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A Survey of MRI-Based Brain Tumor Segmentation Methods

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Abstract: Brain tumor segmentation aims to separate the different tumor tissues such as active cells, necrotic core, and edema from normal brain tissues of White Matter (WM), Gray Matter (GM), and Cerebrospinal Fluid (CSF). MRI-based brain tumor segmentation studies are attracting more and more attention in recent years due to non-invasive imaging and good soft tissue contrast of Magnetic Resonance Imaging (MRI) images. With the development of almost two decades, the innovative approaches applying computer-aided techniques for segmenting brain tumor are becoming more and more mature and coming closer to routine clinical applications. The purpose of this paper is to provide a comprehensive overview for MRI-based brain tumor segmentation methods. Firstly, a brief introduction to brain tumors and imaging modalities of brain tumors is given. Then, the preprocessing operations and the state of the art methods of MRI-based brain tumor segmentation are introduced. Moreover, the evaluation and validation of the results of MRI-based brain tumor segmentation are discussed. Finally, an objective assessment is presented and future developments and trends are addressed for MRI-based brain tumor segmentation methods.

Key words: brain tumor; Magnetic Resonance Imaging (MRI); segmentation

1 Introduction

Tumor is an uncontrolled growth of cancer cells in any part of the body. Tumors are of different types and have different characteristics and different treatments[1]. At present, brain tumors are classified as primary brain tumors and metastatic brain tumors. The former begin in the brain and tend to stay in the brain, the latter begin as a cancer elsewhere in the body and spreading to the brain.

Brain tumors are divided into two types: benign and malignant. In fact, the most widely used grading scheme has been issued by the World Health Organization (WHO)[2]. It classifies brain tumors into grade I to IV under the microscope. In general, grade I and grade II are benign brain tumor (low-grade); grade III and grade IV are malignant brain tumor (high-grade). Usually, if low-grade brain tumor is not treated, it is likely to deteriorate to high-grade brain tumor. The 2012 CBTRUS (Central Brain Tumor Registry of the United States) Statistical Report has also showed that brain tumors are the second leading cause of cancer-related deaths in children under age 20 and in males ages 20-39 (leukemia is the first) and the fifth leading cause of cancer-related deaths in females ages 20-39. An estimated 69 720 new cases of primary brain tumors were expected to be diagnosed in 2013 and included both malignant (24 620) and non-malignant (45 100) brain tumors. This estimate is based on an application of age-sex-race-specific incidence rates from the 2013 CBTRUS Statistical Report using SEER and NPCR data to project 2013 US population estimates for the

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respective age-sex-race groups (www.abta.org/about-us/news/brain-tumor-statistics/). Therefore, brain tumor are seriously endangering people's lives and early discovery and treatment have become a necessity. In the clinical aspect, treatment options for brain tumor include surgery, radiation therapy or chemotherapy.

Along with the advance of medical imaging, imaging modalities play an important role in the evaluation of patients with brain tumors and have a significant impact on patient care. Recent years, the emerging new imaging modalities, such as X-Ray, Ultrasonography, Computed Tomography (CT), Magneto Encephalo Graphy (MEG), Electro Encephalo Graphy (EEG), Positron Emission Tomography (PET), Single-Photon Emission Computed Tomography (SPECT), and Magnetic Resonance Imaging (MRI), not only show the detailed and complete aspects of brain tumors, but also improve clinical doctors to study the mechanism of brain tumors at the aim of better treatment. Clinical doctors play an important role in brain tumor assessment and therapy. Once a brain tumor is clinically suspected, radiologic evaluation is required to determine the location, the extent of the tumor, and its relationship to the surrounding structures. This information is very important and critical in deciding between the different forms of therapy such as surgery, radiation, and chemotherapy. Therefore, the evaluation of brain tumors with imaging modalities is now one of the key issues of radiology departments.

MRI is a non-invasive and good soft tissue contrast imaging modality, which provides invaluable information about shape, size, and localization of brain tumors without exposing the patient to a high ionization radiation[3]. MRI is attracting more and more attentions for the brain tumor diagnosis in the clinical[4]. In current clinical routine, the images of different MRI sequences are employed for the diagnosis and delineation of tumor compartments. These sequence images include T1-weighted MRI (T1w), T1-weighted MRI with contrast enhancement (T1wc), T2-weighted MRI (T2w), Proton Density-weighted MRI (PDw), FLuid-Attenuated Inversion Recovery (FLAIR), etc. Figure 1 shows an axial slice of four standard sequences for a glioblastoma (a type of brain tumor) patient[5].

Since T1w allows for an easy annotation of the healthy tissues, it has become the most commonly used sequence images for the brain tumor structure analysis. Moreover, T1-weighted contrast-enhanced sequence images can make the brain tumor borders become brighter because the contrast agent accumulates there due to the disruption of the blood-brain barrier in the proliferative brain tumor region. In these sequence images, the necrotic core and the active cell region can be distinguished easily. In T2w, the edema region can appear brighter than other sequence images of MRI. Since the signal of water molecules is suppressed in the imaging process of FLAIR, FLAIR is regarded as a highly effective sequence image to help separate the edema region from the CSF.

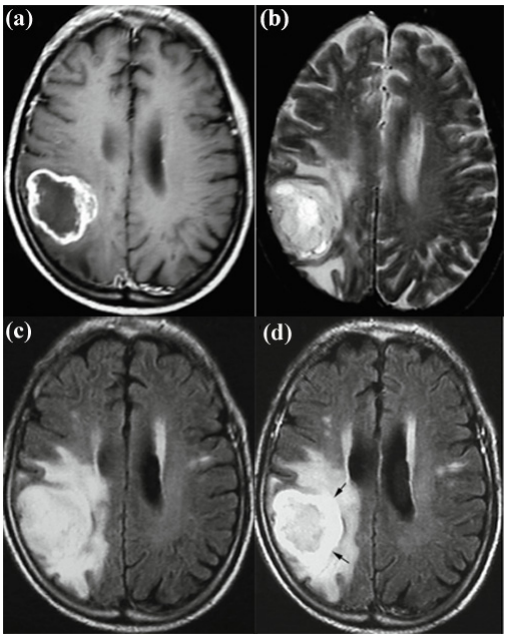

Fig. 1 Four imaging modalities: (a) T1-weighted MRI; (b) T2-weighted MRI; (c) FLAIR; and (d) FLAIR with contrast enhancement[5].

Due to the large amount of brain tumor images that are currently being generated in the clinics, it is not possible for clinicians to manually annotate and segment these images in a reasonable time. Hence, the automatic segmentation has become inevitable. Brain tumor segmentation is to segment abnormal tissues such as active cells, necrotic core, and edema (Fig. 2) from normal brain tissues including GM, WM, and CSF[6]. In recent years, medical imaging and soft computing have made significant advancements in the field of brain tumor segmentation. In general, most of abnormal brain tumor tissues may be easily detected by brain tumor segmentation methods. But accurate and reproducible segmentation results and representation of abnormalities have not been solved all the way. Since brain tumor segmentation has great impact on diagnosis, monitoring, treatment planning

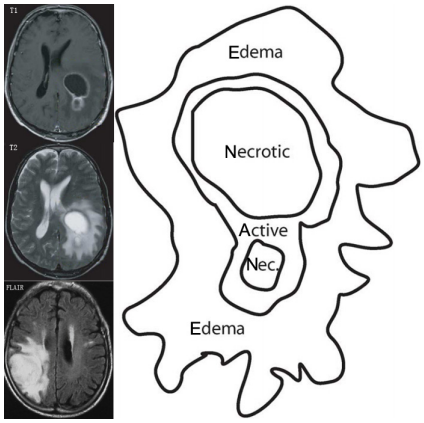

Fig. 2 Left is three types of brain tumor MRI images: T1 with contrast, T2 and FLAIR image; right is three main components after segmenting brain tumor[6].

for patients, and clinical trials, this paper focuses on MRI-based brain tumor segmentation and presents a relatively detailed overview for the current existing methods of MRI-based brain tumor segmentation.

The rest of this paper is organized as follows: In Section 2, we briefly introduce the preprocessing methods of MRI images. In Section 3, we discuss the current different brain tumor segmentation algorithms including conventional methods, classification and clustering methods, and deformable model methods. In Section 4, we analyze the evaluation and validation of the current brain tumor segmentation methods. Finally, in Section 5, an objective assessment is presented and future developments and trends are addressed for MRI-based brain tumor segmentation methods.

2 The Preprocessing of MRI Images

Before the presentation of the brain tumor segmentation methods, the MRI preprocessing operations are introduced because it is directly related to the qualities of the segmentation results. In general, the raw MRI images need to be preprocessed to realize the segmentation purposes. These pre-processing operations include de-noising, skull-stripping, intensity normalization, etc, and have direct impact on the results of brain tumor segmentation.

Image de-noising is a standard preprocessing task for MRI. Noise in MRI image makes it difficult to precisely delineate regions of interest between brain tumor and normal brain tissues. For this reason, it is necessary to preprocess MRI image to reduce noise and to enhance contrast between regions. Many de-noising methods for MRI image have been proposed, such as Anisotropic Diffusion Filtering (ADF)[7, 8], wavelets[9, 10], Non-Local Means (NLM)[11-13], and Independent Component Analysis (ICA)[14, 15]. ADF is the current most popular method for the de-noising of brain tumor MRI images. A critical review of the effects of de-noising algorithms on MRI brain tumor segmentation was discussed in Ref. [16]. It concluded that, although the noise of images was reduced, it has always existed and became a negative effect on the brain tumor segmentation.

