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To cite this article: Stefan Bauer *et al* 2013 *Phys. Med. Biol.* **58** R97

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TOPICAL REVIEW

A survey of MRI-based medical image analysis for brain tumor studies

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Received 11 February 2013, in final form 28 March 2013

Published 6 June 2013

Online at stacks.iop.org/PMB/58/R97

Abstract

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. While the pioneering approaches applying automated methods for the analysis of brain tumor images date back almost two decades, the current methods are becoming more mature and coming closer to routine clinical application. This review aims to provide a comprehensive overview by giving a brief introduction to brain tumors and imaging of brain tumors first. Then, we review the state of the art in segmentation, registration and modeling related to tumor-bearing brain images with a focus on gliomas. The objective in the segmentation is outlining the tumor including its sub-compartments and surrounding tissues, while the main challenge in registration and modeling is the handling of morphological changes caused by the tumor. The qualities of different approaches are discussed with a focus on methods that can be applied on standard clinical imaging protocols. Finally, a critical assessment of the current state is performed and future developments and trends are addressed, giving special attention to recent developments in radiological tumor assessment guidelines.

(Some figures may appear in colour only in the online journal)

1. Introduction

This review is intended to give an overview of the state of the art in magnetic resonance imaging (MRI)-based medical image analysis for brain tumor studies. It also provides a brief background on brain tumors in general and non-invasive imaging of brain tumors in order to give a comprehensive insight into the field.

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1.1. Brain tumors

With a prevalence of less than 1‰ in the western population, brain tumors are not very common; however, they are among the most fatal cancers (DeAngelis 2001). A recent study estimated the US incidence rate for primary tumors of the brain or nervous system to be around 25 per 100 000 adults with approximately one-third of the tumors being malignant and the rest either benign or borderline-malignant (Kohler *et al* 2011). The word ‘tumor’ is of latin origin and means swelling. Today, it is frequently associated with a neoplasm, which is caused by uncontrolled cell proliferation.

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) (Kleihues *et al* 1993). It classifies brain tumors into grades I–IV with increasing aggressiveness.

Gliomas are the most frequent primary brain tumors in adults and account for 70% of adult malignant primary brain tumors. They arise from glial cells and can be classified into four WHO grades, where high-grade gliomas are of grade III or IV. Grades I and II tumors may be considered as semi-malignant tumors that carry a better prognosis, while grades III and IV tumors are malignant tumors that almost certainly lead to a subject’s death. The WHO grade IV gliomas are also called glioblastoma multiforme (GBM). They are the most common malignant primary brain tumors in humans, exhibiting very rapid growth (Deimling 2009). These tumors are infiltrative and spread mostly along the white matter fiber tracts (Giese *et al* 2003). They form abnormal vessels and exhibit a necrotic core. This and the surrounding edema leads to a mass effect, which they exert on the healthy tissues of the brain. Regarding tumor angiogenesis, current understanding is based on the fact that low-grade gliomas are moderately vascularized tumors, whereas high-grade gliomas show prominent microvascular proliferations and areas of high vascular density (Plate and Risau 1995). Average survival time for GBM is one year (Krex *et al* 2007). Treatment options for gliomas include surgery, radiation therapy or chemotherapy, including combinations of all these (DeAngelis 2001).

Meningiomas are the most common extra-axial intracranial neoplasms. They account for 15–20% of intracranial neoplasms. They are non-glial neoplasms that originate from the arachnoid cap cells of the meninges. Treatment is usually performed by surgery and/or radiation therapy (Greenberg *et al* 1999).

Primary brain tumors must be differentiated from metastatic brain tumors that originate most frequently from lung, breast, melanoma, renal and colon cancers and account for approximately 40% of intracranial neoplasms.

Due to clinical relevance and the amount of prior work in MRI-based medical image processing, the focus of this review will be on gliomas.

1.2. Imaging of brain tumors

The standard technique for the brain tumor diagnosis is MRI (DeAngelis 2001, Wen *et al* 2010). MRI is a non-invasive technique, which provides good soft tissue contrast (Liang and Lauterbur 2000) 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. In particular, PET imaging can provide additional information (Chen 2007); however, so far MRI remains the accepted standard and therefore we will focus on MRI-based methods.

