classification of lesions into three main categories:

A. Chronic hypointense areas on T1w sequences Black holes seen in a T1w MRI may correspond to a lesion in severe inflammatory state, accompanied or not with tissue damage, and can be enhanced by injection of gadolinium. Also, a persistent black hole reflects the presence of a lesion, a chronic demyelination and axonal loss.

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B. Active lesions

o They include transitional hyposignals on T1w sequences: Some non-persistent hypointense areas indicate acute inflammatory lesions. These temporary lesions can be better visualized by the injection of contrast.

o Hyperintense lesion on T1w images enhanced with gadolinium: Active lesions prove the existence of ruptures of the blood-brain barrier and acute inflammation. These lesions correspond to hypointense areas in GD-T1w sequences. The same areas appear hyperintense in T2w images. The appearance of these lesions enhanced is the most determinative indicator of the disease activity.

C. Common lesions

Some lesions appear only on T2w and PDw images as hyperintense areas. This duo weighted sequences is essential for the affirmation of infringement by the affection. In addition, it provides a means of lesion load assessing that reflect the evolutionary stage of the disease and indicate the effectiveness of therapeutic trials.

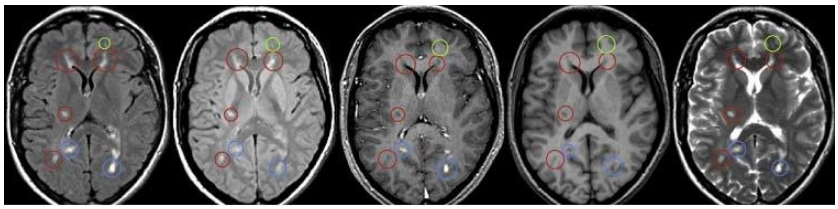

Fig. 1. MS lesions on MRI

Various types of MS lesions are present: (blue) Enhancing lesions, (green) T 2 lesions, (red) black holes. Many brilliant regions are observed on Gd-T1 and FLAIR MRI. Mostly, they are mislabeled as lesions .

GENERAL PRINCIPLE OF LESION SEGMENTATION

The estimation of lesion load returns to count lesions and assess their volume. This requires detecting and defining these lesions in the images. Several methods of semi-automatic and fully automatic segmentation have been developed over the years in order to divide points of the image into "lesion" or "non-lesion". To achieve this purpose, the segmentation is often tarted by a detection step followed by a contouring one.

A. The MS lesions detection phase This step consists in determining the existence of lesion or not in a very specific place called "region of interest". In the context of diagnosis, this step requires a high level of experience. Thus, the doctor often removes uncertain lesions in order to avoid unnecessary treatment.

B. MS lesions contouring phase This step targets volume measurement of certain lesions. The difficulty lies in the accuracy of the contours particularly for active lesions. In fact, these new lesions are being characterized by an inflammatory edema indicating the break of the blood- brain barrier. Consequently, the intensity within the lesion changes slowly and it is difficult to distinguish its outline from the edema. However, in old lesions, there is no edematous area, and then the edges are commonly well mixed and easier to spot. On the other hand, a manual contouring is often difficult to be generated and wastes a lot of time. This encourages developing semi- automatic and even automatic techniques for

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the extraction and the quantification of multiple sclerosis and similar diseases. But the creation of such system is tedious, and diversification can lead to different results.

MS LESIONS SEGMENTATION APPROACHES

During these few years, several methods of MS lesions segmentation have been proposed. These methods have in purpose to segregate points of the image into "lesion" or "non-lesion". Among these techniques, there are those manual, semi-automatic and automatic. Generally, the analysis of these methods divides them in four principal categories of approaches that are successively: simple segmentation and contour detection, segmentation by hierarchical clustering, segmentation by direct classification, and selective segmentation which focuses on active lesions.

A. Simple segmentation and contour detection

This approach is based on the specific signals related to MS lesions in various types of MRI sequences in order to their detection and then their segmentation. The remaining brain tissues in the images are not processed. Indeed, depending on the type of lesions and the MRI sequence used, sclerosis plates are manifested in the form of hypo or hyperintense areas. Thus, the application of a threshold allows locating and delineating various existing lesions. But the success of this method depends mainly on the choice of the threshold. In semi- automatic methods, the user locates a lesion by pointing to its center. Thereafter, a local threshold is applied. The choice of the local threshold can be manual or automatic. Other methods use global thresholds for the localization of active lesions in GD-T1w.

