# Accurate Segmentation of Tumorous Regions in High-Grade Glioma Employing a Multi-parametric (ADC/PWI/T2-W) Image Fusion Approach

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## ABSTRACT

**Purpose:** Glioblastoma Multiforme (GBM) brain tumor is heterogeneous in nature; so, its quantification depends on how to accurately segment different parts of the tumor, i.e. active tumor, edema and necrosis. This procedure becomes more effective when physiological information like diffusion-weighted-imaging (DWI) and perfusion-weighted-imaging (PWI) are incorporated with the anatomical MRI. In this preliminary tumor quantification work, the idea is to characterize different regions of the GBM tumors in an MRI-based multi-parametric approach to achieve more accurate characterization of pathological regions, which cannot be obtained by using individual modalities.

**Methods:** For this purpose, three MR sequences, namely T2-weighted imaging (anatomical MR imaging), PWI and DWI of five GBM patients were acquired. To enhance the delineation of the boundaries of each pathological region (peri-tumoral edema, tumor and necrosis), the spatial fuzzy C-means (FCM) algorithm is combined with the region growing (RG) method.

**Results:** The results show that exploiting the multi-parametric approach along with the proposed segmentation method can improve characterization of tumor cells, edema and necrosis in comparison to mono-parametric imaging approach.

**Conclusion:** The proposed MRI-based multi-parametric segmentation approach has the potential to accurately segment tumorous regions, leading to an efficient design of the treatment planning, e.g. in radiotherapy.

## 1. Introduction

Glioblastoma Multiforme (GBM) brain tumor is the most aggressive form of primary brain tumors, for which the survival duration is usually between 6 to 12 months, mostly due to improper decision making about the extension of tumor invasion and incomplete tumor resection [11]. The treatment plan usually involves surgical tumor resection, followed by radiotherapy and/or chemotherapy, which relies on the anatomical information provided by conventional MRI sequences, such as FLAIR, contrast-enhanced T1-weighted imaging (T1-WI), and T2-WI [6]. In radiotherapy, the whole pathological region (consisting of peri-tumoral edema, enhancing tumor and necrosis) observed as hyperintensity area on FLAIR images, is used as the target of therapy. However, this region may contain uncontaminated tissue, while missing some tumor cells diffused in the surrounding tissue

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[4]. This issue could be overcome by segmenting various regions of the pathological tissue, to make the targeting more focused on the viable tumor cells; thus, it increases the success rate while exposing the patient to less radiation.

Conventionally, the tumoral region is defined as the enhancing region observed in the contrast-enhanced T1-W images, and the peri-tumoral edema is usually defined as the hyperintensity portion on T2-W or FLAIR images, located outside the enhancing area. However, due to infiltrative nature of the GBM tumors, it has been shown that there exists the possibility of tumor invasion in the surrounding tissue and peri-tumoral edema which, if not resected or destroyed, could increase the probability of tumor recurrence [4]. Therefore recently, functional MRI modalities such as diffusion- and perfusion- weighted imaging (DWI and PWI) which provide deeper insight about the physiological behavior of glial tumors, have gained a great deal of interest [2, 9].

It has been proposed that diffusion measurements are advantageous in discriminating normal from abnormal tissues to some extent, but unable to differentiate tumorous regions [9]. The apparent diffusion coefficient (ADC) values calculated by DWI reflect the extent of diffusion restriction in the tissue under investigation: the necrosis and the edematous regions can be identified by higher ADC values. However, T2-W MRI has been reported to be more successful in characterizing the boundaries of peri-tumoral edema than DWI [8, 9]. Despite, this area may still contain tumor cells. On the other hand, regional cerebral blood volume (rCBV) parameter calculated from PWI has shown high correlation with angiogenesis and tumor aggressiveness. Thus, it can be used to reliably identify the tumor margins [8]. Nevertheless, DWI and PWI are non-specific in determination of the tumor margins [7].

