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# Segmentation and volume quantification of MR Images for the detection and monitoring multiple sclerosis progression

Styliani P. Zelilidou, Evanthia E. Tripoliti, *Senior Member IEEE*, Kostas I. Vlachos, Spyridon Konitsiotis, Dimitrios I. Fotiadis, *Fellow IEEE*

***Abstract*— Multiple Sclerosis (MS) lesions detection and disease's progression monitoring at the same time, play an important role. The purpose of this research is to demonstrate a method for detecting MS plaques and volume estimation from MR Images for monitoring the progression of the disease and the brain atrophy caused. In the proposed research, a clustering-based method is utilized in order to delineate MS plaques in brain, based on anatomical information, brain geometry and lesion features. In addition to volumetric information concerning lesions and whole brain volume, volume quantification is employed to estimate MS atrophy by measuring Brain Parenchymal Fraction (BPF). In the present study, Fluid Attenuated Inversion Recovery (FLAIR) images were utilized for the detection of MS lesions and BPF evaluation, while T1-weighted MR Images utilized in volume estimation. 30 MS patients were included in a dataset consisted of 3D FLAIR and T1-weighted MR images in order to evaluate the proposed technique. MRI scans performed in two different clinical visits, a baseline and a visit after 6 months. The results extracted in segmentation of MS lesions in terms of sensitivity is 73.80 %. The BPF at baseline estimated to 0.82 ± 0.01, and at 1st follow up, 0.83 ± 0.01. Finally, the brain volume loss between baseline and after 6 months is 0.4%.**

***Keywords*— MRI segmentation, brain atrophy, progression estimation, multiple sclerosis**

## I. Introduction

Multiple Sclerosis (MS) can be characterized as a chronic heterogeneous autoimmune demyelinating disorder of the Central Nervous System (CNS), a condition with a long and uncertain clinical history that progresses to impairment over time. MS causes the breakdown of myelin sheaths on neuronal axons, leading signal transmission to be disrupted in various areas of the CNS. As a result, clinical evidence vary depending on the location and the severity of the disease, followed by loss of vision, balance, or memory, fatigue, walking difficulties among other. [1].

Demyelination occurs as a result of the disease, affecting mostly the white matter of the brain or spinal cord, characterized as lesions, which can be observed on a Magnetic Resonance Image (MRI). There are many methods to diagnose MS disease including clinical tests, laboratory tests, lumbar puncture, but the most sensitive, more accurate and non-invasive method is MR Imaging. Also, MRI scans allows the experts to evaluate the patients' reaction to medical therapy, determine the course of disease and the inability caused physically or mentally [2].

Several approaches have been developed over the last few years, for segmenting MS lesions on brain MR Images and estimating brain volume. A brief description of MRI segmentation techniques in MS is presented in the study of M. Shanmuganathan *et al.* [3], where a classification on the segmented methods is discussed. In the MICCAI challenge 2016 several approaches are examined by Commowick *et al.* [4]. Finally, an extensive study on volume atrophy and brain parenchymal fraction is presented by M. Vågberg [5].

In the proposed approach, the main purpose is the MS plaques detection and monitoring the course or the disease based on volumetric information. For this purpose, extensive research on how volume quantification can provide information about the diseases' course and the impairment caused is presented, in addition to a previous published work [6]. The whole process is performed automatically, without the user intervention allowing the implementation of a computer aided tool providing to the experts all the necessary information for the assessment of the patient.

## II. Materials and Methods

### A. Dataset

30 MS patients were recruited at the baseline and 29 in the follow up in the Neurological Clinic of University Hospital of Ioannina, while the MR Images were acquired by the Ippokratio Ioanninon S.A, within ProMiSi project [7]. The project's aim is to develop a tool for the detection of MS lesions and study the progression of the disease, by utilizing brain atrophy information. Prior to the procedure, the patients completed a written informed consent form (University Hospital of Ioannina, Ethic Committee Name: The board of the University Hospital of Ioannina Approval Code: 16/9-5-2019 Approval Date: 9/05/2019).

