A survey on Glioblastoma Multiforme Tumor Segmentation through MR images

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Abstract—Magnetic Resonance Imaging(MRI)-based medical image analysis for brain tumor studies is gaining attention in recent times due to an increased need for efficient and objective evaluation of large amounts of data. Gliomas are the most common primary brain tumors, evolving from the cerebral supportive cells. Brain tumor segmentation consists of separating the different tumor tissues (solid or active tumor, edema, and necrosis) from normal brain tissues: gray matter (GM), white matter (WM), and cerebrospinal fluid(CSF). Currently, most of brain tumor segmentation approaches arise from the supervised learning standpoint, which requires a labelled training dataset from which to infer the models of the classes. The performance of these models is directly determined by the size and quality of the training corpus, whose retrieval becomes a tedious and time-consuming task. On the other hand, unsupervised approaches avoid these limitations but often do not reach comparable results than the supervised methods. This article presents an overview of the most relevant Glioblastoma multiforme tumor segmentation methods, conducted after the acquisition of the image. Both Supervised and Unsupervised techniques are emphasized.

Index Terms— Glioblastoma Multiforme(GBM),Brain Tumor, Segmentation, MRI

1. INTRODUCTION

Medical imaging techniques play a key role for brain tumour diagnosis due to the intracraniallocation and the unspecificity of clinical symptoms of such lesions [1].Brain tumors can be classified according to their origin or degree of aggressiveness. Primary brain tumors arise in the brain, while metastatic brain tumors frequently originate from other parts of the body. The most widely used grading scheme today has been introduced by the World Health Organization (WHO). It classifies brain tumors into grades I to IV with increasing aggressiveness. Gliomas are the most common primary brain tumors, whereof 70% are among the group of malignant gliomas (anaplastic astrocytoma WHO grade III, glioblastoma multiforme WHO gradeIV) [2]. Both low and high-grade glioma can have very irregular shapes and grow anisotropically. Therefore, it can be expected that varying the slice orientation and location, due to positional changes of the head in the scanner, may have a significant impact on the reliability of tumor size estimates derived from linear measurements. Despite of significant advances in imaging, introduction of novel chemotherapeutic agents, and technological development, the median life expectancy of patients with GBM is less than 12 months, with only 5% of these patients surviving five years after diagnosis[3]. Quantifying the volume and other morphological characteristics of a tumor is an important indicator of the disease progression in retrospective studies[4], as well as the efficacy of the therapy [5]. Conventionally, such assessments are often done using so-called McDonald criteria [6], a 2-D evaluation of the largest tumor diameters. This technique, however, falls short in accurate quantification of the tumor volume due to its 2-D description of the tumor structure. The central concept for this quantification is segmenting the whole pathology into various underlying components from magnetic resonance images (MRI). Usually automatic segmentation is more reproducible and therefore preferable over manual delineations. However, the automatic segmentation of GBMs is considered very challenging as the pathology is highly heterogeneous and may consist of several components including necrosis (dead central part), enhancing tumor ring and edema (swelling). Moreover gliomas are highly variable in their size as well as shape and might cause deformation of surrounding tissues (mass-effect).Some artifacts of MR imaging also increase the difficulty of tumor segmentation. Imperfection of the RF pulses and the location of RF coils may introduce nonuniformity in MR images.

In the last years many researchers in the field of medical imaging and soft computing have made significant advances in the field of brain tumor segmentation. Mostof these techniques fall into the supervised learning approach. However, supervised learning requires an expensive, time-consuming and biased task to retrieve sufficiently large set of labelled samples from which to learn discriminant functions for the posterior segmentation [7]. Furthermore, the supervised approaches are limited to the sizeand quality of the dataset, among other limitations such as the over-fitting

to the training corpus[8]. Moreover, spatio-temporal changes in clinical environment such as new MR machines, protocols or centres may distort the data and hence could affect the performance of the supervised models [9].

Unsupervised learning tackles these limitations in a more straightforward way. Unsupervised learning does not require a training dataset from which to learn the models of the classes, but directly uses the patient specific data to find natural groupings of observations, called clusters. Hence, unsupervised learning builds an intra-patient segmentation model, which is independent from the differences between other patient's data. By the opposite, the absence of previous manual segmentations to guide the learning process makes the segmentation more challenging and often lead to a worse performance with respect to supervised approaches. This paper presents an overview of the most relevant existing Glioblastoma multiforme tumor segmentation methods applied after the acquisition of the image. This work is divided into six sections. First, section 2 gives the structure of brain. Then, in section 3, Imaging of Glioblastoma multiforme tumors, section 4 Manual Segmentation, section 5 the concepts of unsupervised and supervised segmentation are presented. Subsequently, the most relevant existing methods for the segmentation of GBM tumors are introduced and discussed in section 6. Finally, the paper conclusions are summarized in section 7.