Skull stripping is an important preprocessing step for the analysis of MRI images[17-20]. For example, Fig. 3 shows a result of skull stripping. Skull stripping is the process of delineation and removal of non-cerebral tissue region such as skull, scalp, and meninges from the brain soft tissues[21]. The accuracy in skull striping process affects the efficiency in detecting tumor, pre-surgical planning, cortical surface reconstruction, and brain morphometry[22], and has been considered as an essential step for brain tumor segmentation[23]. Removal of the skull region reduces the chances of misclassifying diseased tissues[24]. The process of skull stripping is faced with many challenges due to the complexity of the human brain, variability in the parameters of MR scanners, and individual characteristics[25]. Poor quality and low contrast images also contribute to difficulties in segmenting the images precisely[24]. Many of robust skull stripping algorithms have been proposed to reduce these influences[26].

Intensity normalization[27] is a very critical step for the preprocessing of MRI, especially when classification and clustering methods are used for the segmentation. However, due to the confounding effects caused by the differences in brain tumor appearance, the segmentation of tumor-bearing images are more challenging than healthy images. A pathology-robust normalization method was proposed to improve both

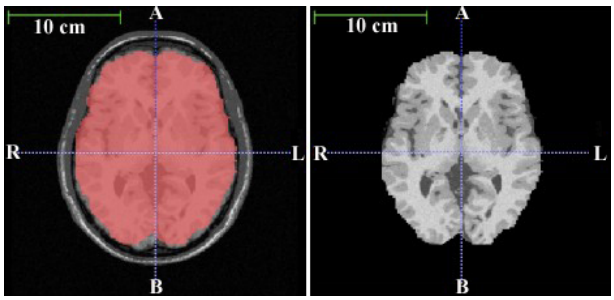

Fig. 3 Skull-stripping result shown on an axial slice of one T1-weighted Brainweb image. From left to right: Original image with mask overlay; Brain tissues after applying the skull-stripping mask[20].

global and local constraints for MRI images[28]. In general, before the operation of the segmentation started, a bias-field correction was employed to reduce the effect of magnetic field inhomogeneities during image acquisition[29].

When operating on multi-modal images, pre-processing always includes the registration of all modalities in a common space of reference. In most cases, this is performed using a linear transformation model with the Mutual Information (MI) similarity metric[30] and resampling in order to ensure voxel-to-voxel correspondence across all modalities.

3 Brain Tumor Segmentation Methods

Nowadays, brain tumor segmentation methods can be organized into different categories based on different principles. In the clinic, brain tumor segmentation methods are usually classified into three main categories including manual, semi-automatic, and fully automatic segmentations based on the degree of required human interaction[31-33].

For manual brain tumor segmentation, the experts of brain tumor must master the information presented in the brain tumor images and some additional knowledge such as anatomy because manual brain tumor segmentation aims to manually draw the boundaries of the brain tumor and paint the regions of anatomic structures with different labels[31]. To date, manual segmentation is widely applied to clinical trial. In the clinic, since many of brain tumor images are emerging, the manual segmentation of the different regions of brain tumor will become an error-prone and time-consuming task for the experts and yield poor results in a way. Therefore, more advanced segmentation methods such as semi-automatic and fully automatic segmentation methods are required to address this problem.

For semi-automatic brain tumor segmentation, it mainly consists of the user, interaction, and software computing. In the semi-automatic brain tumor methods, the user needs to input some parameters and is responsible for analyzing the visual information and providing feedback response for the software computing. The software computing is targeted at the realization of brain tumor segmentation algorithms. The interaction is in charge of adjusting segmentation information between the user and the software computing. The semi-automatic brain tumor segmentation methods were divided into three main processes: initialization, feedback response, and evaluation[32]. Although brain tumor semi-automatic segmentation methods can obtain better results than manual segmentation, it also comes into being different results from different experts or the same user at different times. Hence, fully automatic brain tumor segmentation methods were proposed.

For fully automatic brain tumor segmentation, the computer determines the segmentation of brain tumor without any human interaction. In general, a fully automatic segmentation algorithm combines artificial intelligence and prior knowledge. With the development of machine learning algorithms that can simulate the intelligence of humans to learn effectively, the study of fully automatic brain tumor segmentation has become a popular research issue.

The semi-automatic and fully automatic segmentation of tumor brain images are faced with great challenges due to usually exhibiting unclear and irregular boundaries with discontinuities and partial-volume effects for brain tumor images. This paper divides the current MRI-based brain tumor segmentation methods into three major categories: conventional methods, classification and clustering methods, and deformable model methods.

3.1 Conventional methods

In this paper, conventional brain tumor segmentation methods mainly include the use of standard image processing methods such as threshold-based methods[34,35] and region-based methods[36]. Threshold-based and region-based methods are commonly employed in two-dimensional image segmentation[37].

3.1.1 Threshold-based methods

Threshold-based method is a simple and effective segmentation method by comparing their intensities with one or more intensity thresholds. At present, threshold-based methods are classified into global and local thresholdings.

If an image contains objects with homogeneous intensity or the contrast between the 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[38]. In addition, the Gaussian distribution was applied to determine the thresholds in normal brain MRI image[39].

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.

3.1.2 Region-based methods

Region-based segmentation methods examine pixels in an image and form disjoint regions by merging neighborhood pixels with homogeneity properties based on a predefined similarity criterion[40]. The region growing and the watershed segmentation methods are part of the region-based methods and are generally used in the process of brain tumor segmentation.

The region growing is the simplest and most commonly region-based segmentation method and is used to extract a connected region of similar pixels from an image[41]. Region growing starts with at least one seed that belongs to the structure of interest. Neighbors of the seed are checked and those satisfying the similarity criteria are added to the region. The similarity criteria are determined by a range of pixel intensity values or other features in the image. Seeds can be chosen manually or provided by an automatic seed-finding procedure[42]. 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[42]. 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[43,44]. The primary disadvantage of region growing method is the partial volume effect[45] 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 tissues types, because the voxel may represent more than one kind of tissue types[46]. Some segmentation methods incorporate the region growing process as a refinement step[47]. A fuzzy information fusion framework was proposed for the automatic segmentation of brain tumor using MRI[48]. The registration of multispectral images was the first step for the creation of this framework including a priori knowledge, fuzzy feature fusion, and an adjustment by fuzzy region growing.

The basic principle of watershed segmentation method can be explained by a metaphor based on the behavior of water in a landscape. When it rains, drops of water falling in different regions will follow the landscape downhill. The water will end up at the bottom of valleys. For each valley there will be a region from which all water drains into it. At points where water comes from different basins meets, dams will be built. When the water level reach the highest peak in the landscape, the process is stopped. As a result, the landscape is partitioned into regions separated by dams, called watershed lines or watersheds. Some researchers used multi-scale watershed transformation to segment brain tumors[49,50]. An analysis of user-assisted hierarchical watershed segmentation methods of brain tumors from MRI data was performed[51]. The quantitative and qualitative results showed that the segmentation time and precision were improved significantly and it outperformed manual segmentation. The analysis also identified some disadvantages in the watershed method for brain tumor segmentation. To improve these disadvantages, some methods had been proposed. A multi-parameter watershed segmentation algorithm that was used for detection of tumor in 2-D and 3-D brain MRI was proposed[52]. A marker-based improved watershed algorithm by utilizing the prior knowledge of the test images for the segmentation of brain tumors was proposed[53]. The watershed segmentation methods usually suffer from over-segmentation. To avoid over-segmentation and produce a reasonable segmentation, some advanced methods have been proposed[54-56].

In conclusion, 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 accord with the requirements of clinical doctors.

3.2 Classification and clustering methods

Machine learning provides an effective way to automate the analysis and diagnosis for medical images. It can potentially reduce the burden on radiologists in the practice of radiology[57], which can learn complex relationships or patterns from empirical data and make accurate decisions[58]. Machine learning algorithms can be organized into different categories based on different principles. This method is classified into supervised learning, semi-supervised learning, and unsupervised learning algorithms based on the utilization of labels of training samples[59].

In supervised learning, each sample contains two parts: One is input observations or features and the other is output observations or labels[60]. Usually the input observations are causes and the output observations are effects. The purpose of supervised learning is to deduce a functional relationship from training data that generalizes well to testing data. The form of the relationship is a set of equations and numerical coefficients or weights. Classification algorithm is a representative method of the supervised learning.

In unsupervised learning, we only have one set of observations and there is no label information for each sample[61]. Usually these observations or features are caused by a set of unobserved or latent variables. The main purpose of unsupervised learning is to discover relationships between samples or reveal the latent variables behind the observations. Clustering algorithm is a representative method of the unsupervised learning.

Semi-supervised learning combines supervised and unsupervised learning[62]. It utilizes both labeled data and unlabeled data during the training process. Semi-supervised learning algorithms were developed mainly because the labeling of data is very expensive or impossible in some applications[63].

In fact, most of brain tumor segmentation algorithms are based on classification or clustering methods in the literature such as Fuzzy C-Means (FCM), k-means, Markov Random Fields (MRF), Bayes, Artificial Neural Networks (ANN), Support Vector Machines (SVM), Atlas-based, etc. In this section, FCM, Atlas-based, MRF, and SVM for segmenting brain tumor are discussed.

3.2.1 FCM algorithms

FCM is a method of clustering which divides one group of data into two or more clusters. This method[64] is frequently used in pattern recognition. Straightly speaking, this algorithm works by assigning membership to each data point corresponding to each cluster center on the basis of distance between the cluster and the data point. The nearer the data is to the cluster center the more possible its membership towards the particular cluster center is. The advantages of FCM algorithm include: (1) Giving the best result for overlapped data set and comparatively better than k-means algorithm. (2) Unlike k-means where data point must exclusively belong to one cluster center, assigning the membership of data points to more than one cluster center. As a result, a data point may belong to more than one cluster center. (3) The application of FCM to MR data has shown encouraging results[65]. Therefore, FCM for segmenting brain tumors is becoming a fruitful research area.