The proposed approach evaluated by utilizing a dataset consisted on 3D MRI FLAIR and T1-weighted images,

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D.I. Fotiadis is with the Unit of Medical Technology and Intelligent Information Systems, University of Ioannina, GR 45110, Ioannina, Greece and FORTH, GR 45110, Ioannina, Greece (phone: +302651009006, e-mail: fotiadis@.uoi.gr).

S. Zelilidou and E. Tripoliti are with the Unit of Medical Technology and Intelligent Information Systems, Dept. of Materials Science and Engineering, University of Ioannina, GR45110, Ioannina, Greece (e-mail: stylianizelil@gmail.com, etripoliti@gmail.com).

S. Konitsiotis is with the Dept. of Neurology, Medical School, University of Ioannina, GR45110, Ioannina, Greece (e-mail.: skonitso@gmail.com)

K. Vlachos is with Ippokratio Ioanninon S. A., GR45333, Ioannina, Greece (e-mail: kovlahos@gmail.com)

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acquired from 30 MS patients. Manual annotation performed in all of the 30 FLAIR images, by an expert radiologist in order to delineate MS lesions. All brain images were acquired on a MRI scanner, 1.5 Tesla Siemens Achieva Nova. The 3D FLAIR MRI consists of 180 contiguous sagittal 1 mm slices and T1-weighted images consist of 110 contiguous sagittal 1.3 mm slices. As a follow up study, both MRI sequences acquired at a first visit (baseline) and a follow up visit after 6 months. It should be noticed that one patient left the study on the 1st follow up visit.

### B. *Lesion Segmentation – The Proposed Technique*

The pipeline of the proposed methodology, as it analyzed on a previous published study [6], is depicted in Fig 1. However, further analysis on the volumetric quantification and brain atrophy estimation is presented below.

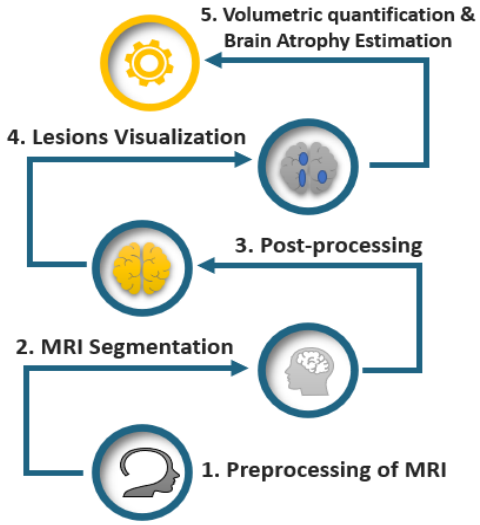


Figure 1. Pipeline of the proposed approach.

*Preprocessing*

Preprocessing step is followed by three stages: i*mage denoising* (Fig. 2b), in which a spatially adaptive non-local means is applied in the initial image (Fig. 2a) [8], s*kull stripping* for extracting the brain (Fig. 2c), i*mage enhancement* of the skull stripped image in order to enrich its contrast by applying the Partitioned Iterated Function Systems (PIFS) [9] (Fig. 2d).

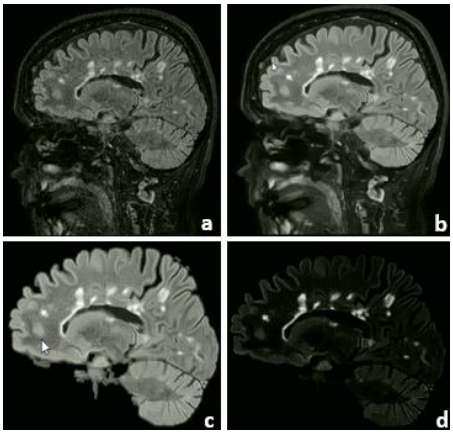


Figure 2: Example of the pre-processing steps. (a) Initial Image, (b) Denoising Image, (c) Brain extraction, and (d) Enhanced Image.