2. STRUCTURE OF BRAIN

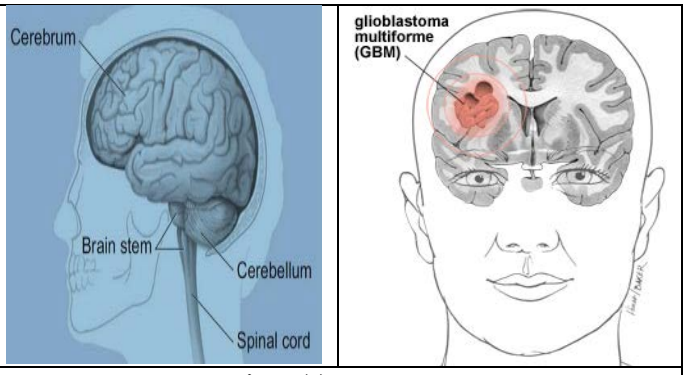
The three major parts of the brain that control different activities:

2.1 Cerebrum: The cerebrum uses information from our senses to tell us what is going on around us and tells our body how to respond. It controls reading, thinking, learning, speech, and emotions. The cerebrum is divided into the left and right cerebral hemispheres. The right hemisphere controls the muscles on the left side of the body. The left hemisphere controls the muscles on the right side of the body.

2.2 Cerebellum: The cerebellum controls balancing actions like walking and standing, and other complex actions.

2.3 Brain stem: The brain stem connects the brain with the spinal cord. It controls breathing, body temperature, blood pressure, and other basic body functions.

Fig. 1 (a)	Fig. 1 (b)



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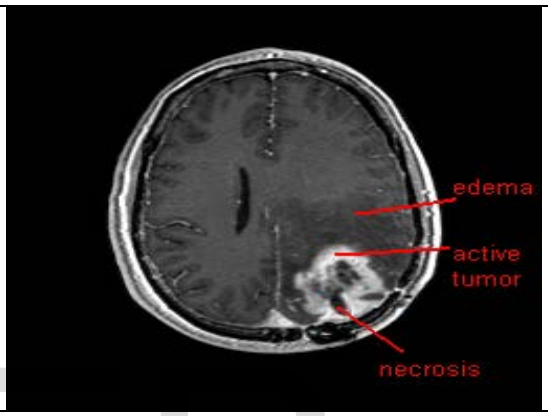

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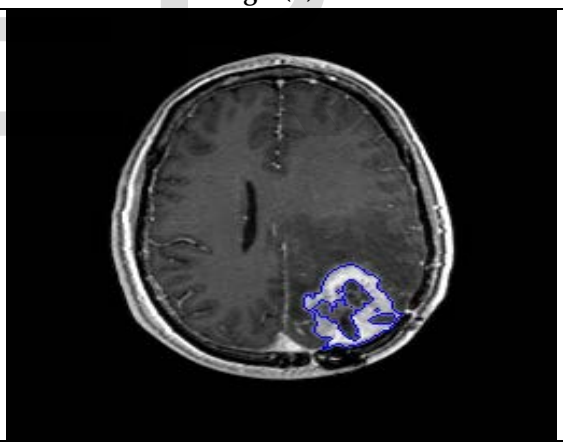


Fig.1(e)

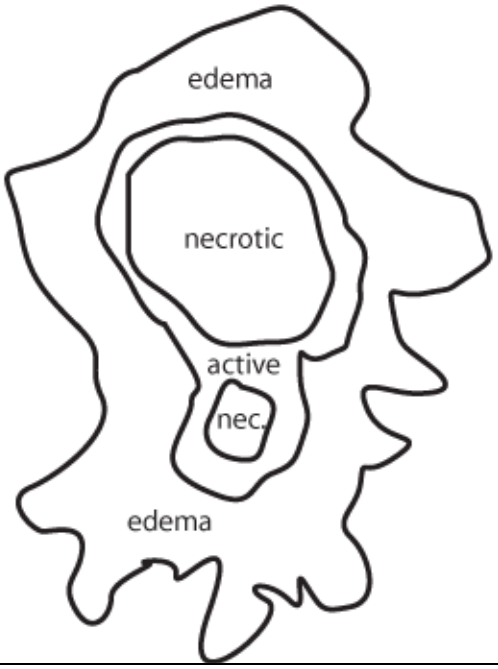


Fig. 1 (a) gives the basic structure of brain.[10], Fig. 1(b) Show GBM Tumor, Fig.1(c) and (d) Example of the a GBM brain tumor on a T1w post contrast MR image slice and the corresponding tumor contour Fig(1) (e) different heterogeneous regions of the brain tumor and label them as edema, active, or necrotic

3. IMAGING OF BRAIN TUMORS:

MR imaging (MRI), invented in 1970, is a popular method in medical imaging. MRI scanning is relatively safe and unlike other medical imaging modalities, MRI is a non-invasive technique, which provides good soft tissue contrast[11] and is widely available in clinics. It is used in combination with other imaging modalities, such as computed tomography (CT), Positron Emission Tomography (PET) and Magnetic Resonance Spectroscopy (MRS) to provide the most exact information about tumor morphology and metabolism. Especially PET imaging can provide additional information[12], however so far MRI remains the accepted standard and therefore we will focus on MRI-based methods.