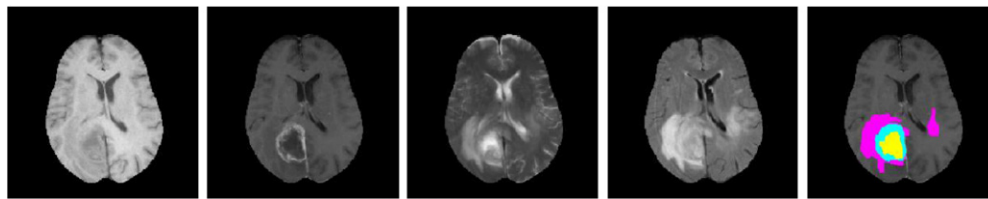


Figure 1. One axial slice of an MR image of a high-grade glioma patient. From left to right: T₁-weighted image, T₁-weighted image with contrast enhancement, T₂-weighted image, T_{2FLAIR}-weighted image and manual segmentation into necrotic (yellow), active (green), edema (pink) tumor compartments. Necrosis and active tumor regions were segmented based on the T₁-weighted image with contrast enhancement, whereas the edema region was segmented based on the registered T_{2FLAIR}-weighted image.

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 subregions. In current clinical routine, different MRI sequences are employed for the diagnosis and delineation of tumor compartments (Drevelgas and Papanikolaou 2011). These sequences include T₁-weighted MRI (T₁), T₁-weighted MRI with contrast enhancement (T_{1c}), T₂-weighted MRI (T₂) and T₂-weighted MRI with fluid-attenuated inversion recovery (T_{2FLAIR}); 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 response assessment in neuro-oncology (RANO) guidelines with a slice thickness of ≤ 5 mm without a gap between the slices (Pope and Hessel 2011). For volumetry, high-resolution 3D volume images are performed, including at least contrast-enhanced T₁-weighted images with isotropic resolution. Figure 1 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 the 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. T_{2FLAIR} (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 hyperintense/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 (3D measures).

Despite all the advantages that non-invasive imaging offers, it should be noted that a final diagnosis can only be made after biopsy and histology. It must also be emphasized that in gliomas, in contrast to metastatic brain tumors, the imageable component of the tumor is only part of the complete extent of the tumor. The imageable component and physiological information of the tumor depend on the tumor cell distribution and the image modality (Kelly *et al* 1987, Tovi 1993).

1.3. Image analysis for brain tumors

This review is focused on the image analysis for brain tumor studies. The image analysis deals with automatic or semi-automatic methods to help interpret the acquired images. Due to the large amount of data, which are currently being generated in the clinics, it is not possible to manually annotate and segment the data in a reasonable time. Usually, the domain of medical image analysis is divided into segmentation and registration, as well as into several further areas such as enhancement, visualization, quantification and modeling (Bankman 2008). For brain tumor studies, segmentation, registration and modeling appear to be the most important and the most challenging, so the remainder of this review focuses on these aspects.

Image segmentation (Pham *et al* 2000) aims at partitioning an image into several segments. These segments can be chosen according to structures of interest, tissue types, functional areas, etc. Balafar *et al* (2010) presented a recent review targeted at brain segmentation specifically. Image registration (Maintz and Viergever 1998) aims at aligning two different images in a common reference space. This is especially important for aligning images taken at different points in time during longitudinal studies or for aligning images from different modalities taken from the same patient, but also for brain morphometry. Klein *et al* (2009) compared nonlinear algorithms for the brain registration specifically. Finally, image-based modeling and simulation (Neal and Kerckhoffs 2010) can help in disease understanding, treatment planning and decision making.

The primary use of MRI-based medical image analysis for brain tumor studies is in diagnosis, patient monitoring and treatment planning, but it could also be useful in clinical trials. The segmentation is crucial for monitoring tumor growth or shrinkage in patients during therapy, for tumor volume measurements and it also plays an important role in surgical planning or radiotherapy planning, where not only the tumor has to be outlined, but also surrounding healthy structures are of interest. In current clinical practice, the segmentation is usually still done manually, which is time consuming and tedious for the radiologists and is also of limited use for an objective quantitative analysis. Concrete application areas for the registration include multi-modal and longitudinal alignment of inpatient images, but also aligning pre-, intra- and post-operative images as well as deformable registration for atlas-based segmentation or position mapping of gliomas for statistical analysis.

Although high-grade gliomas are not the most common cancers, they are among the most deadly. Novel therapies have improved patients' prognosis and novel clinical trial designs have gained in importance to further investigate the response of gliomas to different treatment regimens. A most accurate description of changes in tumor size and physiology is therefore mandatory. For many years now, treatment response of gliomas has been evaluated by MR and CT imaging; a set of guidelines, usually referred to as the Macdonald criteria (Macdonald *et al* 1990), is available to monitor the assessment of tumor response after treatment. These criteria include changes in tumor size and new or increasing enhancement. However, this approach carries some important limitations (Clarke and Chang 2009). Although the Macdonald criteria represented an important step in neuro-oncology research, it is now clear that the evaluation of gadolinium enhancement alone is not adequate to characterize tumor growth or response. The RANO working group has defined novel criteria for tumor progression dependent on measurable or non-measurable lesions in at least two directions (Wen *et al* 2010). Automatic 3D volumetric assessment of gliomas would offer the next important step forward to better understand tumor dynamics and response to treatment.