Hence, each MRI modality is advantageous in providing some information about the tumor, but not necessarily capable to characterize it properly. In order to better identify the alterations caused by disease, the physiology-based information must be used as a supplement to the anatomy-based knowledge in a multi-parametric approach. To this end, incorporating the information provided by DWI and PWI with conventional MRI seems to be the leading solution for accurate evaluation of the extent of tissue involvement with tumor, improving the treatment planning and ultimately increasing the chance of patient's survival [10].

On the other hand, as the number of images and the amount of information are increased, the interpretation and decision making procedures become more complicated, subjective and time-consuming. In order to facilitate the decision making, MRI-based image segmentation methods for delineation of the tumor boundaries could be beneficial. However, automatic or semi-automatic segmentation of GBM tumors is a challenging issue, for which a vast number of image segmentation methods with large variability between their performances have been proposed [1]. The variety (in terms of reproducibility) among the results achieved with each method arises from infiltration of tumor cells into the surrounding tissues, irregular borders of glioma tumors, diversity between the amount of tumor contrast uptake between different patients (due to dissimilar vascularization) and different imaging protocols ) [1]. More specifically, GBM is surrounded by a mixture of cytotoxic and vasogenic types of edema. Vasogenic edema in brain may modestly enhance after contrast administration due to the local inflammation in blood-brain barrier which makes the local vessels relatively leaky and this may be a source of error when one attempts to delineate the exact interface between edema and the tumor in T1-w images with contrast enhancement (T1w+C). On the contrary, the high signal in PWI is due to neoangiogenesis, an absent process in peritumoral edema. So, PWI can define tumor-edema interface more accurately than T1-w+C (frequently used in segmentation studies [12].

In this work, we exploit accurate information from quantitative DWI/PWI maps (ADC/rCBV), incorporated with high-resolution T2-w image in an MRI-based multiparametric tissue characterization approach, to accurately segment the tumor, necrosis and peri-tumoral edema from the normal brain tissue in GBM brain tumors. For segmentation, we employ the formulations of fuzzy C-means (FCM) and region growing (RG) algorithms [3], to take into account the advantages of both methods for better characterization of pathological tissues.

The paper is organized as follows: section II describes how the data obtained by different modalities are combined, followed by the proposed segmentation approach. In section III, results are summarized. In section IV, the discussions on the achievements are presented.

## 2. Methods

### 2.1. Data Acquisition

The images for this experiment were acquired from five patients being diagnosed with Glioblastoma Multi-

forme (GBM) tumor with histopathological assessment after the surgery. The MR data for each patient were acquired on a 3 T MR scanner (Siemens MAGNETOM Tim TRIO). Each sequence was applied with the following specifications: T2-WI was performed using SE sequence with TE/TR = 96/5000 ms, image matrix = 308 × 384, FOV = 17.6 × 21.9 $cm^2$, slice thickness = 6 mm. PWI was performed using a GE-EPI sequence with: TE/TR = 45/2340 ms, flip angle = 60°, image matrix = 128 × 128, FOV = 23 × 23 $cm^2$, slice thickness = 5mm, number of measurements = 50 at 1 sec/volume and number of slices = 21. The acquisition was performed before and immediately after injection of 15cc of Gd-DTPA (0.2 mmol/kg) as the contrast agent with a flow rate of 5ml/sec, followed by injection of 20 cc of normal saline solution. DW images were acquired with GE-EPI sequence with: TE/TR = 137/4300 ms, image matrix = 192×192, FOV = 22 × 22 $cm^2$, number of slices = 21, slice thickness = 5 mm, b-values of 0 and 1000 s/$mm^2$ in three orthogonal directions.

### 2.2. Pre-processing and Analysis

All the images were reconstructed to a 128×128 matrix, rigidly registered for motion correction, resliced and coregistered with PWI images using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/). In order to reduce the noise while preserving the edges, anisotropic diffusion filter was applied to the DWI images. The PWI images were skull-stripped using SPM8 and the relative cerebral blood volume (rCBV) maps were generated on the slices containing tumor, edema, and/or necrosis regions. The ADC-maps were created from DWI images.