In the study of brain tumor segmentation, brain tumor was segmented into tissue classes including active cells, necrotic core, and edema using unsupervised FCM clustering algorithm[66]. Using this algorithm, it is possible to generate segmentation images that display clinically important neuroanatomic and neuropathologic tissue contrast information from raw MR image data. Subsequently, some researchers incorporate additional information into the feature vectors being clustered using FCM. The MRI images are processed by a system which integrates knowledge-based methods with multispectral histogram analysis was proposed to deal with the segmentation of brain tumor[67]. A knowledge-based fuzzy clustering approach was proposed and implemented for the segmentation of the MRI images of brain tumor followed by 3-D connected components to build the tumor shape[68]. Based on fuzzy knowledge and modified seeded region growing, a novel image segmentation method called Fuzzy Knowledge-based Seeded Region Growing (FKSRG) was proposed[69]. Experimental results demonstrate that the FKSRG method segments multispectral MR images much more effectively than the functional MRI of the Brain Automated Segmentation Tool, k-means, and SVM methods.

Since 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[70]. 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[71].

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[72]. 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. The Genetic Algorithms (GAs) are good at reaching a near optimal solution but have trouble finding an exact solution while Particle Swarm Optimization (PSO) enhances the search for an optimal solution. The combination of GAs and PSO was presented to determine the optimum value of degree of attraction[73]. To improve the accurate determination of stage and size of tumor, a combined method of the *k*-means and fuzzy *c*-means algorithms was proposed to deal with the segmentation of brain tumor[1]. This method allows the segmentation of tumor tissue with accuracy and reproducibility comparable to manual segmentation. In addition, it also reduces the time for the progress of the segmentation.

3.2.2 Atlas-based algorithms

Atlas-based algorithm was firstly introduced to register different images[74]. Subsequently, atlas-based segmentation approaches have been widely used for guiding brain tissue segmentation. Atlases can be used to restrict the tumor location and also for generative classification models. In general, atlas-based algorithm for the segmentation of brain tumor includes three steps: Firstly, an affine registration brings the atlas and the patient into global correspondence; secondly, the seeding of a synthetic tumor into the brain atlas provides a template for the brain tumor; thirdly, the deformation of the seeded atlas by optical flow principles and brain tumor growth[75].

Some researchers used atlases not only to impose spatial constraints, but also to provide probabilistic information about the tissue model. They employed a probabilistic tissue model and used an Expectation Maximization (EM) method[76] to segment brain tumor by modifying an atlas with patient-specific information about tumor location from different MRI modalities[77, 78]. The methods in these two papers can be considered as atlas-based methods by considering the biomechanical[79] and shape[80] prior information into the atlas-based deformable registration. The advantage of this category of methods is that domain knowledge can be integrated into the better consideration of atlas-based segmentation, while the disadvantage is that the variability of such prior information is difficult to account for. A method based on a priori model of lesion growth that assumes radial expansion of the lesion from its starting point for brain atlas deformation in the presence of large space-occupying tumors was proposed and gained the good segmentation results of brain tumor. Since existing brain atlases are usually constructed by equally averaging pre-segmented images in a population, these processing methods will reduce local inter-subject structural variability and lead to lower segmentation guidance capability[75]. A multi-region-multi-reference framework for atlas-based neonatal brain segmentation[81] was proposed to improve this problem. A new approach was proposed to combine a healthy brain atlas with a latent brain tumor atlas to segment brain tumors from multi-sequence images using a generative probabilistic model and spatial regularization[82]. Figure 4 shows parts of the results for this method. A review of the automated approaches for atlas-based segmentation of magnetic resonance brain images was presented[83]. This review aimed to point out the strengths and weaknesses of atlas-based methods and suggest new research directions. Recently, the localization based on a brain atlas is used for their multi-modal segmentation of optic pathway gliomas to perform classification with a probabilistic tissue model[84].

A precise atlas is the key to the atlas-based methods. The atlas has a close relationship with the effectiveness and practicability of these methods. At present, some atlases such as Brodmann, Talairach-

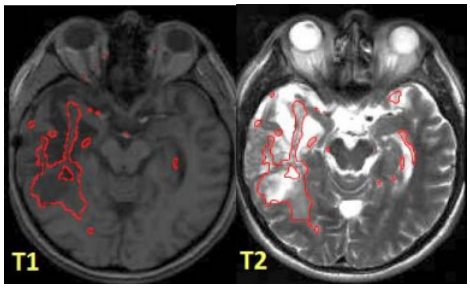

Fig. 4 Examples of the results of T1 and T2 brain tumor segmentation[82].

Tournoux, BrainWeb, and Whole Brain have been used as shown in Table 1.

3.2.3 MRF algorithms

MRF had been proposed as it can provide a way to integrate spatial information into the clustering or classification process[89]. In clustering methods, it reduces both the possible problem of overlapping and the effect of noise on the result[90]. In the particular case of brain tumor segmentation, if a region is strongly labeled as brain tumor or non-brain tumor, MRF will determine if the neighbor of the labeled region is the same. Conditional Random Fields (CRF) had been proposed to build probabilistic models to segment and label sequence data[91]. MRF and CRF algorithms can represent complex dependencies among data sets to gain a high accuracy for the results of brain tumor segmentation[28].

The different tissues such as GM, WM, CSF, Active Cells (AC), Necrotic Core (NC), and Edema (E) could be modeled by a Mixture Model (such as GMM) and trained the MRF with the Iterated Condition Modes (ICM) algorithm[92]. The different models of the different tissues can easily segment each tissue. A multi-layer MRF framework was proposed to detect brain abnormalities[93]. The main layers included input, spatial locations, structural coherence, and region intensities. The multi-layer MRF framework assumed that if the attributes of lower-level layers shared strong similarities, a given voxel would change its high-level classification in the evolving presence of tumor. To improve the quality of tumor segmentation in clinical applications where low-resolution sequences are commonly used together with high-resolution images, an algorithm based on Spatial accuracy-weighted Hidden Markov random field and Expectation maximization (SHE) approach for both automated tumor and enhanced-tumor segmentation was proposed[94]. SHE incorporates the spatial interpolation accuracy of low-resolution images into the optimization procedure of the Hidden MRF (HMRF) to segment tumor using multi-channel MR images with different resolutions. In SHE algorithm, the tumor segmentation results were more accurate. An automatic method was presented to segment brain tissues from volumetric MRI brain tumor images[95]. The method is based on non-rigid registration of an average atlas in combination with a biomechanically justified tumor growth model to simulate soft-tissue deformations caused by the tumor mass-effect. The tumor growth model, which is formulated as a mesh-free MRF energy minimization problem, ensures correspondence between the atlas and the patient image, prior to the registration step. This method is non-parametric, simple, and fast compared to other approaches while maintaining similar accuracy. A fully automated hierarchical probabilistic framework was proposed for segmenting brain tumours from multispectral human brain MRI using multiwindow Gabor filters and an adapted MRF framework[96]. In this framework, brain tumors were segmented into edema and non-edema by using BraTS database as shown in Fig. 5. Figure 5 denoted that this algorithm's labels correspond closely to the expert's labels.

Table 1 The current existing atlases.

Name	Representation	Ref.
Brodmann	The first brain atlas	[85]
Talairach-Tournoux	Construct a three-dimensional coordinate to provide a standard space	[86]
BrainWeb	Widely used in the brain MRI images analysis	[87]
Whole Brain	Used in neurosurgery at Harvard Medical School	[88]

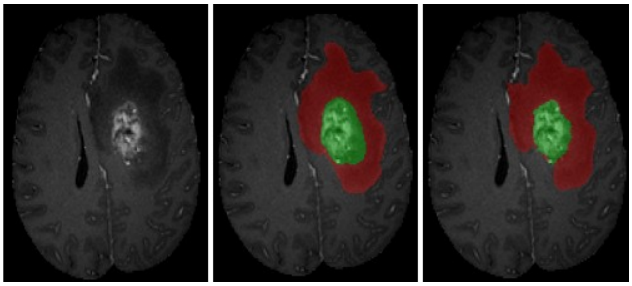

Fig. 5 From left to right: the unlabelled T1C slice, expert labelling, and this algorithm labels (red, edema, green, non-edema)[96].

3.2.4 SVM algorithms

The original SVM algorithm was invented by Vladimir N. Vapnik and the current standard incarnation was proposed by Cortes and Vapnik in 1993 and published in 1995[97]. SVM was treated as a parametrically kernel-based method to deal with supervised classification problems[98]. SVM has been widely used in the field of brain tumor segmentation[99-103], mainly owing to its great classification ability.

A brain tumor segmentation method by exploring one-class SVM has been proposed[99]. This method had the ability of learning the nonlinear distribution of the image data without prior knowledge, via the automatic procedure of SVM parameters training and an implicit learning kernel and achieved better segmentation results for the extraction of the brain tumors, compared to the fuzzy clustering method. Some researchers used a high number of MRI modalities to create voxel-wise intensity-based feature vectors, which they classified by SVM[100, 101]. This method was able to not only segment the healthy tissues, but also segment sub-compartments of healthy and tumor regions. A very similar approach based on SVM has been proposed[102], but this method only segmented one tumor region and used a lower number of modalities. Later, this method was improved by the feature selection with kernel class separability and obtained better results[103]. A multi-kernel based SVM integrated with a feature selection and a fusion process was proposed to segment the brain tumor from multi-sequence MRI images[104]. This method consists of two steps: classifying the tumor region using a multi-kernel SVM which performs on multi-image sources and obtains relative multi-result and ameliorating the contour of the tumor region using both the distance and the maximum likelihood measures. Compared with traditional single kernel SVM, the results of this method showed a diminution of the total error and improvement of accuracy. A fully automatic method for brain tissue segmentation was proposed[105], which combined SVM classification using multispectral intensities and textured with subsequent hierarchical regularization based on CRF. This method used a hierarchical approach to add robustness and speed by allowing to apply different levels of regularization at different stages and had good results as shown in Fig. 6. In conclusion, SVM has demonstrated great potential and usefulness in brain tumor segmentation for MRI images.