A previous review of the field was done by Angelini *et al* (2007). In the meantime however, there has been significant progress, with the most important methods having been developed after 2007, mostly due to the rapid advancements in machine learning (Wang and Summers

2012). Therefore, this review aims at providing an update on the state of the art in image analysis for brain tumor studies.

The methods presented here have been collected mostly from Pubmed and Google scholar. We included more than 150 journal papers and conference papers from the most important conferences in the field (MedIA, IEEE TMI, NeuroImage, MRI, MRM, JMRI, PMB; MICCAI, IPMI, IEEE ISBI and others). For the time before 2007, we included only the historically most relevant contributions; for the rest, we refer to Angelini *et al* (2007).

The remainder of this review is structured as follows: in the *Methods and Results* section (section 2), we present the different approaches and briefly summarize their results. The section is subdivided into methods for the evaluation of accuracy and validation (section 2.1), segmentation (section 2.2), registration (section 2.3) and integrated approaches (section 2.4). Within each subsection, we tried to group related methods together. Finally, in the *Discussion and Outlook* section (section 3), we review the state of the art in general, compare it to the clinical requirements and conclude about the applicability of the current methods, before we give an outlook on possible future directions and trends.

2. Methods and results

2.1. Evaluation and validation methods

Validation and comparison against the state of the art is crucial for any newly developed method. Therefore, before diving into the presentation of the different approaches, we would like to briefly cover the possibilities and challenges for evaluating and validating methods in the brain tumor image analysis.

It would be optimal to compare any method against the real case. However, this is a big challenge in this field, if not impossible. In the lack of a well-accepted ground truth, the current gold standard for the evaluation is to compare with manual segmentations by an expert. However, this is an extremely time-consuming and tedious task; additionally, it is not objective. Mazzara *et al* (2004) reported intra-rater volume variabilities of $20 \pm 15\%$ and inter-rater volume variabilities of $28 \pm 12\%$ for manual segmentations of brain tumor images. Weltens *et al* (2001) found even larger values for inter-observer variability. One way to overcome this problem would be to use an algorithm that combines several expert segmentations in an optimal way like STAPLE (Warfield *et al* 2004). This method was applied for the evaluation of brain tumor segmentations by Archip *et al* (2007a); however in most cases, there are not enough expert segmentations available for using that method. Recently, Xu *et al* (2012) suggested to use web-based collaborative manual tumor labeling by a large number of briefly trained non-experts to address this problem and they reported encouraging results. A more subjective but occasionally used way is to employ a semi-automatic segmentation with a different well-accepted method as an intermediate result (e.g. Kikinis and Pieper 2011, Gao *et al* 2012, Egger *et al* 2013), which is manually corrected by a human expert where necessary. This approach still lacks in objectivity, but it alleviates the burden from the clinician to spend a large amount of time for the segmentation.

Another possibility for a first sanity check is to assess results on a synthetic dataset including ground truth. Although synthetic data lack important characteristics of real images, it has been used by many groups for initially assessing both segmentation and registration methods on healthy datasets with the BrainWeb phantoms (Cocosco *et al* 1997). For brain tumor studies, Prastawa *et al* (2009) made a similar attempt to provide simulated multi-sequence tumor image data including an objective ground truth, which was also based on the BrainWeb phantom and combined with a well-defined and accepted tumor-growth model.

The most common way to quantitatively evaluate segmentation or registration results is to calculate the overlap with the ground truth. Usually, the Dice similarity coefficient (DSC) or the Jaccard coefficient are used (Crum *et al* 2006). They can range from 0 to 1 with 0 indicating no overlap and 1 indicating perfect overlap. Other possibilities for the registration evaluation include manual landmark definition and calculation of landmark errors or surface distances. For a more qualitative assessment, checkerboard images can be shown or the outline of a structure can be analyzed visually. Zou *et al* (2004) compared the three different validation metrics: area under the receiver operating characteristic (ROC) curve, mutual information (MI) and DSC for the probabilistic brain tumor segmentation. They concluded that for overall classification accuracy, the area under the ROC curve should be used; when interested in sensitivity to changes in tumor size, MI is the metric of choice and for the spatial alignment evaluation, the Dice coefficient is best.