Similarly, the regional minima have been used to identify low signal intensity corresponding to the lesions appearing on T1w image. The problem with using global threshold methods is the incorporation of false positives in the segmentation. They correspond to zones returning no plate but having a similar signal. Thus, manual intervention is required to remove them. While, the region growing algorithm can refine lesion's contour, other methods use a priori knowledge to distribute voxels into groups according to their characteristics such as intensity or their coordinates.

B. Segmentation by hierarchical clustering

In this approach, a first step is to separate the image points into two classes: first class encompassing voxels parts of healthy tissue corresponding to the non-pathological WM, GM and CSF, and another class with the residual voxels that are not classified in the first category. Then, the points of the second class are divided in turn into two sub-classes: lesion and non-lesion. For the latter classification, two strategies have been proposed. The first is the use of a priori knowledge for the classification of voxels in the WM. The other method compares the voxel to be classified with those of the GM on T1w image and those of CSF on T2w image, and if they have similar characteristics, they will be labeled as lesions.

In this approach, the phase of healthy tissues Identification in a sequence allows characterizing them in order to recognize them in new sequences and subsequently makes easy the determination of irregular areas. In this context, some methods suggest the use of masks for the various brain tissues to facilitate the detection of anomalies.

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C. Segmentation by direct classification

In this approach, the voxels of the brain are directly divided into four main classes that are: CSF, WM, GM and lesions. Often, these methods require a prior pretreatment step to reduce classification errors caused by noise such that the partial volume. A variety of methods have been proposed depending on the number and types of MRI sequences used. Some of them employ T2w and DPw images to build masks for lesions and WM relating to each of those two modalities. Combining between the masks corresponding to several types of images gives chance to a better identification of true lesions and eliminating aberrations. Some works use the T1, T2 and PD weighted MRI sequences and are based on processing chains using classifier such as neural network .

Other methods use T2w and T2-FLAIR sequences to distinguish between CSF and tissues of the brain parenchyma. Then the brain parenchyma is divided into WM, GM and lesions with referring to a DPw sequence .

D. Selective segmentation

The methods included in this family are used as part of the longitudinal study and monitoring of the disease progression. For this, they are interested in the changes that have occurred on a series of temporally separated images. They aim to discover the damage in continual development in terms of size, shape and locating. The easiest way is to calculate the difference between the images. Mutations can be obtained by a simple threshold of calculated images or by statistical methods of locating transformations .Other methods of comparing the various images are based on the analysis of a strain field. Indeed, the areas presenting the greatest deformation correspond to active lesions. Furthermore, the value of the transformation determines the lesion load variations in quantity and volume. Some methods are interested in the study of the variations of intensity curves related to each of the voxels present in the multitude of images to examine. The regions associated to curves that return the largest part of changes, coincide the most likely with the lesions. Other techniques offer extra study of the curves related to adjacent voxels in order to refine the classification by using T2w image or various sequences .

Proposed Method :

In this study, we introduce a new automatic MS detection strategy. It does not need atlas or training database and overcomes defects of previously mentioned methods. The proposed procedure has four stages in order to segment the brain tissues and MS lesions. The first stage is pre-processing which includes intensity in homogeneity correction and skull removing. In the second stage, which is called the brain tissue classification, the brain tissues are classified into three classes of WM, GM, CSF, and some voxels will be rejected as outliers. In the third stage, candidate lesions are detected from outliers with the Mahala Nobis distance and in the fourth stage; MS voxels are separated from the candidate lesion.

Database :

Our database images were acquired from two different hospitals in Isfahan to evaluate the performance of the proposed automatic segmentation of brain tissues and lesions in different scanning machines. Twenty-five patients were scanned by using the same protocol of T1-w, T2-w, and T2-FLAIR. All the

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images were acquired by two 1.5-T MR systems and in axial view with the slice thickness of 5 mm. The patients were between 11 and 45 years old and the same imaging protocol was used for them.