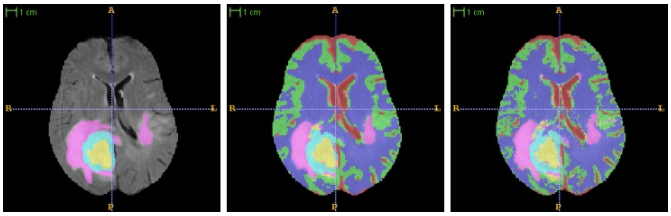

Fig. 6 From left to right: manual segmentation, hierarchical SVM-classification with CRF-regularization, and non-hierarchical SVM-classification without regularization[105].

Apart from the above three methods, many of classification or clustering algorithms were used to realize the segmentation of MRI-based brain tumor. Table 2 shows some relatively good algorithms for brain tumor segmentation of MRI in recent years.

3.3 Deformable model methods

Due to the appearance of 3-D MRI data, the segmentation of these data has become a challenging problem[108, 109]. The challenge is to extract boundary elements belonging to the same structure and integrate these elements into a coherent and consistent model of the structure. Therefore, model-based segmentation methods including parametric and geometric deformable models were proposed to improve this problem. The widely recognized potency of deformable models stems from their ability to segment images of anatomic structures by exploiting constraints derived from the image data together with a priori knowledge about the location, size, and shape of these structures. Deformable models are capable of accommodating the often significant variability of biological structures over time and across different individuals[110]. Furthermore, deformable models support highly intuitive interaction mechanisms that allow medical researchers and clinicians to bring their expertise to bear on the model-based image interpretation task when necessary[111]. The following sections explain the parametric and geometric deformable models including some approaches appearing in the literature for brain tumor segmentation.

3.3.1 Parametric deformable models

Parametric Deformable Models (PDM) were also known as snakes and active contour models. Snakes were first introduced in 1988[112]. If an appropriate initialization is done, a snake can locate object contours well. In parametric deformable models, the important

Table 2 Some relatively good algorithms of MRI-based brain tumor segmentation.

Method	Presentation	Ref.
Combination of *k*-means and fuzzy *c*-means	Better accuracy and reproducibility	[1]
FKSRG	Lower over- and under-segmentation	[69]
Multi-region + multi-reference framework	Higher tissue overlap rates and lower standard deviations	[81]
Generative probabilistic model + spatial regularization	Improvement over the traditional multivariate tumor segmentation (25 glioma)	[82]
Probabilistic model + localization	More robust applied to monitor disease progression	[84]
Non-rigid registration + atlas + MRF	Multivariate tumor segmentation	[82]
SVM + CRF	10 multispectral patient datasets more detail segmentation low computation times	[105]
Decision Forests + tissue-specific Gaussian mixture models	Segmenting the individual tissue types simultaneously such as AC, NC, E, etc.	[106]
SVM + Kernel feature selection	Good results tested in T1w, T2w and T1c, low computation time	[107]

step of brain tumor segmentation is to find the boundary of brain tumors. Snakes have been widely used for its sensitivity in detecting the boundary of brain tumors.

Facts proved that the resolution of the boundary found by the snake is better than the conventional edge detection algorithms such as the Laplacian, Canny, and Sobel[113,114]. Some researchers think that the external energy of snake function is only zero at the edges and positive in homogeneous regions[115]. Many of researchers aim to improve the snakes performance. The Gradient Vector Flow (GVF) snake and the balloon model were proposed to improve the results of brain tumor segmentation on T1 brain tumor MRI[116]. GVF snake was proposed to address the traditional snakes problems of short capture range and inability to track at boundary concavity. The balloon model permits to enlarge the snakes capture range. A parametric deformable model was proposed by spatial relations as refinement step to provide an accurate estimation of the boundaries of any type of brain tumors on T1 MRI[117]. A method combining segmentation and deformable registration of brain scans of glioma patients to a normal atlas was presented[118]. The proposed method is based on the Expectation Maximization (EM) algorithm that incorporates a glioma growth model for atlas seeding, a process which modifies the normal atlas into one with a tumor and edema. The modified atlas is registered into the patient space and utilized for the posterior probability estimation of various tissue labels. EM iteratively refines the estimates of the registration parameters, the posterior probabilities of tissue labels, and the tumor growth model parameters. It's worth noting that the initial position of the PDM sometimes needs to be manually located close enough to the desired boundary to avoid converging to wrong boundaries.

3.3.2 Geometric deformable models

When using parametric deformable models for the segmentation of 3-D MRI data, one disadvantage is the difficulty of naturally handling topological changes for the splitting and merging of contours. Geometric Deformable Models (GDM, also known as level sets) had been proposed to improve this problem[119]. Although these methods notably improved the initialization of parametric active contours and provided that the initial contour was placed symmetrically with respect to the boundaries of interest, in practice this is difficult to achieve because many of brain tumor segmentation methods cannot deal with regularly shaped objects[120]. Since snakes with constant propagation need careful initialization and can leak through weak or missing boundary parts, level-set snakes were proposed and had more significant advantages than conventional statistical classification and mathematical morphology[121]. For example, a knowledge-based segmentation algorithm by combining pixel-intensity distributions and level set snakes is presented[122]. This algorithm gained a more accurate boundaries. A Charged Fluid Framework (CFF) was used by some researchers and governed by Poissons equation as a deformable model to perform brain tumor segmentation[123]. Later, the Charged Fluid Model (CFM) was proposed to extend and modify the

CFF for brain tumor segmentation[124].

A region-based active contour model was proposed in a variable level set formulation for the segmentation of brain tumor[125]. It defined a data fitting energy in terms of a contour and two fitting functions that locally approximated the image intensities on the two sides of the contour. The level set formulation included a regularization term, from which a curve evolution equation was derived for energy minimization. The regularity of the level set function was intrinsically preserved by the level set regularization term to ensure accurate computation avoiding expensive re-initialization of the evolving level set function. Some researchers derived a local intensity clustering property from brain tumor and other images with intensity inhomogeneities and defined a local clustering criterion function for the intensities in a neighborhood of each point[126]. The local clustering criterion was integrated over the neighborhood center to define an energy functional, which was converted to a level set formulation. Minimization of this energy was achieved by an interleaved process of level set evolution and estimation of the bias field. A tumor-cut algorithm was introduced[127] which combines the tumor segmentation using cellular automata with a level set evolving on the tumor probability map to impose spatial smoothness.

In most cases, deformable model is not used alone, but it is used with other algorithms such as FCM, MRF, ANN, etc. This can incorporate the advantage of the two or more algorithms to improve the accuracy of brain tumor segmentation.

4 Evaluation and Validation

The validity of brain tumor segmentation is an important issue in medical image analysis because it has a direct impact on surgical planning. Calculating the overlap with the ground truth has become the most common way to quantitatively evaluate segmentation results. In the field of brain tumor segmentation, the Jaccard coefficient and the Dice Similarity Coefficient (DSC) are the most commonly used evaluation standards[128]. They can range from 0 to 1 with 0 indicating no overlap and 1 indicating perfect overlap. Three different validation metrics including area under the Receiver Operating Characteristic (ROC) curve, Mutual Information (MI), and DSC were compared for the probabilistic brain tumor segmentation[129]. They concluded that the area under the ROC curve should be used for overall classification accuracy, MI is the metric of choice when interested in sensitivity to changes in tumor size, and the Dice coefficient is the best for the spatial alignment evaluation.

Some years ago, a majority of researchers validated their algorithms on a limited number of cases from their own data due to the lack of brain tumor database with ground-truth segmentations that is available to a broad community of clinicians and researchers. This makes it difficult to compare the performance of different methods against each other in a standard way. Therefore, the accuracy, validity, and robustness of the individual methods cannot be directly compared with each other because the different metrics were used. Until recently, a synthetic data was presented to realize a purpose of consistent comparison[130], but so far only few groups tested their methods on these images. The current most popular open MRI database for an objective comparison of brain tumor segmentation algorithms is the BraTS[131]. Tables 3 and 4 show some current open tools and databases for brain tumor segmentation, respectively.

5 Conclusions and Outlook

This paper has provided a comprehensive overview of the state of the art MRI-based brain tumor segmentation methods. Many of the current brain tumor segmentation methods operate MRI images due to the non-invasive and good soft tissue contrast of MRI and employ

Table 3 The current open tools.

Name	Link	Ref.
TumorSim	www.nitrc.org/projects/tumorsim	[130]
FSL	fsl.fmrib.ox.ac.uk	[132]
3D Slicer	www.slicer.org	[133]
MedInria	med.inria.fr/	[134]
GLISTR	www.rad.upenn.edu/sbia/software/glistr/	[118]
MIPAV	mipav.cit.nih.gov	[135]
StripTs	www.istb.unibe.ch/content/research	[20]
FreeSurfer	surfer.nmr.mgh.harvard.edu	[136]
MITK	www.mitk.net/	[137]
BraTumIA	www.istb.unibe.ch/content/research	[138]

Table 4 The current open databases.

Name	Link	Ref.
BraTS	www2.imm.dtu.dk/projects/BRATS2012/	[131]
BrainWeb	brainweb.bic.mni.mcgill.ca/brainweb/	[139]
IBSR	www.nitrc.org/projects/ibsr	[140]

classification and clustering methods by using different features and taking spatial information in a local neighborhood into account. The purpose of these methods is to provide a preliminary judgment on diagnosis, tumor monitoring, and therapy planning for the physician.

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 brain tumor in many cases. 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. Recently, some standard clinical acquisition protocols focusing on feasibility studies are trying to formulate to improve the clinical applications more quickly. Apart from the evaluation of accuracy and validity for the results of brain tumor segmentation, computation time is also an important criterion. The current standard computation time is in general a few minutes. The real-time segmentation will be hard to achieve, but computation time over a few minutes is unacceptable in clinical routine. Another crucial aspect for brain tumor segmentation methods is robustness. If an automatic segmentation technique fails in some cases, clinicians will lose their trust and not use this technique. Therefore, the robustness is also one of the major assessment criteria for each new method applied in clinical practice. Some current brain tumor segmentation methods provide robust results within a reasonable computation time.