*Segmentation of MS plaques*

K-means algorithm [10] utilized for the detection of MS plaques, constituting the suggested technique's main step. For more accurate lesion detection, the number of clusters is set equal to 5. In the output cluster, the regions of interest are detected, furthermore false positives are delineated.

*Post - Processing*

The post-processing step, consists of eight rules, which implemented for further elimination of false positives. The rules are based on information about different lesion features such as intensity, anatomical location, size and texture information. MS lesions occur in different brain areas, however the corpus callosum, the ventricle and the cerebellum are the main areas of interest, based on medical findings and clinical tests. For that reason, the elimination rules are based on the anatomical location of MS lesions, their size, intensity, and texture information.

*Eliminating rules of false positives*

The rules resulted, based on different lesion features, are implemented on the FLAIR MR Images in order to remove objects that are not characterized as MS plaques [6].

*MS lesions visualization*

After the implementation of the rules, the delineated lesions are projected in the initial image. In the output image, the delineated areas are demarcated with blue color. Fig. 3 depicts an example of the defined plaques and a comparison is made with the manual annotation of the radiologist. Manual annotation is performed on each slice by the expert delimiting each time the lesions.

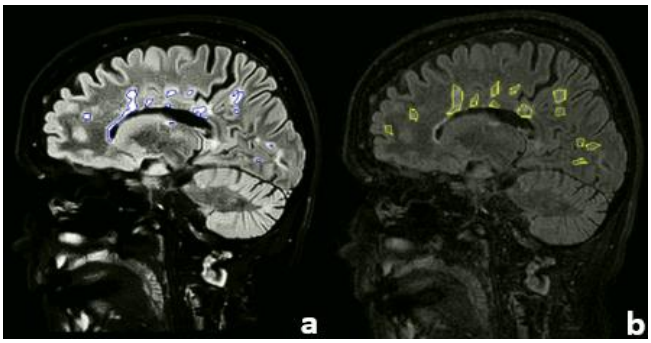


Figure 3: (a) Lesion Segmentation of the proposed method, (b) Manual Demyelination.

*Volumetric and Brain Atrophy Estimation*

Information on brain atrophy and lesions volume can be provided in volume quantification step. When the lesion load is determined, information on the lesions volume can be obtained. Lesion load refers as the number of the lesions that are detected on a MRI scan, and is crucial for the evaluation of the diseases' activity, and disability caused by MS.

An estimation of the lesion load is performed in each patient in this study based on the true positives of the final segmented image, while plaques' number estimation accomplished manually by the expert, an example of the

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comparison among the segmented image and the annotated on a patient's slice is depicted on Fig. 4. Manual annotation performed on the FLAIR images on each slice of the dataset by the expert, delimiting each time the occurring lesions.

Brain Parenchymal Fraction provides information on the brain atrophy on most neurodegenerative diseases, among them the disease of MS, while information on the disease's impairment can be achieved [5]. Brain Parenchymal Fraction calculation is the main indicator for monitoring MS progression and for estimating the atrophy caused by the disease.

Three steps are included on the proposed approach for calculating the BPF. Firstly, the MRI scans of FLAIR sequence are utilized for segmenting the brain in white matter (GM), gray matter (GM) and cerebrospinal fluid (CSF). Segmentation of the 3D FLAIR image into the three tissues, GM, WM and CSF, achieved by the implementation of a Gaussian mixture model proposed by Ashburner et al. [11]. The Bayesian rule is used to assign on each voxel a probability of belonging to a particular class of the brain tissue, WM, GM and CSF. The rule is based on the intensity of voxels that correspond to a certain brain tissue, as well as information from prior probability maps built by a large number of data points. Then, for each brain tissue, GM, WM and CSF, volume is calculated as:

$$TissueVolume = \sum_{i=1}^{n}\left(Pixel_{no} \cdot {Pixel_{sp}}^{2} \cdot Slice_{th}\right) \quad (1)$$

where, $n$ is the number slices in the MRI scan, $Pixel_{no}$ refers to the total number of the pixels calculated in each slice, $Pixel_{sp}$ is the distance between the centers of each two-dimensional pixel and $Slice_{th}$ is the thickness between the slices of the FLAIR image. In our case, slice thickness is 1 mm and pixel spacing is 0.5729 mm, on the FLAIR MRI sequence.