MRI makes it possible to produce markedly different types of tissue contrast by varying excitation and repetition times, which makes it a very versatile tool for imaging different structures of interest. Due to the nature and appearance of brain tumors, one MRI sequence is not sufficient to fully segment the tumor including all its sub regions. In current clinical routine, different MRI sequences are employed for diagnosis and delineation of tumor compartments. These sequences include T1-weighted MRI (T1), T1-weighted MRI with contrast enhancement (T1c), T2-weighted MRI (T2) and T2-weighted MRI with fluid attenuated inversion recovery (T2FLAIR), however acquisition parameters of these modalities are not standardized. Patients with gliomas are usually examined by the previously described MR imaging protocols according to the RANO guidelines with a slice thickness of 5mm without a gap between the slices. For volumetry, high-resolution 3D volume images are performed, including at least contrast enhanced T1-weighted images with isotropic resolution. Figure 2 shows an axial slice of the four standard sequences for a glioma patient including manually drawn tumor regions.

T1-weighting is the most commonly used sequence for structural analysis, it also allows for an easy annotation of the healthy tissues. In T1-weighted contrast enhanced images (Gadolinium-DTPA), the tumor borders appear brighter because the contrast agent accumulates there due to the disruption of the blood-brain barrier in the proliferative tumor region. In this sequence, the necrotic and the active tumor region can be distinguished easily. In T2-weighted MRI, the edema region, which surrounds the tumor appears bright. T2FLAIR (FLAIR) is a special sequence, which helps in separating the edema region from the cerebrospinal fluid (CSF) because the free water signal is suppressed. The radiological definition of the tumor margins in the clinical context are often manually determined by the radiologist on the T2 and post-gadolinium T1 images by thresholding boundaries between T2 hyper intense / T1 contrast-enhanced lesions and the surrounding healthy tissue to define the outer margins of a tumor. Clinical measurements of the tumor size traditionally incorporate either the product of the major and minor axis (2D measures) or of the three main axes of a tumor (3Dmeasures).

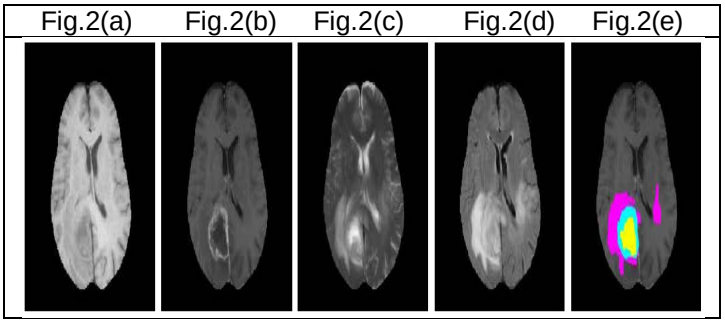


Figure 2.One axial slice of an MR image of a high-grade glioma patient. From left to right: T1-weighted image, T1-weighted image with contrast enhancement, T2-weightedimage, T2FLAIR-weighted image and manual segmentation into necrotic (yellow), active(green), edema (pink) tumor compartments. Necrosis and active tumor region were segmented based on the T1-weighted image with contrast enhancement, whereas the edema region was segmented based on the registered T2FLAIR-weighted image[13].

4.MANUAL SEGMENTATION

Manual segmentation of brain tumors involves manually drawing the boundaries of the tumor and structures of interest, or painting the region of anatomic structures with different labels [14].In manual segmentation, human experts (radiologists/anatomists/trained technologists) not only make use of the information presented in the image but also make use of additional knowledge such as anatomy. Manual delineation requires software tools with sophisticated graphical user interfaces to facilitate drawing regions of interest and image display. In practice, the selection of the tumor region, which is the region of interest (ROI), is a tedious and time consuming task. MRI scanners generate multiple two-dimensional cross-sections (slices), and the human expert has to go through the dataset slice by slice for choosing the most representative ones from which the relevant regions are carefully delineated [15]. Manual segmentation of brain tumors is also typically done based on a single image with intensity enhancement provided by an injected contrast
agent[16]. However if the person drawing the ROI is not a radiologist/anatomist/trained technologist who is well versed with that brain anatomy, it will most likely yield poor segmentation results.

4.1 Semiautomatic segmentation: In semiautomatic brain tumor segmentation, the intervention of a human operator is often needed to initialize the method, to check the accuracy of the result, or even to manually correct the segmentation result. Most of the current research is targeted at semiautomatic segmentation of brain tumors with the intention of having the least human interaction possible. The main components of an interactive brain tumor segmentation method are the computational part, the interactive part, and the user interface.

4.2 Automatic Segmentation: Fully automatic segmentation can be done incorporating within the algorithms human intelligence and prior knowledge about intensity and other tissue information, shape, size, symmetry, and normal anatomic variability to improve segmentation results. Furthermore, it would be desirable to have an unsupervised fully automatic segmentation method to avoid the use of patient-specific training. The use of some pre or post processing methods may give more reasonable segmentation results, which reflect the layout of regions of interest.