In the lack of a brain tumor database with ground-truth segmentations, that is available to a broad community of clinicians and researchers, so far most authors validated their algorithms on a limited number of cases from their own data. This makes it difficult to compare the performance of different methods against each other in an unbiased way. Therefore, and due to the different metrics used, the accuracy and speed of the individual methods, which have been collected from the respective publications, cannot be directly compared with each other. Until recently, the only data available, which could serve such a purpose of general comparison, were the synthetic data of Prastawa *et al* (2009), but so far only few groups tested their methods on these images. For the related topic of MS lesion segmentation from brain MRI (García-Lorenzo *et al* 2013), an open database has been available for some time (Styner *et al* 2008). Such an open image database has long been missing for an objective comparison of brain tumor segmentation algorithms; however, an effort in this direction has finally been undertaken by the BraTS challenge at MICCAI 2012⁴.

2.2. Segmentation of brain tumor images

The segmentation of tumor-bearing brain images is a challenging task for several reasons. Firstly, high-grade gliomas usually exhibit unclear and irregular boundaries with discontinuities. Contrast uptake and image acquisition time after contrast injection can vary, which changes tumor appearance significantly and it is debatable if and how the non-imageable component of the tumor should be handled by segmentation algorithms. Additionally, tumor subregions can only be separated when several modalities are combined, which requires an accurate registration as a pre-processing step. Finally, clinical datasets are usually acquired in a highly anisotropic way, leading to a much higher intra-slice resolution than inter-slice resolution. This causes problems with partial-volume effects for the segmentation, but also registration and resampling of the different modalities in a common space of reference. A diagram illustrating the major steps during the segmentation pipeline of most algorithms is shown in figure 2. In the following, the different algorithms are discussed according to the major blocks of this pipeline.

2.2.1. Image pre-processing. Most algorithms rely on some kind of pre-processing for image preparation and image enhancement. Image denoising is a standard pre-processing task for MRI. Many approaches have been suggested, the most popular ones being based on anisotropic diffusion filtering (Weickert 1998). Diaz *et al* analyzed different denoising algorithms for the specific task of brain tumor segmentation (Diaz *et al* 2011). They concluded that, although

⁴ www2.imm.dtu.dk/projects/BRAATS2012/.

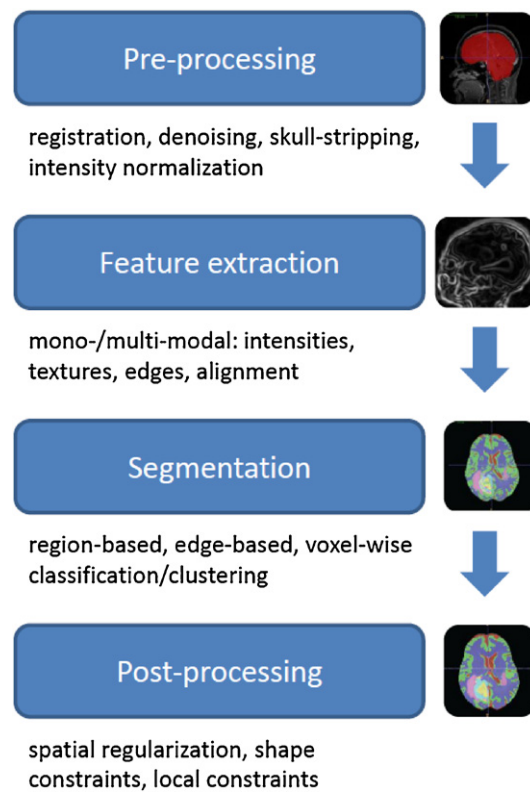


Figure 2. Illustration of the main blocks used for building up the segmentation pipeline of most algorithms included in this review.

image noise was reduced, many algorithms introduced artifacts which had a negative effect on the segmentation.

Intensity normalization (Nyúl and Udupa 1999) is a very critical task for MRI, especially when classification methods are used for the segmentation. However, for tumor-bearing images, this is more challenging than for healthy images due to the confounding effects caused by the differences in tumor appearance. Ekin (2011) developed an intensity-normalization technique for MRI, which they claimed was robust to pathologies. Most approaches employ a bias-field correction (Vovk *et al* 2007) before the segmentation is applied, in order to compensate for the effect of magnetic field inhomogeneities during image acquisition.

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 MI similarity metric (Mang *et al* 2008) and resampling in order to ensure voxel-to-voxel correspondence across all modalities.

Most approaches for the brain tumor segmentation rely on a skull-stripping step (Fennema-Notestine *et al* 2006) before the actual segmentation is performed. Speier *et al* (2011) recently presented a skull-stripping method dedicated to glioma images, which was able to handle images containing resection cavities.

2.2.2. Image features for segmentation algorithms. The features used for the segmentation of brain tumors largely depend on the type of tumor and its grade because different tumor types and grades can vary a lot in appearance (e.g. contrast uptake, shape, regularity, location,

etc). Additionally, feature selection will also depend on the sub-compartment of the tumor, which is to be segmented.