Although the main attention of many researchers is brain tumor segmentation algorithms and not the feature extraction for brain tumor, the latter might be more important especially when considering the variance in appearance of different brain tumor grades and types in actual applications. In the future, the feature extraction for brain tumor might be worthwhile to take a closer look at relevant and meaningful features and would be interesting to explore how new features can be designed to obtain better results. This could improve the accuracy, validity, and robustness of MRI-based brain tumor segmentation.

MRI-based brain tumor segmentation techniques have already shown great potential in detecting and analyzing tumors in clinical practice and will undoubtedly continue to be improved in the future. With the development of MRI techniques, more advanced MRI modalities such as Magnetic Resonance Spectroscopy (MRS), Diffusion Tensor Imaging (DTI), and Perfusion Imaging (PI) are gaining more attention in the brain tumor segmentation[141, 142]. For example, a group called Section of Biomedical Image Analysis (SBIA) has worked on these modalities for over 15 years[100, 143]. These modalities can be used for the localization of the different areas of the brain tumor. PI data[144, 145], DTI data[146, 147], and MRS data[148, 149] have been used to segment brain tumor from normal tissues by the existence of machine learning methods. Along with the advance of studies in the area, brain tumor automatic segmentation technology has the potential to provide better prognostic information and optimize treatment options.

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References

[1] M. P. Gupta and M. M. Shringirishi, Implementation of brain tumor segmentation in brain mr images using *k*-means clustering and fuzzy *c*-means algorithm, *International Journal of Computers & Technology*, vol. 5, no. 1, pp. 54-59, 2013.

[2] D. N. Louis, H. Ohgaki, O. D. Wiestler, W. K. Cavenee, P. C. Burger, A. Jouvet, B. W. Scheithauer, and P. Kleihues, The 2007 who classification of tumours of the central nervous system, *Acta Neuropathologica*, vol. 114, no. 2, pp. 97-109, 2007.

[3] Z.-P. Liang and P. C. Lauterbur, *Principles of Magnetic Resonance Imaging: A Signal Processing Perspective*. The Institute of Electrical and Electronics Engineers Press, 2000.

[4] P. Y. Wen, D. R. Macdonald, D. A. Reardon, T. F. Cloughesy, A. G. Sorensen, E. Galanis, J. DeGroot, W. Wick, M. R. Gilbert, A. B. Lassman, et al., Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group, *Journal of Clinical Oncology*, vol. 28, no. 11, pp. 1963-1972, 2010.

[5] A. Drevelegas and N. Papanikolaou, Imaging modalities in brain tumors, in *Imaging of Brain Tumors with Histological Correlations*. Springer, 2011, pp. 13-33.

[6] J. J. Corso, E. Sharon, S. Dube, S. El-Saden, U. Sinha, and A. Yuille, Efficient multilevel brain tumor segmentation with integrated bayesian model classification, *Medical Imaging, IEEE Transactions on*, vol. 27, no. 5, pp. 629-640, 2008.

[7] Y.-L. You, W. Xu, A. Tannenbaum, and M. Kaveh, Behavioral analysis of anisotropic diffusion in image processing, *Image Processing, IEEE Transactions on*, vol. 5, no. 11, pp. 1539-1553, 1996.

[8] J. Weickert, *Anisotropic Diffusion in Image Processing*, vol. 1. Teubner Stuttgart, 1998.

[9] T. Ogden, *Essential Wavelets for Statistical Applications and Data Analysis*. Springer, 1997.

[10] R. D. Nowak, Wavelet-based rician noise removal for magnetic resonance imaging, *Image Processing, IEEE Transactions on*, vol. 8, no. 10, pp. 1408-1419, 1999.

[11] A. Buades, B. Coll, and J.-M. Morel, A non-local algorithm for image denoising, in *Computer Vision and Pattern Recognition, 2005. CVPR 2005. IEEE Computer Society Conference on*, IEEE, 2005, vol. 2, pp. 60-65.

[12] J. V. Manjón, P. Coupé, L. Martí-Bonmatí, D. L. Collins, and M. Robles, Adaptive non-local means denoising of mr images with spatially varying noise levels, *Journal of Magnetic Resonance Imaging*, vol. 31, no. 1, pp. 192-203, 2010.

[13] S. Prima and O. Commowick, Using bilateral symmetry to improve non-local means denoising of mr brain images, in *Biomedical Imaging (ISBI), 2013 IEEE 10th International Symposium on*, IEEE, 2013, pp. 1231-1234.

[14] P. Hoyer, Independent component analysis in image denoising, Master degree dissertation, Helsinki University of Technology, 1999.

[15] K. Phatak, S. Jakhade, A. Nene, R. Kamathe, and K. Joshi, De-noising of magnetic resonance images using independent component analysis, in *Recent Advances in Intelligent Computational Systems (RAICS), 2011 IEEE*, IEEE, 2011, pp. 807-812.

[16] I. Diaz, P. Boulanger, R. Greiner, and A. Murtha, A critical review of the effects of de-noising algorithms on mri brain tumor segmentation, in *Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE*, IEEE, 2011, pp. 3934-3937.

[17] C. Fennema-Notestine, I. B. Ozyurt, C. P. Clark, S. Morris, A. Bischoff-Grethe, M. W. Bondi, T. L. Jernigan, B. Fischl, F. Segonne, D. W. Shattuck, et al., Quantitative evaluation of automated skull-stripping methods applied to contemporary and legacy images: Effects of diagnosis, bias correction, and slice location, *Human Brain Mapping*, vol. 27, no. 2, pp. 99-113, 2006.

[18] A. H. Zhuang, D. J. Valentino, and A. W. Toga, Skull-stripping magnetic resonance brain images using a model-based level set, *NeuroImage*, vol. 32, no. 1, pp. 79-92, 2006.

[19] R. Roslan, N. Jamil, and R. Mahmud, Skull stripping magnetic resonance images brain images: Region growing versus mathematical morphology, *International Journal of Computer Information Systems and Industrial Management Applications*, vol. 3, pp. 150-158, 2011.

[20] S. Bauer, L.-P. Nolte, and M. Reyes, Skull-stripping for tumor-bearing brain images, arXiv preprint arXiv: 1204.0357, 2012.

[21] S. F. Eskildsen, P. Coupé, V. Fonov, J. V. Manjón, K. K. Leung, N. Guizard, S. N. Wassef, L. R. Østergaard, and D. L. Collins, Beast: Brain extraction based on nonlocal segmentation technique, *NeuroImage*, vol. 59, no. 3, pp. 2362-2373, 2012.

[22] F. Ségonne, A. Dale, E. Busa, M. Glessner, D. Salat, H. Hahn, and B. Fischl, A hybrid approach to the skull stripping problem in mri, *Neuroimage*, vol. 22, no. 3, pp. 1060-1075, 2004.

[23] N. F. Ishak, R. Logeswaran, and W.-H. Tan, Artifact and noise stripping on low-field brain mri, *Int. J. Biology Biomed. Eng*, vol. 2, no. 2, pp. 59-68, 2008.

[24] S. Shen, W. Sandham, M. Granat, and A. Sterr, Mri fuzzy segmentation of brain tissue using neighborhood attraction with neural-network optimization, *Information Technology in Biomedicine, IEEE Transactions on*, vol. 9, no. 3, pp. 459-467, 2005.

[25] J. G. Park and C. Lee, Skull stripping based on region growing for magnetic resonance brain images, *NeuroImage*, vol. 47, no. 4, pp. 1394-1407, 2009.

[26] W. Speier, J. E. Iglesias, L. El-Kara, Z. Tu, and C. Arnold, Robust skull stripping of clinical glioblastoma multiforme data, in *Medical Image Computing and Computer-Assisted Intervention-MICCAI 2011*, Springer, 2011, pp. 659-666.

[27] L. G. Nyu and J. K. Udupa, On standardizing the mr image intensity scale, *Image*, vol. 1081, 1999.

[28] A. Ekin, Pathology-robustmr intensity normalizationwith global and local constraints, in *Biomedical Imaging: From Nano to Macro, 2011 IEEE International Symposium on*, IEEE, 2011, pp. 333-336.

[29] M. Shah, Y. Xiao, N. Subbanna, S. Francis, D. L. Arnold, D. L. Collins, and T. Arbel, Evaluating intensity normalization on mris of human brain with multiple sclerosis, *Medical Image Analysis*, vol. 15, no. 2, pp. 267-282, 2011.

[30] A. Mang, J. A. Schnabel, W. R. Crum, M. Modat, O. Camara-Rey, C. Palm, G. B. Caseiras, H. R. Jäger, S. Ourselin, T. M. Buzug, et al., Consistency of parametric registration in serial mri studies of brain tumor progression, *International Journal of Computer Assisted Radiology and Surgery*, vol. 3, nos. 3-4, pp. 201-211, 2008.

[31] D. L. Pham, C. Xu, and J. L. Prince, Current methods in medical image segmentation 1, *Annual Review of Biomedical Engineering*, vol. 2, no. 1, pp. 315-337, 2000.

[32] N. Sharma and L. M. Aggarwal, Automated medical image segmentation techniques, *Journal of Medical Physics/Association of Medical Physicists of India*, vol. 35, no. 1, p. 3, 2010.

[33] S. Bauer, R. Wiest, L.-P. Nolte, and M. Reyes, A survey of mri-based medical image analysis for brain tumor studies, *Physics in Medicine and Biology*, vol. 58, no. 13, p. R97, 2013.

[34] H. Suzuki and J.-I. Toriwaki, Automatic segmentation of head mri images by knowledge guided thresholding, *Computerized Medical Imaging and Graphics*, vol. 15, no. 4, pp. 233-240, 1991.