The final step is the quantification of the brain parenchymal fraction utilizing Eq. (2).

$$BPF = \frac{V_{GM}+V_{WM}}{V_{GM}+V_{WM}+V_{CSF}} \quad (2)$$

where $V_{GM}$: volume of gray matter, $V_{WM}$: volume of white matter, and $V_{CSF}$: volume of cerebrospinal fluid.

Finally, whole brain volume is estimated by utilizing T1-weighted images. Brain volume is a three-step approach, where in the first step segmentation of the T1-w image into gray matter, white matter and cerebrospinal fluid, is performed as described above, based on the study of Ashburner et al. [11]. Volume of each tissue is calculated based on Eq. (3)

$$Vol_{tissue} = \sum_{i=1}^{n}(white_{pixel} \cdot {Pixel_{sp}}^{2} \cdot Slice_{sp} \quad (3)$$

where $n$ is the number slices in the T1-w image, $white_{pixel}$ refers to the total white pixels in each slice, $Pixel_{sp}$ describes the distance between the centers of each two-dimensional pixel and $Slice_{sp}$ is the slice thickness between slices. In the T1-w image pixel spacing is 0.7971 mm and slice thickness 1.3 mm.

Whole brain volume is calculated in the third step, using Eq. (4).

$$V = \sum(V_{WM} + V_{GM} + V_{CSF}) \quad (4)$$

where, $V_{GM}$ is the volume of gray matter, $V_{WM}$: volume of white matter, and $V_{CSF}$: volume of the cerebrospinal fluid.

## III. RESULTS

Lesion load estimation is reported in Table I, which compares the proposed study to manual annotation and describe the lesions number at the Baseline, and the 1st Follow Up. As a result of the remyelination of MS areas and the fact that some of the plaques appear higher intensity than baseline, after 6 months, the number and the size of the lesion has decreased.

TABLE I. LESION LOAD

| | Baseline | 1st Follow Up |
|---|---|---|
| **Manual Annotated Lesions** | 8179 | 7397 |
| **Proposed Methods' Lesions** | 6032 | 4993 |

For each patient, an estimation of brain atrophy is performed at baseline and during the 6-month follow-up (Table II). The mean BPF in baseline was 0.82 ± 0.01, and in the follow up, 0.83 ± 0.01. Based on the study presented by M. Vågberg [5], the results are very promising. However, for an objective estimation of brain atrophy, a second follow up visit (12 months) could provide more information. The third visit is currently under progress, and the results will be available soon.

TABLE II. BRAIN PARENCHYMAL FRACTION

| Patient | BPF/patient (Baseline) | BPF/patient (1st Follow up) |
|---|---|---|
| **001** | 0.830 | 0.830 |
| **002** | 0.853 | 0.850 |
| **003** | 0.861 | 0.856 |
| **004** | 0.766 | 0.770 |
| **005** | 0.830 | 0.830 |
| **006** | 0.761 | 0.760 |
| **007** | 0.839 | 0.870 |
| **008** | 0.772 | 0.780 |
| **009** | 0.771 | 0.790 |
| **010** | 0,773 | 0.754 |
| **011** | 0.829 | 0.856 |
| **012** | 0.913 | 0.900 |
| **013** | 0.825 | 0.812 |
| **014** | 0.880 | 0.884 |
| **015** | 0.769 | 0.767 |
| **016** | 0.799 | - |
| **017** | 0.864 | 0.831 |
| **018** | 0.782 | 0.757 |
| **019** | 0.897 | 0.877 |
| **020** | 0.815 | 0.834 |
| **021** | 0.878 | 0.890 |
| **022** | 0.890 | 0.879 |
| **023** | 0.890 | 0.890 |
| **024** | 0.819 | 0.858 |
| **025** | 0.787 | 0.837 |
| **026** | 0.851 | 0.883 |
| **027** | 0.871 | 0.868 |
| **028** | 0.819 | 0.824 |
| **029** | 0.769 | 0.747 |
| **030** | 0.837 | 0.842 |