PRE PROCESSING :

To reach better and accurate segmentation, some preprocessing steps such as skull removing and intensity inhomogeneity correction are needed. So, in this step, these pre-processing were done as the followings.

Intensity Inhomogeneity Correction

Intensity inhomogeneity in raw MRIs leads to incorrect segmentation results. This inhomogeneity is because of the small varying biased field (BF); so that voxels with same coordinate have different intensities. Intensity inhomogeneity changes the mean and variance of image intensity in a particular area of the image which decreases the segmentation accuracy. Since BF alters slowly, it only contains low frequencies and, as a result, blurs the images (or destroys high frequencies). The real aim of inhomogeneity correction is to restore these high frequencies to the images.

LPF method is effective and faster in comparison to the other similar intensity correction methods, which use an optimization phase to find the biased field. Results of all stages of this algorithm have been illustrated in image

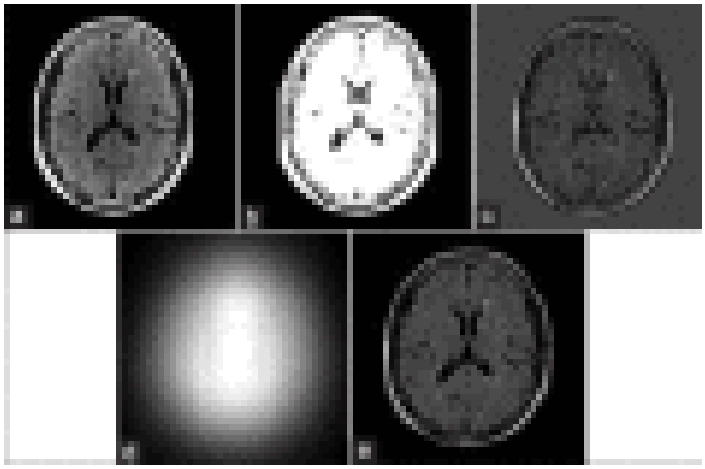

Fig 2. Result of intensity inhomogeneity correction, (a) input image, (b) automatic determination of the threshold lower level and segmentation of the input image to data (white) and background (black), (c) filling the noise locations with the average image

Skull Removing :

Because of the similarity between skull intensity and other tissues of the brain, it may affect the segmentation phase and usually it is removed from brain image. Since the skull is more obvious and detectable in T1-w, we used this image to detect the exact location of skull and remove it from all three image sequences. The skull is brighter than other brain parts and usually has a component with no rupture. Therefore, we used the morphological operation to extract and remove the skull. The first operation is detecting the connected component as shown in third portion of above image As it has been

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seen, skull is extracted as the first connected component. After removing this component from the brain image, still there are many pixels, which do not belong to GM, WM, and CFS, they are remains of the skull. Otsu's threshold algorithm was applied to detect brighter pixels as remains of the skull shown in fourth part of above image. After these two phases, some remote and unconnected pixels remains which can be removed by morphological operation such as erosion, dilation, and filling. Results of each phase of this process have been shown below:

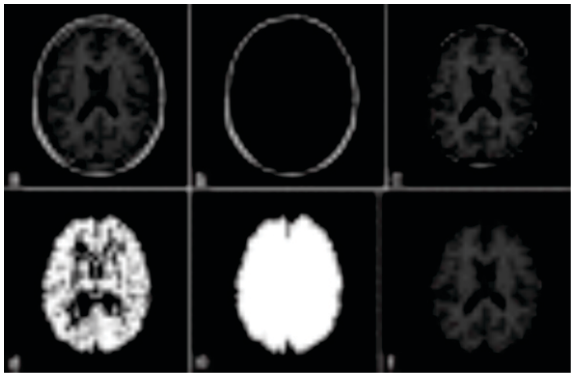

Fig 3. Result of skull removing, (a) is the brain image of one of the 25 patient which were studied in this research, (b) the first component of the image, (c) removing the first component of the image, (d) the processed image after applying Otsu's thresholding

Brain Tissue Classification :

Brain can be classified into three distinct classes; WM, GM, and CSF. Assuming that intensity variation in each class has Gaussian distribution, we used GMM to separate these classes from each other. In GMM, K Gaussian distributions (three classes in this work) are considered and each sample (voxel) belongs to the class, which maximizes the probability distribution function. GMM parameters (covariance matrix and mean of each class) should be determined during the classification process. The first step is registering T1- w to T2-w and T2-FLAIR so that each sequence has the same number of voxels and each voxel in one sequence exactly corresponds to the same voxel in other sequences.