### 2.3. Spatial Fuzzy C-means (FCM) Algorithm

Medical images are inherently fuzzy and can be considered as the combination of intensities belonging to the various tissue types beside other unwanted intensities. Thus, it is of paramount importance to take this property into account. Spatial FCM is an unsupervised clustering method utilized in medical image segmentation [5]. This technique tries to iteratively partition the image pixels into C clusters, by minimizing the following cost function:

$$J_{FCM} = \sum_{m=1}^{C}\sum_{n=1}^{N} \mu_m^l \left\| p_n - c_m \right\|^2, \quad (1)$$

Where $N$ denotes the total number of image pixels, $C$ is the number of clusters, $p_n$ and $c_m$ are respectively the image pixel and the centroid of the $m$th cluster, ||.|| is the norm, $\mu_{mn}$ is the membership function which can be computed by:

$$\mu_m = \frac{\left\| p_n - c_m \right\|^{-2/(l-1)}}{\sum_{k=1}^{C} \left\| p_n - c_m \right\|^{-2/(l-1)}} \quad (2)$$

with $l$>1 (l controls the degree of fuzziness). The centroids are updated iteratively using

$$c_i = \frac{\sum_{n=1}^{N} \mu_m^l \, i_n}{\sum_{n=1}^{N} \mu_m^l} \quad (3)$$

The membership function must satisfy the following relations:

$$\sum_{m=1}^{C} \mu_m = 1, \; 0 \le \mu_m \le 1, \; \sum_{n=1}^{N} \mu_m > 0. \quad (4)$$

The algorithm is ideally optimized when high membership values are achieved in pixels with close proximity to the centroid, while pixels far apart have low values. In this application, due to heterogeneous GBM tumor margins with its surrounding tissue, specifically in the quantitative maps, the FCM is employed to create several clusters for each image:

- **T2-W** images are classified into three clusters: tissues with hyperintensity values (CSF and pathological region except for necrosis), tissues with hypointensity values (necrosis and normal tissue), and background;

- **rCBV** maps are classified into two clusters (since skull-stripping has been performed prior to quantification, the background cluster is eliminated here): tissues with high perfusion (including tumor), tissues with low perfusion (including necrosis);

- **ADC** maps are classified into four clusters: tissues with high diffusion (CSF), with intermediate diffusion (vessels and pathological region excluding necrosis), with low diffusion (white matter, gray matter, and necrosis), and with no diffusion (background and skull).

### 2.4. Region Growing (RG) Algorithm

One of the most commonly used region-based methods for image segmentation is the Region Growing approach, which starts with selecting n seed points, from which regions grow by seeking for neighboring pixels meeting the

similar criteria as the seed points. The similarity criterion is defined based on texture, homogeneity, topology or other properties of the image. Region growing method has several advantages in medical image segmentation context, such as its good performance in the presence of noise, the capability to separate the regions with similar properties, and its simple concept. Since we are interested in creating region masks, we use RG in conjunction with FCM method [3].

Here, the RG approach is utilized to extract each tissue from individual clusters. We used the mean intensity of the seed points and the neighboring pixels are added to the current region if their intensities are nearest to the mean of the region and less than a pre-defined threshold. The initial seed point is selected manually in each cluster of interest.

## 2.5. FCM-RG Method for Tumorous Tissue Characterization

Hereafter, the overall segmentation algorithm is referred to as FCM-RG method. The procedure is carried out as follows (Figure 1.):

— FCM clustering of the ADC and T2-W images, followed by application of RG with some morphological image processing methods to create individual pathological masks (P1 and P2), to be added to generate the final pathological mask (P)

— FCM clustering of rCBV map, followed by employing RG to one of the clusters to segment the initial necrosis (N1) and to the other one to separate the initial tumorous region (T1),

— Taking the intersection of each of N1 and T1 regions with P, to obtain final necrosis (N) and tumor (T) masks,

— Excluding T and N pixels from P, to obtain pure edema area (E), with no tumor invasion.