[35] G. Harris, P. Barta, L. Peng, S. Lee, P. Brettschneider, A. Shah, J. Henderer, T. Schlaepfer, and G. Pearlson, MR volume segmentation of gray matter and white matter using manual thresholding: Dependence on image brightness, *American Journal of Neuroradiology*, vol. 15, no. 2, pp. 225-230, 1994.

[36] R. Adams and L. Bischof, Seeded region growing, *Pattern Analysis and Machine Intelligence, IEEE Transactions on*, vol. 16, no. 6, pp. 641-647, 1994.

[37] C. Vijayakumar and D. C. Gharpure, Development of image-processing software for automatic segmentation of brain tumors in mr images, *Journal of Medical Physics/Association of Medical Physicists of India*, vol. 36, no. 3, p. 147, 2011.

[38] Y.-C. Sung, K.-S. Han, C.-J. Song, S.-M. Noh, and J.-W. Park, Threshold estimation for region segmentation on mr image of brain having the partial volume artifact, in *Signal Processing Proceedings, 2000. WCCC-ICSP 2000. 5th International Conference on*, IEEE, 2000, vol. 2, pp. 1000-1009.

[39] A. Stadlbauer, E. Moser, S. Gruber, R. Buslei, C. Nimsky, R. Fahlbusch, and O. Ganslandt, Improved delineation of brain tumors: An automated method for segmentation based on pathologic changes of 1H-MRSI metabolites in gliomas, *Neuroimage*, vol. 23, no. 2, pp. 454-461, 2004.

[40] K.-P. Wong, Medical image segmentation: Methods and applications in functional imaging, in *Handbook of Biomedical Image Analysis*. Springer, 2005, pp. 111-182.

[41] G. Mittelhaeusser and F. Kruggel, Fast segmentation of brain magnetic resonance tomograms, in *Computer Vision, Virtual Reality and Robotics in Medicine*. Springer, 1995, pp. 237-241.

[42] M. R. Kaus, S. K. Warfield, A. Nabavi, P. M. Black, F. A. Jolesz, and R. Kikinis, Automated segmentation of mr images of brain tumors 1, *Radiology*, vol. 218, no. 2, pp. 586-591, 2001.

[43] V. F. Chong, J.-Y. Zhou, J. B. Khoo, J. Huang, and T.-K. Lim, Tongue carcinoma: Tumor volume measurement, *International Journal of Radiation Oncology Biology Physics*, vol. 59, no. 1, pp. 59-66, 2004.

[44] Y. Salman, M. Assal, A. Badawi, S. Alian, and M. E. El-Bayome, Validation techniques for quantitative brain tumors measurements, in *Engineering in Medicine and Biology Society, 2005. IEEE-EMBS 2005. 27th Annual International Conference of the*, IEEE, 2006, pp. 7048-7051.

[45] M. Sato, S. Lakare, M. Wan, A. Kaufman, and M. Nakajima, A gradient magnitude based region growing algorithm for accurate segmentation, in *Image Processing, 2000. Proceedings. 2000 International Conference on*, IEEE, 2000, vol. 3, pp. 448-451.

[46] S. Lakare and A. Kaufman, 3D segmentation techniques for medical volumes, Center for Visual Computing, Department of Computer Science, State University of New York, 2000.

[47] Y. M. Salman, Modified technique for volumetric brain tumor measurements, *Journal of Biomedical Science and Engineering*, vol. 2, p. 16, 2009.

[48] W. Dou, S. Ruan, Y. Chen, D. Bloyet, and J.-M. Constans, A framework of fuzzy information fusion for the segmentation of brain tumor tissues on mr images, *Image and Vision Computing*, vol. 25, no. 2, pp. 164-171, 2007.

[49] M. Letteboer, W. Niessen, P. Willems, E. B. Dam, and M. Viergever, Interactive multi-scale watershed segmentation of tumors in mr brain images, in *Proc. of the IMIVA Workshop of MICCAI*, Citeseer, 2001.

[50] E. Dam, M. Loog, and M. Letteboer, Integrating automatic and interactive brain tumor segmentation, in *Pattern Recognition, 2004. ICPR 2004. Proceedings of the 17th International Conference on*, IEEE, 2004, vol. 3, pp. 790-793.

[51] J. E. Cates, R. T. Whitaker, and G. M. Jones, Case study: An evaluation of user-assisted hierarchical watershed segmentation, *Medical Image Analysis*, vol. 9, no. 6, pp. 566-578, 2005.

[52] R. Ratan, S. Sharma, and S. Sharma, Multiparameter segmentation and quantization of brain tumor from mri images, *Indian Journal of Science and Technology*, vol. 2, no. 2, pp. 11-15, 2009.

[53] S. D. Salman and A. A. Bahrani, Segmentation of tumor tissue in gray medical images using watershed transformation methods, *International Journal of Advancements in Computing Technology*, vol. 2, no. 4, pp. 123-127, 2010.

[54] A. Bleau and L. J. Leon, Watershed-based segmentation and region merging, *Computer Vision and Image Understanding*, vol. 77, no. 3, pp. 317-370, 2000.

[55] V. Gies and T. M. Bernard, Statistical solution to watershed over-segmentation, in *International Conference on Image Processing*, 2004.

[56] J. Kong, J. Wang, Y. Lu, J. Zhang, Y. Li, and B. Zhang, A novel approach for segmentation of mri brain images, in *Electrotechnical Conference, 2006. MELECON 2006. IEEE Mediterranean*, IEEE, 2006, pp. 525-528.

[57] R. O. Duda, P. E. Hart, and D. G. Stork, *Pattern Classification*. John Wiley & Sons, 2012.

[58] C. M. Bishop, *Pattern Recognition and Machine Learning*, vol. 1. Springer New York, 2006.

[59] T. M. Mitchell, The discipline of machine learning, Carnegie Mellon University, School of Computer Science, 2006.

[60] E. Alpaydin, *Introduction to Machine Learning*. MIT Press, 2004.

[61] T. Hastie, R. Tibshirani, J. Friedman, and J. Franklin, The elements of statistical learning: Data mining, inference and prediction, *The Mathematical Intelligencer*, vol. 27, no. 2, pp. 83-85, 2005.

[62] O. Chapelle, B. Schölkopf, and A. Zien, ed., *Semi-Supervised Learning*, vol. 2. MIT Press Cambridge, 2006.

[63] C. Christakou, L. Lefakis, S. Vrettos, and A. Stafylopatis, A movie recommender system based on semi-supervised clustering, in *Computational Intelligence for Modelling, Control and Automation, 2005 and International Conference on Intelligent Agents, Web Technologies and Internet Commerce, International Conference on*, IEEE, 2005, vol. 2, pp. 897-903.

[64] J. C. Bezdek, *Pattern Recognition with Fuzzy Objective Function Algorithms*. Kluwer Academic Publishers, 1981.

[65] L. O. Hall, A. M. Bensaid, L. P. Clarke, R. P. Velthuizen, M. S. Silbiger, and J. C. Bezdek, A comparison of neural network and fuzzy clustering techniques in segmenting magnetic resonance images of the brain, *Neural Networks, IEEE Transactions on*, vol. 3, no. 5, pp. 672-682, 1992.

[66] W. Phillips II, R. Velthuizen, S. Phuphanich, L. Hall, L. Clarke, and M. Silbiger, Application of fuzzy c-means segmentation technique for tissue differentiation in mr images of a hemorrhagic glioblastoma multiforme, *Magnetic Resonance Imaging*, vol. 13, no. 2, pp. 277-290, 1995.

[67] M. C. Clark, L. O. Hall, D. B. Goldgof, R. Velthuizen, F. R. Murtagh, and M. S. Silbiger, Automatic tumor segmentation using knowledge-based techniques, *Medical Imaging, IEEE Transactions on*, vol. 17, no. 2, pp. 187-201, 1998.

[68] L. M. Fletcher-Heath, L. O. Hall, D. B. Goldgof, and F. R. Murtagh, Automatic segmentation of non-enhancing brain tumors in magnetic resonance images, *Artificial Intelligence in Medicine*, vol. 21, no. 1, pp. 43-63, 2001.

[69] G.-C. Lin, W.-J. Wang, C.-C. Kang, and C.-M. Wang, Multispectral mr images segmentation based on fuzzy knowledge and modified seeded region growing, *Magnetic Resonance Imaging*, vol. 30, no. 2, pp. 230-246, 2012.

[70] L. Szilagyi, Z. Benyo, S. M. Szilágyi, and H. Adam, Mr brain image segmentation using an enhanced fuzzy c-means algorithm, in *Engineering in Medicine and Biology Society, 2003. Proceedings of the 25th Annual International Conference of the IEEE*, IEEE, 2003, vol. 1, pp. 724-726.

[71] W. Cai, S. Chen, and D. Zhang, Fast and robust fuzzy c-means clustering algorithms incorporating local information for image segmentation, *Pattern Recognition*, vol. 40, no. 3, pp. 825-838, 2007.

[72] L. Szilágyi, S. M. Szilágyi, and Z. Benyó, A modified fuzzy c-means algorithm for mr brain image segmentation, in *Image Analysis and Recognition*. Springer, 2007, pp. 866-877.

[73] M. Forouzanfar, N. Forghani, and M. Teshnehlab, Parameter optimization of improved fuzzy *c*-means clustering algorithm for brain mr image segmentation, *Engineering Applications of Artificial Intelligence*, vol. 23, no. 2, pp. 160-168, 2010.

[74] J. Maintz and M. A. Viergever, A survey of medical image registration, *Medical Image Analysis*, vol. 2, no. 1, pp. 1-36, 1998.

[75] M. B. Cuadra, C. Pollo, A. Bardera, O. Cuisenaire, J.-G. Villemure, and J. Thiran, Atlas-based segmentation of pathological mr brain images using a model of lesion growth, *Medical Imaging, IEEE Transactions on*, vol. 23, no. 10, pp. 1301-1314, 2004.