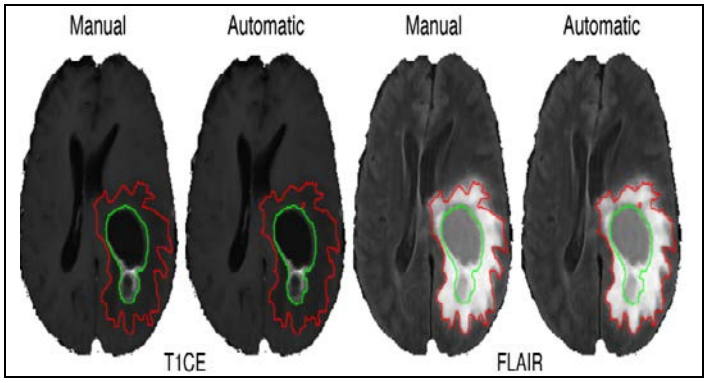


Fig.3 Manual and Automatic Segmentation

5. UNSUPERVISED AND SUPERVISED SEGMENTATION:

5.1 Unsupervised segmentation:

Unsupervised learning does not require a training dataset from which to learn the models of the classes, but directly uses the patient specific data to find natural groupings of observations, called clusters. Hence, unsupervised learning builds an intra-patient segmentation model, which is independent from the differences between other patient's data. The major disadvantages when using unsupervised segmentation methods using image-based features: the number of regions often needs to be pre-specified, tumors can be divided into multiple regions, and tumors may not have clearly defined intensity or textural boundaries. These disadvantages can be reduced by making use of pre-processing techniques such as intensity inhomogeneity correction and intracranial segmentation commonly referred to as "skull stripping". Various techniques of intensity inhomogeneity correction have been proposed in the last three decades. Skull stripping aims to segment the brain tissue from the skull and nonbrain intracranial tissues in magnetic resonance images of the brain. Skull stripping is an important pre-processing step in neuroimaging analysis because brain images must typically be skull stripped before other processing algorithms can be applied.

5.2 Supervised segmentation

Supervised Image segmentation methods differ from unsupervised methods through the use of labeled training data. Supervised classification involves both a training phase that uses labeled data to learn a model that maps from features to labels, and a testing phase that is used to assign labels to unlabeled data based on the measured features. Supervised methods have the potential of reducing the manual engineering task by providing labeled data,

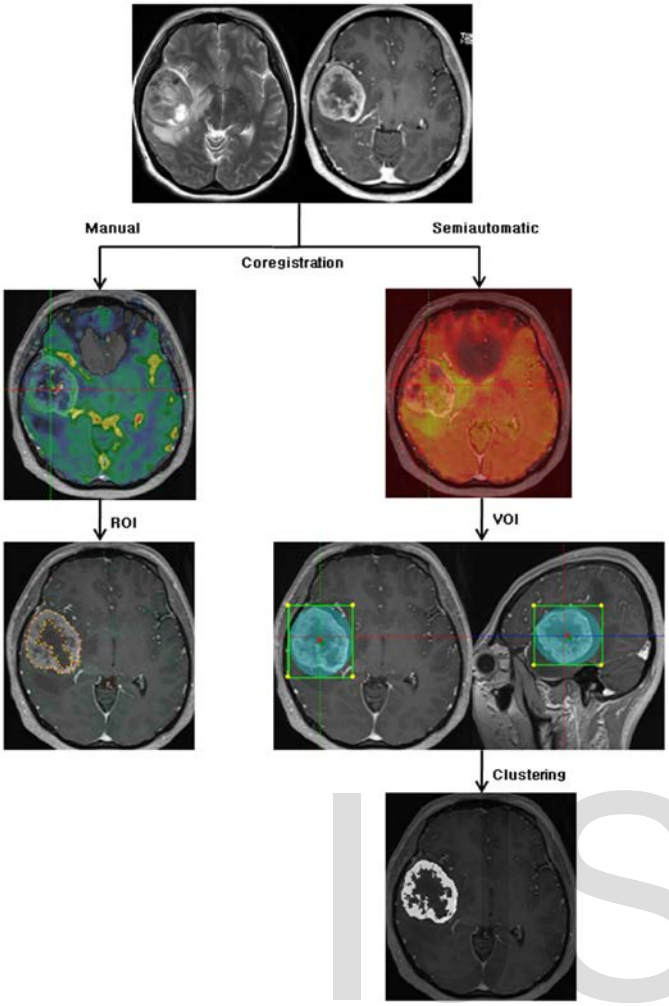


Figure 4.Flowchart of manual and semiautomatic segmentation analysis. Structural imaging (CE-T1WI or T2WI) and nCBV maps were co registered using the manual segmentation method, and then the ranges of tumors were manually depicted by each observer using an ROI (right row). Structural imaging (CE-T1WI or T2WI) and nCBV maps were co registered using the semiautomatic segmentation method; then, the ranges of tumors were depicted by each observer using a VOI. Finally, an appropriate combination of clusters from the various clusters was determined by each observer (left row). CE-T1WI = contrast enhanced T1-weighted imaging; T2WI = T2-weighted imaging; nCBV = normalized cerebral blood volume; ROI = region of interest; VOI = volume of interest.

appropriate features, and appropriate parameters for the learning algorithm. However supervised methods for brain tumor segmentation in MR images often suffer from the disadvantages , Supervised learning requires an expensive, time-consuming and biased task to retrieve a sufficiently large set of labelled samples from which to learn discriminant functions for the posterior segmentation. Furthermore, the supervised approaches are limited to the size and quality of the dataset, among other limitations such as the over-fitting to the training corpus. Moreover, spatio-temporal changes in clinical environment such as new MR machines, protocols or centres may distort the data and hence could affect the performance of the supervised models.