The most common feature used for the brain tumor segmentation is the image intensities. This is based on the assumption that different tissues have different graylevels. Another type of features that are frequently used are local image textures because it has been observed that different tumor areas exhibit different textural patterns (Kassner and Thornhill 2010). Textures can be computed according to different strategies (Tuceryan and Jain 1998). Alignment-based features make use of spatial prior knowledge, which is often encoded by the registration of a standard atlas to the patient image or by making use of symmetries between left and right brain hemispheres. Intensity gradients or edge-based features can be used for evolving a contour toward the tumor border. Recently, context-aware features modeling mid- or long-range spatial contexts similar to Lepetit *et al* (2005) and Shotton *et al* (2011) are becoming more popular.

Depending on the data available, all these features can either be computed from one single modality or from multi-modal images. Researchers have also combined different features from different modalities in order to improve their segmentation results.

For the task of brain tumor image analysis, Schmidt *et al* (2005) explored different features for the voxel-based classification and concluded that combining textural and alignment-based features allowed for substantial performance increases. Ahmed *et al* (2011) investigated the efficacy of different image features and feature fusion strategies for pediatric brain tumor images. They argued that in multi-modal images, texture features had advantages over intensity or shape features.

2.2.3. Segmentation algorithms. Based on the previous section, we categorize segmentation algorithms according to the features they use. Therefore, we distinguish region- or edge-based methods, which mostly rely on deformable models, and classification or clustering methods, which make use of voxel-wise intensity and texture features. Many methods employ additional constraints for the regularization; this is discussed in a separate section. Another group of methods is based on the atlas-based segmentation. Atlas-based methods will be described later in sections 2.3 and 2.4 because the segmentation relies on registration methods.

Region- or edge-based methods. Deformable models make use of regional characteristics or edge detection in the images (McInerney and Terzopoulos 1996). In most cases, a level-set is evolved toward the tumor boundary by searching for the largest gradient in the image or by employing region properties. Wang *et al* (2009) employed a fluid vector flow model to evolve a contour toward the tumor boundary edge in T_1 -weighted images. Sachdeva *et al* (2012) made use of content-based intensity and texture patterns to evolve an active contour toward the tumor boundary in different MRI modalities.

Ho *et al* (2002) derived a tumor probability map from the difference image between T_1 and T_{1c} , which formed the basis for the evolution of a region-competition level-set algorithm applied. Rexilius *et al* (2007) initialized a region-growing algorithm with a tumor map, which was obtained from a multi-spectral histogram model adaptation. Harati *et al* (2011) suggested a fuzzy-connectedness algorithm, which made use of region properties but had no spatial constraints. Seeding was automatically performed on T_1 -weighted images with a so-called tumor detector matrix. Characteristics of each method are summarized in table 1.

Classification and clustering. In fact, most of the segmentation algorithms proposed so far are based on classification or clustering approaches. This is mostly owed to the fact that with these methods, multi-modal datasets can be handled easily because they can operate on any

Table 1. Segmentation methods for brain tumor images using deformable methods or region-based methods. Evaluation was performed on different datasets; empty cells indicate no reported information. Dim stands for dimensionality, S for supervision. SA means semi-automatic, FA means fully automatic. Type describes the tumor type, which can be as follows: G—glioma, HGG—high-grade glioma, LGG—low-grade glioma, M—meningioma, Met—metastasis.

Authors	Modalities	Method	Accuracy	Speed	Dim	S	Type
<i>Edge-based methods</i>							
Wang <i>et al</i> (2009)	T ₁	Fluid vector flow	0.6 (Tanimoto)	5 s	2D	SA	
Sachdeva <i>et al</i> (2012)	T ₁ , T _{1c} , T ₂	Content-based active contour model	0.72–0.98		2.5D	SA	G, M
<i>Region-based methods</i>							
Ho <i>et al</i> (2002)	T ₁ , T _{1c}	Level-set evolution with region competition	0.85–0.93 (Jaccard)		3D	FA	G, M
Rexilius <i>et al</i> (2007)	T _{1c} , T ₂ , T _{2flair}	Multi-spectral histogram model adaptation for region growing	0.73 (Jaccard)	10 min	3D	SA	G
Harati <i>et al</i> (2011)	T _{1c}	Fuzzy connectedness	>0.9 (similarity index)	2.5 min		FA	G, M

chosen feature vector. In most cases, the features on which these algorithms operate include voxel-wise intensities and frequently also local textures. The general idea is to decide for every single voxel individually to which class it belongs based on its feature vector. Classification requires training data to learn a classification model, based on which new instances can be labeled. Clustering, on the other hand, works in an unsupervised way and groups data based on certain similarity criteria (Wang and Summers 2012).