[76] A. P. Dempster, N. M. Laird, and D. B. Rubin, Maximum likelihood from incomplete data via the em algorithm, *Journal of the Royal Statistical Society*, vol. 39, no. 1, pp. 1-38, 1977.

[77] N. Moon, E. Bullitt, K. Van Leemput, and G. Gerig, Automatic brain and tumor segmentation, in *Medical Image Computing and Computer-Assisted Intervention—MICCAI 2002*. Springer, 2002, pp. 372-379.

[78] M. Prastawa, E. Bullitt, N. Moon, K. Van Leemput, and G. Gerig, Automatic brain tumor segmentation by subject specific modification of atlas priors, *Academic Radiology*, vol. 10, no. 12, pp. 1341-1348, 2003.

[79] A. Mohamed, D. Shen, and C. Davatzikos, Deformable registration of brain tumor images via a statistical model of tumor-induced deformation, in *Medical Image Computing and Computer-Assisted Intervention-MICCAI 2005*. Springer, 2005, pp. 263-270.

[80] T. Liu, D. Shen, and C. Davatzikos, Deformable registration of tumor-diseased brain images, in *Medical Image Computing and Computer-Assisted Intervention-MICCAI 2004*. Springer, 2004, pp. 720-728.

[81] F. Shi, P.-T. Yap, Y. Fan, J. H. Gilmore, W. Lin, and D. Shen, Construction of multi-region-multi-reference atlases for neonatal brain mri segmentation, *Neuroimage*, vol. 51, no. 2, pp. 684-693, 2010.

[82] B. H. Menze, K. Van Leemput, D. Lashkari, M.-A. Weber, N. Ayache, and P. Golland, A generative model for brain tumor segmentation in multi-modal images, in *Medical Image Computing and Computer-Assisted Intervention-MICCAI 2010*. Springer, 2010, pp. 151-159.

[83] M. Cabezas, A. Oliver, X. Lladó, J. Freixenet, and M. Bach Cuadra, A review of atlas-based segmentation for magnetic resonance brain images, *Computer Methods and Programs in Biomedicine*, vol. 104, no. 3, pp. e158-e177, 2011.

[84] L. Weizman, L. Ben Sira, L. Joskowicz, S. Constantini, R. Precel, B. Shofty, and D. Ben Bashat, Automatic segmentation, internal classification, and follow-up of optic pathway gliomas in mri, *Medical Image Analysis*, vol. 16, no. 1, pp. 177-188, 2012.

[85] K. Brodmann, *Vergleichende Lokalisationslehre der Gro hirnrinde*. Springer, 1909.

[86] J. Talairach and P. Tournoux, *Co-Planar Stereotaxic Atlas of the Human Brain: 3-dimensional proportation System—An Approach to Cerebral Imaging*. New York, USA: Thieme Medical Publishers, 1988.

[87] A. Evans, S. Marrett, J. Torrescorzo, S. Ku, and L. Collins, Mri-pet correlation in three dimensions using a volume-of-interest (voi) atlas, *Journal of Cerebral Blood Flow & Metabolism*, vol. 11, pp. A69-A78, 1991.

[88] M. Shenton, R. Kikinis, W. McCarley, P. Saiviroonporn, H. Hokama, A. Robatino, D. Metcalf, C. Wible, C. Portas, D. Iosifescu, et al., Harvard brain atlas: A teaching and visualization tool, in *Proceedings of the 1995 Biomedical Visualization*, 1995, pp. 10-17.

[89] R. Kindermann and J. L. Snell, *Markov Random Fields and Their Applications*, vol. 1. American Mathematical Society Providence, RI, 1980.

[90] T. N. Tran, R. Wehrens, and L. Buydens, Clustering multispectral images: A tutorial, *Chemometrics and Intelligent Laboratory Systems*, vol. 77, no. 1, pp. 3-17, 2005.

[91] J. Lafferty, A. McCallum, and F. C. Pereira, Conditional random fields: Probabilistic models for segmenting and labeling sequence data, in *Proceedings of the 18th International Conference on Machine Learning 2001 (ICML 2001)*, 2001.

[92] A.-S. Capelle, O. Alata, C. Fernandez, S. Lefèvre, and J. Ferrie, Unsupervised segmentation for automatic detection of brain tumors in mri, in *Image Processing, 2000. Proceedings. 2000 International Conference on*, IEEE, 2000, vol. 1, pp. 613-616.

[93] D. T. Gering, W. E. L. Grimson, and R. Kikinis, *Recognizing Deviations from Normalcy for Brain Tumor Segmentation*. Springer, 2002.

[94] J. Nie, Z. Xue, T. Liu, G. S. Young, K. Setayesh, L. Guo, and S. T. Wong, Automated brain tumor segmentation using spatial accuracy-weighted hidden markov random field, *Computerized Medical Imaging and Graphics*, vol. 33, no. 6, pp. 431-441, 2009.

[95] S. Bauer, L.-P. Nolte, and M. Reyes, Segmentation of brain tumor images based on atlas-registration combined with a markov-random-field lesion growth model, in *Biomedical Imaging: From Nano to Macro, 2011 IEEE International Symposium on*, IEEE, 2011, pp. 2018-2021.

[96] N. K. Subbanna, D. Precup, D. L. Collins, and T. Arbel, Hierarchical probabilistic gabor and mrf segmentation of brain tumours in mri volumes, in *Medical Image Computing and Computer-Assisted Intervention-MICCAI 2013*. Springer, 2013, pp. 751-758.

[97] C. Cortes and V. Vapnik, Support-vector networks, *Machine Learning*, vol. 20, no. 3, pp. 273-297, 1995.

[98] V. Vapnik, *The Nature of Statistical Learning Theory*. Springer, 2000.

[99] J. Zhou, K. Chan, V. Chong, and S. Krishnan, Extraction of brain tumor from mr images using one-class support vector machine, in *Engineering in Medicine and Biology Society, 2005. IEEE-EMBS 2005. 27th Annual International Conference of the*, IEEE, 2006, pp. 6411-6414.

[100] H. Cai, R. Verma, Y. Ou, S.-K. Lee, E. R. Melhem, and C. Davatzikos, Probabilistic segmentation of brain tumors based on multi-modality magnetic resonance images, in *Biomedical Imaging: From Nano to Macro, 2007. ISBI 2007. 4th IEEE International Symposium on*, IEEE, 2007, pp. 600-603.

[101] R. Verma, E. I. Zacharaki, Y. Ou, H. Cai, S. Chawla, S.-K. Lee, E. R. Melhem, R. Wolf, and C. Davatzikos, Multiparametric tissue characterization of brain neoplasms and their recurrence using pattern classification of mr images, *Academic Radiology*, vol. 15, no. 8, pp. 966-977, 2008.

[102] S. Ruan, S. Lebonvallet, A. Merabet, and J. Constans, Tumor segmentation from a multispectral mri images by using support vector machine classification, in *Biomedical Imaging: From Nano to Macro, 2007. ISBI 2007. 4th IEEE International Symposium on*, IEEE, 2007, pp. 1236-1239.

[103] S. Ruan, N. Zhang, Q. Liao, and Y. Zhu, Image fusion for following-up brain tumor evolution, in *Biomedical Imaging: From Nano to Macro, 2011 IEEE International Symposium on*, IEEE, 2011, pp. 281-284.

[104] N. Zhang, S. Ruan, S. Lebonvallet, Q. Liao, and Y. Zhu, Multi-kernel SVM based classification for brain tumor segmentation of MRI multi-sequence, in *Image Processing (ICIP), 2009 16th IEEE International Conference on*, IEEE, 2009, pp. 3373-3376.

[105] S. Bauer, L.-P. Nolte, and M. Reyes, Fully automatic segmentation of brain tumor images using support vector machine classification in combination with hierarchical conditional random field regularization, in *Medical Image Computing and Computer-Assisted Intervention-MICCAI 2011*. Springer, 2011, pp. 354-361.

[106] D. Zikic, B. Glocker, E. Konukoglu, A. Criminisi, C. Demiralp, J. Shotton, O. Thomas, T. Das, R. Jena, and S. Price, Decision forests for tissue-specific segmentation of high-grade gliomas in multi-channel mr, in *Medical Image Computing and Computer-Assisted Intervention-MICCAI 2012*. Springer, 2012, pp. 369-376.

[107] N. Zhang, S. Ruan, S. Lebonvallet, Q. Liao, and Y. Zhu, Kernel feature selection to fuse multi-spectral MRI images for brain tumor segmentation, *Computer Vision and Image Understanding*, vol. 115, no. 2, pp. 256-269, 2011.

[108] H. Delingette, M. Hebert, and K. Ikeuchi, Shape representation and image segmentation using deformable surfaces, *Image and Vision Computing*, vol. 10, no. 3, pp. 132-144, 1992.

[109] D. García-Lorenzo, S. Francis, S. Narayanan, D. L. Arnold, and D. L. Collins, Review of automatic segmentation methods of multiple sclerosis white matter lesions on conventional magnetic resonance imaging, *Medical Image Analysis*, vol. 17, no. 1, pp. 1-18, 2013.

[110] H. Tek and B. B. Kimia, Shock-based reaction-diffusion bubbles for image segmentation, in *Computer Vision, Virtual Reality and Robotics in Medicine*. Springer, 1995, pp. 434-438.

[111] T. McInerney and D. Terzopoulos, Deformable models in medical image analysis: A survey, *Medical Image Analysis*, vol. 1, no. 2, pp. 91-108, 1996.

[112] M. Kass, A. Witkin, and D. Terzopoulos, Snakes: Active contour models, *International Journal of Computer Vision*, vol. 1, no. 4, pp. 321-331, 1988.