6.Segmentation methods:

The Underlying objective of the medical image segmentation is to partition it into different anatomical structures, there by separating the components of interest. In the case of brain tumors, the segmentation consists of separating the different tumor tissues such as solid or active tumor, edema, and necrosis, from the normal brain tissues such as gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). Thebrain tumor segmentation requires an objective measure that can be used to define the homogeneity of each tissue.

6.1 General Problems in MRI Segmentation:

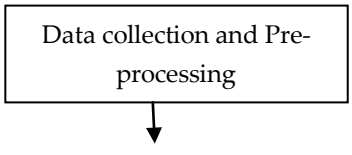
The main difficulties in segmentation process are

- Noise
- The bias field
- The partial-volume effect

6.1.1 Existing de-noising methods:

It is difficult to remove noise from MRI images and state-of-art methods in removing the noise are substantial. Methods vary from standard filters to more advanced filters, from general methods to specific MRI de-noising methods such as linear filtering methods, nonlinear filtering methods, anisotropic nonlinear diffusion filtering, a Markov random field (MRF) models, wavelet models, non-local means models (NL-means) and analytically correction schemes.

These methods have advantages and disadvantages. None of the methods is better than others in terms of computation cost, de-noising, quality of de-noising and boundary preserving. Therefore, de-noising is still an open issue and de-noising methods need improvement. Linear filters are conceptually simple. They update value of a pixel by (weighted) average of its neighborhood. These filters reduce noise but degrade image details and the edges of the image; therefore, restored image looks blurred. In contrast to linear filters, nonlinear filters have better performance in edge preserving but degrade fine structure; therefore, the resolution of the image is reduced[17] Different de-noising methods have been proposed in the literature Anisotropic nonlinear diffusion, Markov random field method (MRF), Wavelet-based methods, Analytical correction method etc.



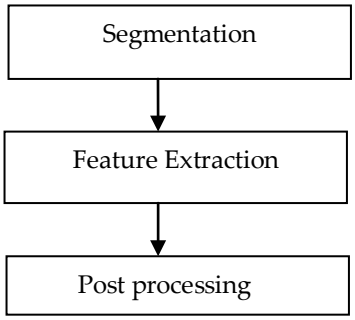


Figure 4.Main blocks in GBM Tumor segmentation Process

6.1.2 Inhomogeneity correction:

Generally, intensity inhomogeneity is considered as a smooth spatially varying function which alters intensity inside originally homogeneous regions. It is considered multiplicative or additive. Usually in MR images, noise is considered independent of inhomogeneity and image models as multiplicative of image and inhomogeneity plus noise. Inhomogeneity correction methods are categorized in two groups:

- prospective methods
- retrospective methods.

6.1.2.1Prospective methods

These methods consider inhomogeneity as an error of the imaging process that can be corrected by estimating inhomogeneity field of MRI acquisition system. Some of these methods are listed here:

1.Phantom Based: Inhomogeneity field can be estimated by taking the image of a uniform phantom, then, scaling and smoothing the image[18]

2. Multi-coil: Surface and body are two common types of coils, usually, surface type has good (signal to noise ratio SNR) but high inhomogeneity, while body type has low inhomogeneity but poor SNR. It is proposed to combine both types to have an image with good SNR and less inhomogeneity[19]

6.1.2.2Retrospective methods

These methods don't assume any information about acquisition methods and are more general therefore, they can correct both MR scanner-induced and patient-induced inhomogeneity.

These methods are listed here:

1.Surface Fitting Methods: These methods use image features which have information about inhomogeneity. A parametric surface is fitted to the features. The result surface represents an inhomogeneity field.[20]

2.Segmentation Based: After segmentation, inhomogeneity correction is very simple. Therefore these methods merge these two steps to benefit from each other[19]

3.Histogram Based Methods: These methods use a histogram of image usually without using a priori knowledge about image.

4.High-frequency Maximization: Iteratively, inhomogeneity is estimated by maximizing the high frequency information of distribution of tissue intensity[18]

5.Information Minimization: These methods assume inhomogeneity as extra information

6.Filtering Methods: Filtering methods consider inhomogeneity as a low-frequency artifact which can be separated from image by low-pass filtering. For most of medical images this assumption is not correct. Two most important filtering inhomogeneity correction methods are (a) homomorphic filtering and (b) homomorphic un-sharp masking. (a) Homomorphic Filtering: The image background is usually altered; then, log-transformedof input image is subtracted by log-transformed of its low-pass filtered via homomorphicfilter[20]. (b) Homomorphic Un-sharp Mask: The corrected image is obtained by dividing the low-pass filtered image by a constant to preserve mean or median intensity. When homomorphic filtering is performed a streak artifact is produced on boundary between tissues. Guillemaud proposed a method to eliminate this artifact on boundary between backgrounds and object[21].