Clustering was introduced into the brain tumor segmentation community by Schad *et al* (1993) who analyzed texture patterns of different tissues. Phillips *et al* (1995) employed fuzzy c-means clustering and Vaidyanathan (1995) compared this to kNN clustering for the tumor volume determination during therapy on multi-spectral 2D image slices. Clark *et al* (1998), from the same group, further developed this approach to incorporate knowledge-based techniques. Later, Fletcher-Heath *et al* (2001) also combined fuzzy clustering with knowledge-based techniques for the brain tumor segmentation from multi-sequence MRI.

Later, there have been tremendous advances in developing more powerful discriminative classification methods and these new methods have also found their way into the field of medical image analysis. Cai *et al* (2007) and later Verma *et al* (2008) from the same group used a high number of MRI modalities (diffusion tensor imaging (DTI) channels in addition to the conventional ones) to create voxel-wise intensity-based feature vectors, which they classified with support vector machines (SVMs) (Schoelkopf and Smola 2002). They were able to not only segment the healthy tissues, but also segment sub-compartments of healthy and tumor regions. Ruan *et al* (2007) used a very similar approach based on SVMs, but with a lower number of modalities and they only segmented one tumor region. Later, they claimed that the feature selection using kernel class separability could slightly improve the results compared to their previous approach (Ruan *et al* 2011). Jensen and Schmainda (2009) explored different neural networks to detect brain tumor invasion from multi-parametric MRI (structural, diffusion and perfusion images). Kanaly *et al* (2011) chose a simpler approach by thresholding the voxels of the difference image of pre- and post-contrast T₁-weighted MRI after intensity normalization. Zikic *et al* (2012) later proposed a computationally efficient

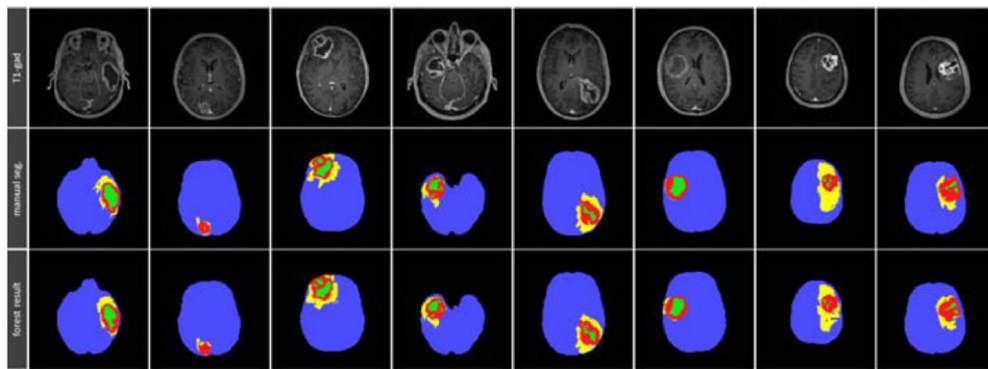


Figure 3. Segmentation results generated from multi-sequence 3D MR images, shown on T_{1c} -weighted axial slices of different patients. The second row shows the manually defined ground truth, the last row shows the results of a fully automatic algorithm, which used T_1 , T_{1c} , T_2 , $T_{2\text{flair}}$ and DTI MRI sequences as an input. The pathologic tissues are separated into active, necrotic and edema compartments. Example from Zikic *et al* 2012. *Lect. Notes Comput. Sci.* **7512** 369–76, with kind permission of Springer Science + Business Media.

approach based on the decision forest classification (Criminisi *et al* 2011) with context-aware features and an additional generative model as an input, which is able to identify tumor sub-compartments from multi-modal images (see figure 3). They claimed that context-aware features eliminate the need for a post-processing step imposing smoothness constraints by spatial regularization. Geremia *et al* (2012) had the idea to generate synthetic tumor images, which can be used to train a discriminative regression forest algorithm using different groups of features. They argued that this approach allowed them not only to segment patient images, but also to estimate latent tumor cell densities. Characteristics of each method are summarized in table 2.

Classification and clustering with additional constraints. It has been remarked that simple voxel-wise classification or clustering methods do not make use of the complete information contained in an image. Therefore, there have been numerous attempts to use additional information to further improve the segmentation result by adding additional constraints, which can be based on some form of neighborhood regularization or on imposing shape or localization constraints for the tumor. Neighborhood constraints are often imposed using a random field regularization method, while shape constraints are mostly handled by deformable models. Atlases can be used to restrict the tumor location and also for generative classification models.