[113] C. Xu and J. L. Prince, Snakes, shapes, and gradient vector flow, *Image Processing, IEEE Transactions on*, vol. 7, no. 3, pp. 359-369, 1998.

[114] A. Singh, D. Terzopoulos, and D. B. Goldgof, *Deformable Models in Medical Image Analysis*. IEEE Computer Society Press, 1998.

[115] T. F. Chan and L. A. Vese, Active contours without edges, *Image Processing, IEEE Transactions on*, vol. 10, no. 2, pp. 266-277, 2001.

[116] S. Luo, R. Li, and S. Ourselin, A new deformable model using dynamic gradient vector flow and adaptive balloon forces, in *APRS Workshop on Digital Image Computing*, 2003, pp. 9-14.

[117] H. Khotanlou, O. Colliot, J. Atif, and I. Bloch, 3D brain tumor segmentation in mri using fuzzy classification, symmetry analysis and spatially constrained deformable models, *Fuzzy Sets and Systems*, vol. 160, no. 10, pp. 1457-1473, 2009.

[118] A. Gooya, K. M. Pohl, M. Bilello, G. Biros, and C. Davatzikos, Joint segmentation and deformable registration of brain scans guided by a tumor growth model, in *Medical Image Computing and Computer-Assisted Intervention-MICCAI 2011*. Springer, 2011, pp. 532-540.

[119] R. Malladi, J. A. Sethian, and B. C. Vemuri, Shape modeling with front propagation: A level set approach, *Pattern Analysis and Machine Intelligence, IEEE Transactions on*, vol. 17, no. 2, pp. 158-175, 1995.

[120] S. Kichenassamy, A. Kumar, P. Olver, A. Tannenbaum, and A. Yezzi, Gradient flows and geometric active contour models, in *Computer Vision, 1995. Proceedings., Fifth International Conference on*, IEEE, 1995, pp. 810-815.

[121] S. Ho, E. Bullitt, and G. Gerig, Level-set evolution with region competition: Automatic 3-D segmentation of brain tumors, in *Pattern Recognition, 2002. Proceedings. 16th International Conference on*, IEEE, 2002, vol. 1, pp. 532-535.

[122] M. Prastawa, E. Bullitt, S. Ho, and G. Gerig, A brain tumor segmentation framework based on outlier detection, *Medical Image Analysis*, vol. 8, no. 3, pp. 275-283, 2004.

[123] H.-H. Chang and D. J. Valentino, Image segmentation using a charged fluid method, *Journal of Electronic Imaging*, vol. 15, no. 2, pp. 023011-023011, 2006.

[124] H.-H. Chang and D. J. Valentino, An electrostatic deformable model for medical image segmentation, *Computerized Medical Imaging and Graphics*, vol. 32, no. 1, pp. 22-35, 2008.

[125] C. Li, C.-Y. Kao, J. C. Gore, and Z. Ding, Minimization of region-scalable fitting energy for image segmentation, *Image Processing, IEEE Transactions on*, vol. 17, no. 10, pp. 1940-1949, 2008.

[126] C. Li, R. Huang, Z. Ding, J. Gatenby, D. N. Metaxas, and J. C. Gore, A level set method for image segmentation in the presence of intensity inhomogeneities with application to mri, *Image Processing, IEEE Transactions on*, vol. 20, no. 7, pp. 2007-2016, 2011.

[127] A. Hamamci, N. Kucuk, K. Karaman, K. Engin, and G. Unal, Tumor-cut: Segmentation of brain tumors on contrast enhanced mr images for radiosurgery applications, *Medical Imaging, IEEE Transactions on*, vol. 31, no. 3, pp. 790-804, 2012.

[128] W. R. Crum, O. Camara, and D. L. Hill, Generalized overlap measures for evaluation and validation in medical image analysis, *Medical Imaging, IEEE Transactions on*, vol. 25, no. 11, pp. 1451-1461, 2006.

[129] N. Archip, F. A. Jolesz, and S. K. Warfield, A validation framework for brain tumor segmentation, *Academic Radiology*, vol. 14, no. 10, pp. 1242-1251, 2007.

[130] M. Prastawa, E. Bullitt, and G. Gerig, Simulation of brain tumors in mr images for evaluation of segmentation efficacy, *Medical Image Analysis*, vol. 13, no. 2, pp. 297-311, 2009.

[131] B. Menze, A. Jakab, S. Bauer, J. Kalpathy-Cramer, K. Farahani, J. Kirby, Y. Burren, N. Porz, J. Slotboom, R. Wiest, et al., The multimodal brain tumor image segmentation benchmark (brats), http://hal.inria.fr/hal-00935640, 2014.

[132] M. Jenkinson, C. F. Beckmann, T. E. Behrens, M. W. Woolrich, and S. M. Smith, Fsl, *Neuroimage*, vol. 62, no. 2, pp. 782-790, 2012.

[133] A. Fedorov, R. Beichel, J. Kalpathy-Cramer, J. Finet, J.-C. Fillion-Robin, S. Pujol, C. Bauer, D. Jennings, F. Fennessy, M. Sonka, et al., 3d slicer as an image computing platform for the quantitative imaging network, *Magnetic Resonance Imaging*, vol. 30, no. 9, pp. 1323-1341, 2012.

[134] N. Toussaint, J.-C. Souplet, and P. Fillard, Medinria: Medical image navigation and research tool by inria, in *Proc. of MICCAI*, vol. 7, 2007.

[135] D. Yang, J. Zheng, A. Nofal, J. Deasy, and I. M. El Naqa, Techniques and software tool for 3d multimodality medical image segmentation, *Journal of Radiation Oncology Informatics*, vol. 1, no. 1, pp. 1-22, 2009.

[136] A. M. Dale, B. Fischl, and M. I. Sereno, Cortical surface-based analysis: I. segmentation and surface reconstruction, *Neuroimage*, vol. 9, no. 2, pp. 179-194, 1999.

[137] I. Wolf, M. Vetter, I. Wegner, M. Nolden, T. Bottger, M. Hastenteufel, M. Schobinger, T. Kunert, and H.-P. Meinzer, The medical imaging interaction toolkit (mitk): A toolkit facilitating the creation of interactive software by extending vtk and itk, in *Medical Imaging 2004*, International Society for Optics and Photonics, 2004, pp. 16-27.

[138] S. Bauer, T. Fejes, J. Slotboom, R. Wiest, L.-P. Nolte, and M. Reyes, Segmentation of brain tumor images based on integrated hierarchical classification and regularization, in *MICCAI BraTS Workshop*, 2012.

[139] C. A. Cocosco, V. Kollokian, R. K.-S. Kwan, G. B. Pike, and A. C. Evans, Brainweb: Online interface to a 3D MRI simulated brain database, in *NeuroImage*, Citeseer, 1997.

[140] S. Valverde, A. Oliver, M. Cabezas, E. Roura, and X. Lladó, Comparison of 10 brain tissue segmentation methods using revisited ibsr annotations, *Journal of Magnetic Resonance Imaging*, 2014. doi: 10.1002/jmri.24517.

[141] S. Cha, Update on brain tumor imaging: From anatomy to physiology, *American Journal of Neuroradiology*, vol. 27, no. 3, pp. 475-487, 2006.

[142] M. Law, Advanced imaging techniques in brain tumors, *Cancer Imaging*, vol. 9, no. Special issue A, p. S4, 2009.

[143] E. I. Zacharaki, S. Wang, S. Chawla, D. Soo Yoo, R. Wolf, E. R. Melhem, and C. Davatzikos, Classification of brain tumor type and grade using mri texture and shape in a machine learning scheme, *Magnetic Resonance in Medicine*, vol. 62, no. 6, pp. 1609-1618, 2009.

[144] J. Sedlacik, A. Winchell, M. Kocak, R. Loeffler, A. Broniscer, and C. Hillenbrand, MR imaging assessment of tumor perfusion and 3d segmented volume at baseline, during treatment, and at tumor progression in children with newly diagnosed diffuse intrinsic pontine glioma, *American Journal of Neuroradiology*, vol. 34, no. 7, pp. 1450-1455, 2013.

[145] B. Lemasson, T. L. Chenevert, T. S. Lawrence, C. Tsien, P. C. Sundgren, C. R. Meyer, L. Junck, J. Boes, S. Galbán, T. D. Johnson, et al., Impact of perfusion map analysis on early survival prediction accuracy in glioma patients, *Translational Oncology*, vol. 6, no. 6, p. 766, 2013.

[146] A. L. Alexander, J. E. Lee, M. Lazar, and A. S. Field, Diffusion tensor imaging of the brain, *Neurotherapeutics*, vol. 4, no. 3, pp. 316-329, 2007.

[147] E. Stretton, E. Geremia, B. Menze, H. Delingette, and N. Ayache, Importance of patient dti's to accurately model glioma growth using the reaction diffusion equation, in *Biomedical Imaging (ISBI), 2013 IEEE 10th International Symposium on*, IEEE, 2013, pp. 1142-1145.

[148] W. Dou, A. Dong, P. Chi, S. Li, and J. Constans, Brain tumor segmentation through data fusion of t2-weighted image and MR spectroscopy, in *Bioinformatics and Biomedical Engineering,(iCBBE) 2011 5th International Conference on*, IEEE, 2011, pp. 1-4.

[149] J. Huo, K. Okada, E. M. van Rikxoort, H. J. Kim, J. R. Alger, W. B. Pope, J. G. Goldin, and M. S. Brown, Ensemble segmentation for gbm brain tumors on MR images using confidence-based averaging, *Medical Physics*, vol. 40, no. 9, p. 093502, 2013.

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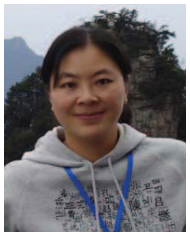

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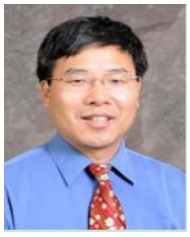

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