Hierarchical Initialization :

To make EM robust against initial point selection, we tried to choose a reasonable start point instead of random ones. GMM was applied to segment only T1- w image with 100 different starting points with the maximum iteration of 50. Segmentation results were used to calculate the parameters of other two images. Since we limited the maximum iteration and only used T1-w image, simulation time decreased considerably and also the initial points were reasonable and not random. For the random initial parameters, the mean of each class is randomly drawn using a uniform distribution between the minimum and maximum of the image and the standard deviation of each class is set to a third of the standard deviation of intensities of the whole image.

After computing the mean and variance of each class for T1-w image, we clustered each voxel of T1-w and other two images too. Initial mean of tissues were set to mode value of these histograms. Furthermore, variance of each tissue (class) for T2-w and T2-FLAR images was estimated as follow:

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$$\sigma_{s,t}^2 = \left(1.4918\, med\left(\left|x_i - \mu_{t,s}\right|\right)\right)^2 \qquad (10)$$

Where t belongs to (GM, WM, and CFS) and s is one of the T2-w and T2-FLAR images and med is median operation. Now, we have all start parameters to initiate the EM algorithm and find the best parameters so that classify each 3D voxel and be sure that EM will converge to optimum maximum more likely.

The trimmed likelihood (TL) was used instead of likelihood to make our process robust against outliers and also FAST-trimmed likelihood estimator (FAST- TLE) was applied to make it faster.

Trimmed Likelihood :

The basic idea consists in maximizing the TL instead of the likelihood.In other words, the likelihood is only computed with the voxels that most likely belong to the model. Hence, we need to do another optimization in order to determine which samples are remote enough and do not fit the model. To speed up this process, we applied FAST-TLE.In this method, first h samples were considered as outliers, randomly and GMM parameters were estimated. In the second step, f(xv(i)) was computed and samples with less f(xv(i)) value were considered as new outliers. These two steps were done till outlier set does not change anymore. It should be noticed that h value should be large enough to guarantee that all MS regions and tissue artifact will be detected and stored in outlier set. In this research, we set h to 10% of all pixels of the sample image. The final result of this step is an outlier set and three different classes and each sample belongs to one of these four sets. MS voxels belong to outlier set and should be extracted from this set.

CONCLUSION :

In this paper, we proposed a new strategy to initiate EM algorithm without any atlas in order to reach accurate results and make the algorithm to converge rapidly. GMM was applied to segment only T1-w image with 100 different starting points where the maximum number of iteration was considered to be 50. Also, the heuristic rules were applied to reject some false alarms and find real MS. These rules help the algorithm to reject the errors introduced by GMM. We used T1-w image sequence to extract the needed information to find initial set points, which reduce the risk of being trapped in local optimums. We used FLAIR image sequence as a standard protocol to detect and locate MS lesions. Even though this sequence is sensitive to periventricular lesions, it is less sensitive to the lesions in posterior fossa, which may increase FP errors. Hence, we used T2-w as complimentary sequence to improve segmentation performance. Our method does not need any atlas or training images. In contrary to the previous methods, which use only image intensity to find MS, we tried to take the advantage of other structural and local information such as size and shape of lesions, which improved segmentation results considerably. Intensity based segmentation can be easily affected by noise and artifact. Doing many experiments and searches, we found optimum values of all thresholds.

Unfortunately, we were not able to compare our approach to other similar methods because of two main reasons. First of all, different studies used different database and second, any MS segmentation algorithm parameters were adapted for especial MR protocol. However, in the researches of Subbanna

et al and Khayati et al.,which were mentioned in the literature, DSC values have been reported as 0.71 and 0.75, respectively, while in our method this parameter was averagely more than 0.82. The results showed better performance of the proposed approach, compared to those of previous works and these results were confirmed by two radiologists. Our purpose in future studies is to provide segmentation procedures that can treat all cases in spite of the type of MS, duration of the disease, or MRI protocol, and which can be incorporated into a complete and consistent framework.

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