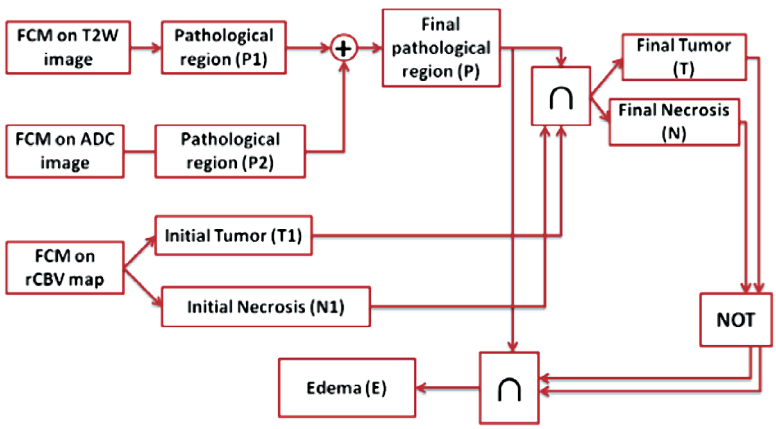


**Figure 1.** The overall segmentation procedure.

## 2.6. Ground Truth for Evaluation

To evaluate the performance of the segmentation algorithm, the GBM tumors were manually segmented by an expert neuroradiologist. The manual segmentation results were considered as the ground truth. Then, the accuracy, sensitivity, and specificity criteria, with the following definitions, were calculated for each case and averaged over all cases to obtain the ultimate values:

$$\textit{Sensitivity} = \text{TP/TP+TN}$$

$$\textit{Specificity} = \text{TN/TN+FP}$$

$$\textit{Accuracy} = \text{TP+TN/TP+FN+TN+FP} \quad (5)$$

Where TP, TN, FN, and FP represent the True Positive, the True Negative, the False Negative and the False Positive detections, respectively.

## 3. Results

The proposed method has been implemented in MATLAB 7.14 (MathWorks, Inc.). The quality of exploiting FCM-RG method was compared in segmentation of mono- and multi-parametric data. In order to evaluate mono-parametric data segmentation results, we applied FCM-RG to T2-W images using four clusters. The fuzzy classes consisted of background, pathological region, edema and necrosis. The tumor region was extracted by subtracting the edema and necrosis regions, from the pathological region, obtained from mono-parametric data.

In Figure 2, the results of segmentation using FCM-RG in multi-parametric data and the manual segmentation results in one of the cases are illustrated. In Table 1 and 2, the evaluation results of segmentation in multi-parametric and mono-parametric oncoming are given. As can be inferred from the results, the multi-parametric approach outperforms the mono-parametric method in segmentation of Tumor and Edema regions. The evaluation parameters do not show significant changes in Necrosis and Pathological regions in both approaches, due to their similar definitions in both methods.