6.2 Segmentation Methods:

There are several segmentation methods have been proposed in recent years. Each and every method has its own advantages and disadvantages. According to [22] the segmentation schemes popularly employed on medical images as rule-based, statistical, atlas-based and deformable model based techniques. Global as well as adaptive thresholding, region growing and region split-and-merge techniques were grouped under the rule based schemes. Atlas based method was broadly categorized as single and multi-atlas-based segmentation. Deformable models include parametric deformable models, geometric level-set based deformable models etc.

6.2.1 Thresholding based methods：

Thresholding is a simple and effective region segmentation method, in which the objects of the image are classified by comparing their intensities with one or more intensity thresholds. The segmentation is achieved by grouping all pixels with intensity greater than the threshold into one class, and all other pixels into another class. Thresholding is often used as an initial step in a sequence of image segmentation process. Its main limitation is that only two classes are generated and it does not work when confronted with structures that lack clear borders [23].

Threshold-based methods are classified into global and local thresholdings[24]. If an image contains objects with homogeneous intensity or objects , and the background is high, global thresholding is the best choice to segment the

objects and the backgrounds. When the contrast of an image is low threshold selection will become difficult.

Local thresholding can be determined by estimating a threshold value for the different regions from the intensity histogram. The threshold values of local thresholding are generally estimated by using the local statistical properties such as the mean intensity value in T1w MRI, by the prior knowledge and by calculating partial volumes of each region to determine the threshold for the segmentation of each component[25]. In addition, the Gaussian distribution was applied to determine the thresholds in normal brain MRI image[26].Due to the special structure of brain tumor, global and local thresholdings are mainly used to determine the approximate location of brain tumor in the brain. In most cases, thresholding is used as the first step in the segmentation process of brain tumor.

6.2.2 Region-based methods:

Region growing is a technique to extract a region of the image based on predefined criteria. In its simplest form, region growing requires a seed point that is manually selected by an operator, and extracts all pixels connected to the initial seed with the same intensity value[27]. To eliminate the dependency on initial seeds and to make the method automatic statistical information and a prior knowledge can be incorporated in the algorithm. Region growing can be so sensitive to noise, that it may cause extracted regions to have holes or even is disconnected. The procedure iterates until no more pixels can be added to the region. The advantage of region growing is that it is capable of correctly segmenting regions that have similar properties and generating connected region. Some researchers have proved that the region growing is an effective approach and less computation intensive than other non-region-based methods for segmenting MR images of brain tumors, especially for the homogeneous tissues and regions[28, 29]. The primary disadvantage of region growing method is the partial volume effect[30] which limits the accuracy of MR brain image segmentation. Partial volume effect blurs the intensity distinction between different tissue classes at the border of the two tissue types, because the voxel may represent more than one kind of tissue.

The good results of brain tumor segmentation by using conventional methods are hard to achieve. In most situations, these methods were used as a preprocessing step in the segmentation of brain tumor. Therefore, more advanced automatic methods were proposed to meet with the requirements of clinical doctors.

6.2.3 Classification and Clustering based methods:

In brain tumor segmentation fuzzy systems allow for the development of methods and algorithms to perform the tasks related to intelligent human behaviors. Clustering was introduced into the brain tumor segmentation community by [31] who analyzed the texture patterns of different tissues. FCM is an iterative algorithm, it is considered as a very time consuming clustering method. In order to reduce the execution time of this algorithm, some solutions such as Fast Generalized FCM (FGFCM) clustering algorithms and Bias-Corrected FCM (BCFCM) algorithm have been proposed. A novel fast and robust FCM framework was introduced for brain tumor segmentation called FGFCM clustering algorithms by incorporating local information[32] BCFCM algorithm provides good quality segmented brain images in a very quick way, which makes it an excellent tool to support virtual brain endoscopy to realize the segmentation of brain tumor[33]. In order to reduce the sensitivity of the standard FCM algorithm with Gaussian, impulse, and intensity non-uniformity noises, a modified FCM-based method that targets accurate and fast segmentation in case of mixed noises was proposed[34]. This method extracts a scalar feature value from the neighborhood of each pixel, using a context dependent filtering technique that deals with both spatial and gray level distances. These features are clustered afterwards by the histogram-based approach of the enhanced FCM algorithm. In order to improve the performance of FCM algorithm, some researchers have introduced a neighborhood attraction, which is dependent on the relative location and features of neighboring pixels. However, determination of degree of attraction is a challenging task which can considerably affect the segmentation results.

6.2.4 Hybrid and soft computing methods:

Region-growing based GrowCut segmentation[35] provided a variability analysis among the segmentation done by different physicians. Four physicians segmented GBMs in ten patients, once using the region-growing based Grow-Cut segmentation module of Slicer, and once by drawing boundaries completely manually, slice-by-slice. The time required for Grow-Cut segmentation was on an average 61% of the time required for the pure manual segmentation. A comparison of Slicer-based segmentation with manual slice-by-slice segmentation exhibited a Dice Similarity Coefficient (DSC) of 88.43 ± 5.23% and a Hausdorff Distance of 2.32 ± 5.23 mm.