Atlases have been used by a number of methods to incorporate spatial prior knowledge into the classification task. Kaus *et al* (2001) suggested to use a brain atlas for guiding a kNN classifier in their adaptive template-moderated classification algorithm. Other researchers used atlases not only to impose spatial constraints, but also to provide probabilistic information about the tissue model. Moon *et al* (2002) and also Prastawa *et al* (2003) employed a probabilistic tissue model and used an expectation–maximization (EM) method (Dempster 1977), which segmented tumor images by modifying an atlas with patient-specific information about tumor location from different MRI modalities. Later, Prastawa *et al* (2004) extended this to work on mono-modal images. Menze *et al* (2010) combined a healthy atlas with a latent tumor atlas to segment brain tumors from multi-sequence images using a generative probabilistic model and spatial regularization. Weizman *et al* (2012) used localization based on an atlas for their

Table 2. Segmentation methods for brain tumor images using classification or clustering, grouped by different approaches. Evaluation was performed on different datasets; empty cells indicate no reported information. Dim stands for dimensionality, S for supervision. SA means semi-automatic, FA means fully automatic. Type describes the tumor type, which can be as follows: G—glioma, HGG—high-grade glioma, LGG—low-grade glioma, M—meningioma, Met—metastasis.

Authors	Modalities	Method	Accuracy	Speed	Dim	S	Type
<i>Classification or clustering methods</i>							
Schad <i>et al</i> (1993)	T ₁ , T ₂	Texture analysis and clustering			2D		HGG, Met
Phillips <i>et al</i> (1995)	T ₁ , T ₂ , PD	Clustering		2–5 min	2D		HGG
Vaidyanathan (1995)	T ₁ , T ₂ , PD	Clustering			2D		HGG, M
Clark <i>et al</i> (1998)	T ₁ , T ₂ , PD	Knowledge-based techniques	0.69–0.99 (% match)		2D	FA	HGG
Fletcher-Heath <i>et al</i> (2001)	T ₁ , T ₂ , PD	Fuzzy clustering + knowledge-based techniques	0.53–0.91 (% match)		2.5D	FA	
Cai <i>et al</i> (2007)	T ₁ , T _{1c} , T ₂ , T _{2flair} , DTI	Probabilistic segmentation based on multi-modality MRI	0.73–0.98 (classification rate)		3D	FA	HGG
Ruan <i>et al</i> (2007)	T ₁ , T ₂ , T _{2flair} , PD	SVM classification	0.99 (TP)		3D	FA	
Verma <i>et al</i> (2008)	T ₁ , T _{1c} , T ₂ , T _{2flair} , DTI	Multi-parametric tissue classification	0.34–0.93 (classification rate)		3D	FA	HGG
Jensen and Schmainda (2009)	T ₁ , T _{1c} , T ₂ , T _{2flair} , DWI, DTI, DSC	Different classifiers on multi-parametric MRI	0.78–0.86 (overlap)		3D	SA	HGG, M
Ruan <i>et al</i> (2011)	T ₂ , T _{2flair} , PD	Image fusion for the brain tumor follow-up		5 min	3D	FA	
Kanaly <i>et al</i> (2011)	T ₁ , T _{1c}	Difference image for volumetric tumor assessment			3D	SA	
Zikic <i>et al</i> (2012)	T ₁ , T _{1c} , T ₂ , T _{2flair} , DTI	Decision forests for tissue-specific segmentation	0.7–0.9 (Dice)	2–3 min	3D	FA	HGG
Geremia <i>et al</i> (2012)	T ₁ , T _{1c} , T ₂ , T _{2flair}	Tumor cell density estimation for the discriminative segmentation	0.55–0.83 (Dice)		3D	FA	G

multi-modal segmentation of optic pathway gliomas, which performed classification with a probabilistic tissue model.

Deformable models (McInerney and Terzopoulos 1996) can be used to impose shape constraints after the previous tissue classification. Cobzas *et al* (2007) and Cobzas and Schmidt (2009) combined the tissue classification using a high-dimensional feature set with the level-set evolution. Popuri *et al* (2012) added a Dirichlet prior to the previous approach to better disambiguate tumor from healthy tissues. Khotanlou *et al* (2009) combined fuzzy clustering and brain symmetry features with the level-set evolution. Hamamci *et al* (2011) introduced the tumor-cut algorithm, which combines the tumor segmentation using cellular automata with a level set evolving on the tumor probability map to impose spatial smoothness.