The whole brain volume estimation was performed on each patient individually and is compared with the manual volume estimation (Table III). Manual volume estimation is performed

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on each slice by delimiting the brain, then the volume is estimated by computing the intensity and geometric properties in the image [12]. The average difference from month 0 to month 6 was small and only 0.4% of brain volume is reduced, yet MS patients lose 0.5 to 1.35% of brain volume per year [13,14], for that reason brain volume loss could be more accurate when the 2nd follow up is completed.

TABLE III. BRAIN VOLUME

| Patient | Volume Baseline (ml) | Manual Volume Baseline (ml) | Volume 1st Follow up (ml) | Manual Volume 1st Follow up (ml) |
|---|---|---|---|---|
| **001** | 1521.9 | 1540.7 | 1530.0 | 1508.0 |
| **002** | 1526.1 | 1513.2 | 1526.1 | 1424.4 |
| **003** | 1773.8 | 1606.7 | 1773.7 | 1667.4 |
| **004** | 1387.1 | 1342.9 | 1353.2 | 1400.9 |
| **005** | 1242.3 | 1188.3 | 1248.9 | 1232.2 |
| **006** | 1197.1 | 1279.8 | 1182.9 | 1208.3 |
| **007** | 1337.3 | 1216.5 | 1314.7 | 1293.4 |
| **008** | 1453.8 | 1410.4 | 1429.3 | 1438.3 |
| **009** | 1370.7 | 1384.2 | 1386.8 | 1423.1 |
| **010** | 1144.8 | 1200.8 | 1113.2 | 1201.5 |
| **011** | 1380.6 | 1377.6 | 1377.9 | 1378.4 |
| **012** | 1489.7 | 1291.8 | 1462.0 | 1336.9 |
| **013** | 1833.4 | 1688.7 | 1823.0 | 1711.6 |
| **014** | 1300.9 | 1245.8 | 1200.0 | 1312.3 |
| **015** | 1426.7 | 1347.3 | 1325.3 | 1401.3 |
| **016** | 1331.6 | 1448.0 | - | |
| **017** | 1535.8 | 1387.5 | 1319.6 | 1248.4 |
| **018** | 1693.6 | 1576.6 | 1384.8 | 1523.6 |
| **019** | 1556.4 | 1530.5 | 1642.5 | 1455.6 |
| **020** | 1424.9 | 1506.0 | 1556.4 | 1492.6 |
| **021** | 1624.5 | 1455.6 | 1438.2 | 1498.4 |
| **022** | 1610.5 | 1484.3 | 1664.0 | 1459.9 |
| **023** | 1467.2 | 1465.6 | 1641.1 | 1394.9 |
| **024** | 1358.0 | 1319.1 | 1440.9 | 1381.2 |
| **025** | 1592.5 | 1401.0 | 1378.6 | 1467.0 |
| **026** | 1585.0 | 1445.9 | 1602.0 | 1521.0 |
| **027** | 1371.8 | 1377.0 | 1571.7 | 1348.1 |
| **028** | 1385.7 | 1297.2 | 1346.2 | 1297.2 |
| **029** | 1385.7 | 1485.8 | 1385.0 | 1486.7 |
| **030** | 1469.0 | 1366.7 | 1472.3 | 1383.8 |

## IV. CONCLUSIONS

To conclude, the proposed approach is based on several lesion characteristics, information about the brain areas where the MS lesions appear, and clinical experience. The key to audit the clinical course of MS and the inability that is caused, can be provided mostly on volumetric estimation of brain images in relation to the plaques and MS brain atrophy. As a result, measuring the BPF and the lesion load can be used to estimate the progression and disability caused by MS disease.