A new framework to segment the Glioblastoma Multiforme (GBM) from brain MRI was constructed based on two well known techniques: Region Growing and Fuzzy C-Means[36]. Furthermore, it considers the intricate nature of the GBM in MRI and incorporates a fuzzy formulation of Region Growing with an automatic initialization of the seed points. The Fuzzy Spatial Growing(FSG) algorithm outperforms the Region Growing and FCM algorithms when the pathological

condition of the tumor have an insufficient contrast enhancement and high fuzziness in the boundary between the tumor and the white matter with Dice Similarity Index 96.38 ± 7.16%. This phenomenon is due to the low cellular metabolism or high infiltration to the neighboring tissue.

Primary segmentation from an unsupervised Fuzzy C Means (FCM) along with the cluster centers of each class was fed to a rule-based expert system. Multispectral histogram analysis was used to isolate the GBM from the rest of the intracranial region, with the region analysis used in performing the final tumor labeling. Knowledge-based Fuzzy C-Means (FCM) was used [37]to estimate glioma volumes from Dynamic Susceptibility Contrast (DSC) images.

A fully automatic and unsupervised brain tumor segmentation method which considers human knowledge[38]. The expert knowledge and the features derived from the MR images are coupled to define heuristic rules aimed to the design of the fuzzy approach. To assess the unsupervised and fully automatic segmentation, intensity-based objective measures are defined, and a new method for obtaining membership functions to suit the MRI data is introduced. The proposed system attempted to segment the enhancing GBM tumor area with the lowest score(Jaccard similarity) of 0.71 and the highest of0.93

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[39], which could not be achieved by exclusively using the anatomical MRI. 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.

Confidence-based Ensemble[40] for GBM brain tumor segmentation that combines multiple segmentation results into a final ensemble one. The method is evaluated on a dataset of 20 cases froma multi-center pharmaceutical drug trial and compared to the fuzzy connectedness method. Three individual methods were used in the framework: fuzzy connectedness, GrowCut, and voxel classification. The combination method is a confidence map averaging (CMA) method. The CMA method shows an improved ROC curve compared to the fuzzy connectedness method ($p < 0.001$). The CMA ensemble result is more robust compared to the three individual methods.

6.2.5 k- Nearest-Neighbors:

A fully automatic method based on a modification of the k-Nearest-Neighbors (kNN) algorithm [41] method was developed and applied to a multi-modal MRI data set with the aim of improving accuracy in assessment of therapy response to bevacizumab in patients with recurrent Gliolastoma. By including missing values in the kNN algorithm, arising from substandard acquisitions or movements, and by performing voxel based classification based solely on MR characteristics rather than spatial/morphologic properties, this method aims to overcome the constraints of existing methods. Classification results were validated using manual labeling of the different tissue classes, MR spectroscopy (MRS), volumetric measurements of the enhanced tumor class using manual delineations and independent unsupervised classification algorithm. Therapy response assessment was performed based on the kNN results, Macdonald's criteria, and manual delineation of the enhancing tumor[42].

6.2.6 Support Vector Machine:

Computerized volumetry and manual segmentation were compared in the retrospective study [43] on MR images of patients with native glioblastoma with the imaging performedat 24–48 h following resection and 2–4 months postoperatively. 1D and 2D measurements were performed by two neuro-radiologists. Computer-assisted volumetry was performed through a combination of region-based active contours and a level set approach. Tumor response was assessed by using established 1D, 2D, and volumetric standards. Twentynine patients were analyzed. Discrepancy in disease status between 1D and 2D compared with computer-assisted volumetry was 10.3% (3/29) and 17.2% (5/29), respectively. The mean time for segmentation between manual and computer-assisted volumetry techniques was 9.7 min and less than one minute, respectively. Inter-observer correlation was highest for volumetric measurements (0.995; 95% Concordance Index (CI), 0.990–0.997) compared with 1D (0.826; 95% CI, 0.695– 0.904) and 2D (0.905; 95% CI, 0.828–0.948) measurements

6.2.7 Other methods:

A method for the automatic segmentation Of Optic Path Gliomas(OPG) from several MRI pulse sequences[44]. This method effectively incorporates prior location, shape, and intensity information. It relies on an anatomical tumor atlas and on a probabilistic tissue model. Unlike other methods, it relies on the tumor localization to define a tumor region of interest and combines the voxel information from several MRI modalities to delineate the ambiguous OPG boundaries.