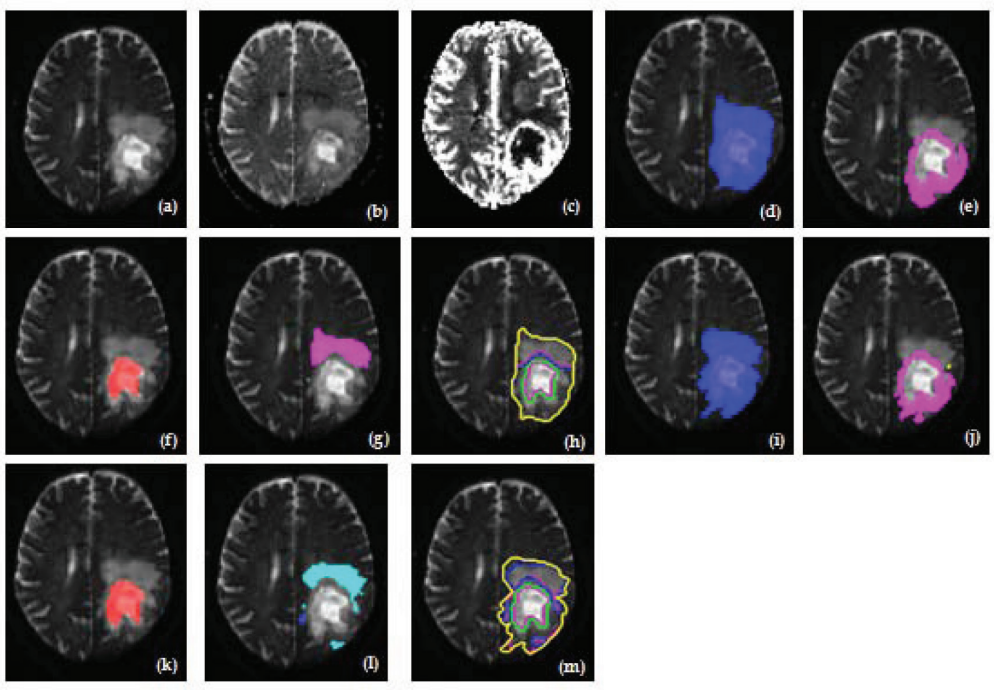


**Figure 2.** (a) T2-W image, (b) ADC map (b-value = 1000), (c) rCBV map; segmentation results of the FCM-RG algorithm: (d) pathological, (e) tumor, (f) necrosis, and (g) edema masks overlayed on T2-W image, (f) the segmentation boundaries (yellow:pathological, blue: edema, pink: tumor, and green: necrosis areas) ; and segmentation results of manual method: (i) pathological, (j) tumor, (k) necrosis, and (l) edema regions overlayed on T2-W image, (m) the segmentation boundaries (yellow:pathological, blue: edema, pink: tumor, and green: necrosis areas).

**Table 1.** Evaluation of the Segmentation Outcomes in Each Region (using FCM-RG method on Multi-parametric data)

| | Accuracy Mean (std.) | Sensitivity Mean (std.) | Specificity Mean (std.) |
|---|---|---|---|
| Pathology | 89.6 (3.38) | 89.71 (1.82) | 89.5 (9.9) |
| Tumor | 84.19 (5.7) | 86.66 (2.93) | 83.42 (6.47) |
| Necrosis | 91.01 (1.88) | 81.43 (6.2) | 99.74 (1.1) |
| Edema | 91.2 (1.5) | 89.84 (8.1) | 95.17 (2.92) |

## 4. Discussion

We proposed a flexible approach for segmentation of Glioblastoma Multiforme (GBM) brain tumors employing an MRI-based multi-parametric imaging approach, to account for the difficulties and complications of the segmentation of this type of tumor. Generally, GBM tumor is heterogeneous and the borders between the tumor

**Table 2.** Evaluation of the Segmentation Outcomes in Each Region (using FCM-RG method on Mono-parametric data)

| | Accuracy Mean (std.) | Sensitivity Mean (std.) | Specificity Mean (std.) |
|---|---|---|---|
| Pathology | 89.73 (2.1) | 89.37 (5.4) | 90.23 (9.1) |
| Tumor | 75.96 (1.07) | 25.71 (10.4) | 92.79 (4.6) |
| Necrosis | 89.65 (2.75) | 78.21 (3.62) | 95.33 (2.6) |
| Edema | 79.7 (1.8) | 75.21 (15.1) | 76.77 (1.6) |

and edema are not well-defined and due to infiltration, the edema region contains tumor cells. Thus, accurate differentiation of the pathological regions becomes difficult. This issue becomes essentially important in treatment planning procedures, such as radiotherapy, where it is important to destroy as much of the tumourous tissue as possible, and at the same time, avoiding as much of uncontaminated tissue as possible.

In this work, spatial Fuzzy C-means (FCM) clustering algorithm was used in combination with region growing (RG) method, referred to as FCM-RG algorithm, to take the fuzzy behavior of the GBM tumor border into account and to take advantage of the RG segmentation method, such as its good performance in the presence of noise and its capability to correctly separate the regions. It was shown that utilizing the FCM-RG method in MRI-based multi-parametric approach outperforms the one applied in MRI-based mono-parametric method, in segmentation of tumor and edema regions. As mentioned before, the accurate separation of these two regions is of utmost importance.

In conclusion, the combination of information provided by anatomical as well as physiological MRI modalities in a multi-parametric framework (T2-W, PWI and DWI) is beneficial in accurate characterization of pathological regions in GBM brain tumors, which could not be achieved by exclusively using the anatomical MRI. Further validation of this work shall be performed by using a larger sample size data, and in order to explore its robustness to inter-patient variations of GBM tumors.

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