The proposed approach is very promising since it is validated on two different datasets, and because of the comparison with the manual segmentation. Moreover, on the first dataset, the sensitivity score is 73.80 %, while on the MICCAI dataset is 71.52%. The sensitivity resulted in Knight et al. [15] is 0.53, Tomas-Fernandez et al. [16] had a score of 0.62±0.19, whilst a score of 0.72 achieved in the presented technique.

As brain atrophy is related to clinical outcomes in MS, the proposed volumetric quantification could provide important information concerning the disease's impairment and treatment efficacy. The extracted results are quite promising, however more accurate estimation can be provided when the 2nd follow up is completed.

Our future aim is the development of a tool that delineates MS lesions, estimates brain volume and lesion load, while an assessment of the diseases' progression can be achieved, by taking into consideration the provided information from the delineated plaques and BPF calculation, among the baseline and the follow-up MRI scans.

## REFERENCES


[1] Marisa P. McGinley et al., *Diagnosis and Treatment of Multiple Sclerosis A Review*, JAMA, Vol.325, p.765-779, 2021

[2] S. Isoglu, *Comparative Multiple Sclerosis Lesion Segmentationin Magnetic Resonance Images*, Electric Electronics, Computer Science, Biomedical Engineerings Meeting (EBBT), IEEE, 2017

[3] M. Shanmuganathan, *Review of advanced computational approaches on multiple sclerosis segmentation and classification*, IET Signal Processing, Vol. 14, Is. 6, p. 333-341, 2020

[4] O. Commowick, *Objective Evaluation of Multiple Sclerosis Lesion Segmentation using a Data Management and Processing Infrastructure, Nature Scientific Reports*, Vol. 8, p. 1-17, 2018

[5] M. Vågberg, *Brain parenchymal fraction in healthy individuals and in clinical follow-up of multiple sclerosis*, Umeå University, 2016

[6] S. Zelilidou, *Segmentation of MR Images for the delineation and monitoring of multiple sclerosis progression based on clustering method*, 2021 IEEE 21st International Conference on Bioinformatics and Bioengineering (BIBE)

[7] E. Tripoliti, *ProMiSi Architecture - A Tool for the Estimation of the Progression of Multiple Sclerosis Disease using MRI*, 2019 IEEE 19th International Conference on Bioinformatics and Bioengineering (BIBE)

[8] J.V. Manjon, *MRI denoising using Non-Local Means*, *Medical Image Analysis*, Vol.12 p.514–523, 2008

[9] G. Koutsouri, *Image contrast enhancement through regional application of partitioned iterated function systems*, *Journal of Electronic Imaging*, Vol. 22, p. 013-033, 2013

[10] T. Mitchel, Machine Learning, Singapore: McGraw-Hill, 1997

[11] J. Ashburner et al., *Voxel-based morphometry — the methods.* Neuroimage Vol.11, p. 805-21, 2000.

[12] A. Fedorov et al., *3D Slicer as an Image Computing Platform for the Quantitative Imaging Network*., Magnetic Resonance Imaging, Vol. 30, No 9, p.1323-41, 2012

[13] N. De Stefano, *Clinical Relevance of Brain Volume Measures in Multiple Sclerosis*, CNS Drugs Vol.28, p.147–156, 2014

[14] R.G. Steen, *Measuring Brain Volume by MR Imaging: Impact of Measurement Precision and Natural Variation on Sample Size Requirements*, American Journal of Neuroradiology, Vol. 28, No.6, p. 1119-1125, 2007

[15] J. Knight, *MS Lesion Segmentation Using FLAIR MRI Only*, In: Proceedings of the 1st MICCAI Challenge on Multiple Sclerosis Lesions Segmentation Challenge Using a Data Management and Processing Infrastructure — MICCAI-MSSEG, O. Commowick, F. Cervenansky, and R. Ameli (Eds), 2016.

[16] X. Tomas-Fernadez, *A New Classifier Feature Space for an Improved Multiple Sclerosis Lesion Segmentation*., IEEE International Symposium on Biomedical Imaging: From Nano to Macro, p.1492-1495, 2011


Manuscript 461 submitted to 2022 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society . Received January 24, 2022.