Experimental results indicate that this method accurately identifies the sharp OPG boundaries and delineates in a consistent and repeatable manner the OPG contours that cannot be clearly identified on the MR images. Gliomas with 15 clinical multi-spectral MRI datasets acquired by a General Electric Signa 3T HDXT scanner. Subjects were pediatric patients 3-7 years old with OPGs. Each scan consists of the three pulse sequences that are mostly frequently used to detect, diagnose, and segment OPGs in the clinical setting: T1- weighted, T2-weighted, and FLAIR. Each dataset has 512 × 512×30 voxels with voxel size 0.5mm×0.5mm×5.0mm. An expert radiologist manually produced ground-truth segmentations for each scan. To quantify the results, for optimal threshold 1.2, the mean volumetric overlap error is 28.6%, and the mean surface distance is 0.67mm. These values are comparable to those of other fully automatic detection methods of brain tumors.

A decision forest that uses context-aware spatial features was used to differentiate necrosis and vasogenic edema in the perifocal region of GBM [45]. This framework integrated a generative model of tissue appearance, from the probabilities obtained through tissue-specific Gaussian mixture models, as additional input to the forest. The validation is performed on a labeled database of 40 multi-channel MR images.

In current practice, radiotherapy planning is primarily based upon T2 FLAIR MRI despite its known lack of specificity in the detection of tumor infiltration. While hyper intensity on T2 FLAIR is widely considered to represent infiltrative tumor, it may also be caused by the presence of vasogenic edema[46]studied a data set of 17 GBM patients treated with anti-angiogenic therapy for which a fast decrease of T2 FLAIR hyper signal was observed, which indicates the resolution of edema. The literature investigated whether multimodal MRI acquisitions including DTI can distinguish between edema and tumor infiltration prior to therapy. Up to 75% of the extent of the edema was characterized using the morphological information from the contrast enhanced T1 image using a random forest classifier. The information from different imaging modalities did not significantly improve the classification.

A fully automatic algorithm is presented for the automatic segmentation of gliomas in 3D MR images[47]. It builds on the discriminative random decision forest framework to provide a voxel-wise probabilistic classification of the volume. It uses multi channel MR intensities (T1, T1C, T2, Flair), spatial prior and long-range comparisons with 3D regions to discriminate lesions. A symmetry feature is introduced accounting for the fact that gliomas tend to develop in an asymmetric way.

A flexible semi-automatic approach was proposed for spherical objects that creates a directed 3D graph. Thereafter, the minimal cost closed set on the graph is computed via a polynomial time s-t cut, creating an optimal segmentation of the tumor[48]. The user can improve the results by specifying an arbitrary number of additional seed points to support the algorithm with grey value information and geometrical constraints. It was tested on 12 magnetic resonance imaging datasets. The ground truth of the tumor boundaries are manually extracted by neurosurgeons. The segmented gliomas are compared with a one click method, and the semi-automatic approach yields an average Dice Similarity Coefficient (DSC) of 77.72% and 83.91%, respectively.

An automated brain tumor segmentation methods based on kernel Dictionary learning (DL)[49]. In this work, kernel extensions of the DL approach are adopted. Both reconstructive and discriminative versions of the kernel DL technique are considered, which can efficiently incorporate multi-modal nonlinear feature mappings based on the kernel trick. Our novel discriminative kernel DL formulation allows joint learning of a task-driven kernel-based dictionary and a linear classifier using a K-SVD-type algorithm. To exploit the multi-modality of the MR imagery, an ensemble kernel based on Gaussian kernel functions was constructed. The discriminative kernel DL method was found to yield a performance almost the same as the reconstructive counterpart with reduced computational burden and Dice Similarity Index of 89.3

6.2.8 Publicly Available Tool boxes and open databases:

Table 1 The current Tool bixes

Name	Link	Ref.
TumorSim	www.nitrc.org/projects/tumorsim	[50]
FSL	fsl.fmrib.ox.ac.uk	[51]
3D Slicer	www.slicer.org	[52]
MedInria	med.inria.fr/	[53]
GLISTR	www.rad.upenn.edu/sbia/software/glistr/	[54]
MIPAV	mipav.cit.nih.gov	[55]
StripTs	www.istb.unibe.ch/content/research	[56]
FreeSurfer	surfer.nmr.mgh.harvard.edu	[57]
MITK	www.mitk.net/	[58]
BraTumIA	www.istb.unibe.ch/content/research	[59]

Table 2 The current open databases.

Name	Link	Ref.
BraTS	www2.imm.dtu.dk/projects/BRATS2012/	[60]
BrainWeb	brainweb.bic.mni.mcgill.ca/brainweb/	[61]
IBSR	www.nitrc.org/projects/ibsr	[62]

7 CONCLUSION:

In this study, we reviewed current studies of the different Glioblastoma Multiforme tumor segmentation and detection methodology for MRI. All the steps for detecting GBM tumor have been discussed including pre-processing steps. Although most of brain tumor segmentation algorithms have relatively good results in the field of medical image analysis, there is a certain distance in clinical applications. Due to a lack of interaction between researchers and clinicians, clinicians still rely on manual segmentation for GBM tumor in many cases. One of the principal reasons might be the lack of standardized procedures. Another two reasons could be the substantial differences with the traditional specialists' way of work, and the deficiency of the existing methods in assisting medical decision with a transparent and interpretable way. The existence of many tools aims to do pure research and is hardly useful for clinicians. Therefore, embedding the developed tools into more user-friendly environments will become inevitable in the future.

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