Neighborhood relationships are often used for spatial regularization after the initial voxel-wise classification. In most case, this is performed with a random field method, either Markov random fields (MRFs) (Kindermann and Snell 1980) or Conditional Random Fields (CRFs) (Lafferty *et al* 2001, Kumar and Hebert 2006). Over the last few years, algorithms based on some form of graph cuts for the segmentation (Boykov and Funka-Lea 2006) have become increasingly popular. These algorithms make use of region-based properties by formulating neighborhood relationships as an energy minimization problem, which is solved by a graph-cut optimization method and the result is interpreted as a segmentation. In many cases, these methods require user-provided seeds; this is why the approaches are often semi-automatic. Lee *et al* (2008) used CRFs for spatial regularization after the previous voxel-wise SVM classification from multiple modalities. Wels *et al* (2008) integrated a probabilistic boosting tree classifier with a graph-cut approach for considering the spatial relationships in pediatric brain tumor images. Birkbeck *et al* (2009) proposed an interactive semi-automatic approach, which was able to include online user corrections and they argued that this method could not only reduce operator time, but also increased repeatability compared to manual segmentation. Hamamci *et al* (2010) proposed a variation of the original graph-cut method using cellular automata for solving the shortest-path problem iteratively. Nie *et al* (2009) used an EM algorithm, which was coupled with a spatial accuracy-weighted hidden MRF. This allowed them to consider anisotropic resolutions of different modalities. Zhu *et al* (2012) also combined the EM segmentation with the MRF regularization, but added a post-processing pipeline including thresholding and morphological operations. Bauer *et al* (2011a) claimed to be able to segment tumor and healthy tissues including sub-compartments based on the SVM classification with the integrated hierarchical CRF regularization. They also made use of prior knowledge about tissue adjacency probabilities. Hsieh *et al* (2011) chose a simple region-growing and knowledge-based post-processing after the fuzzy tissue classification to impose spatial coherence. Corso *et al* (2007) took a different approach and suggested an extended graph-shift algorithm, which performed energy minimization on a dynamic hierarchical representation of the image. In a later publication, they employed a multi-level approach for fusing the Bayesian tissue classification with affinity assignments to perform the segmentation by weighted aggregation (Corso *et al* 2008). Characteristics of each method are summarized in table 3.

2.2.4. Tumor detection algorithms. In contrast to segmentation algorithms, detection algorithms only try to decide if tumor is present and output the approximate tumor location instead of providing a complete segmentation. Saha *et al* (2011) located the tumor and drew a bounding box, instead of segmenting it. This could help in quickly analyzing large amounts of data. It was done with the help of a fast unsupervised change detection method searching for dissimilar regions across the symmetry line of the brain using the Bhattacharya coefficient score. Ambrosini *et al* (2010) employed a template-matching method to detect metastases

Table 3. Segmentation methods for brain tumor images using classification or clustering with additional constraints, grouped by different approaches. Evaluation was performed on different datasets; empty cells indicate no reported information. Dim stands for dimensionality, S for supervision. SA means semi-automatic, FA means fully automatic. Type describes the tumor type, which can be as follows: G—glioma, HGG—high-grade glioma, LGG—low-grade glioma, M—meningioma, Met—metastasis.

Authors	Modalities	Method	Accuracy	Speed	Dim	S	Type
<i>Classification or clustering with global constraints based on atlases</i>							
Kaus <i>et al</i> (2001)	T ₁	Adaptive template-moderated classification	>95% (accuracy)	5–10 min	3D	FA	LGG, M
Moon <i>et al</i> (2002)	T ₁ , T _{1c} , T ₂	Statistical classification with geometric prior	>0.9 (overlap ratio)		3D	FA	G, M
Prastawa <i>et al</i> (2003)	T ₁ , T _{1c} , T ₂	Subject-specific modification of atlas priors	0.49–0.71 (Jaccard)		3D	FA	
Prastawa <i>et al</i> (2004)	T ₂	Outlier detection	0.59–0.89 (Jaccard)	1.5 h	3D	FA	G, M
Menze <i>et al</i> (2010)	T ₁ , T _{1c} , T ₂ , T _{2flair}	Generative model for multi-modal segmentation	0.4–0.7 (Dice)		3D	FA	G
Weizman <i>et al</i> (2012)	T ₁ , T ₂ , T _{2flair}	Classification and follow-up for optic pathway gliomas	0.69 (Dice)	20 min	3D	FA	G
<i>Classification or clustering with constraints based on deformable models</i>							
Cobzas <i>et al</i> (2007)	T ₁ , T _{1c} , T ₂	Variational segmentation with high-dimensional feature set	0.16–0.76 (Jaccard)		3D	FA	G
Khotanlou <i>et al</i> (2009)	T ₁	Fuzzy classification and spatially constrained deformable models	0.92 (similarity index)	4.5 min	3D	FA	HGG, M
Cobzas and Schmidt (2009)	T _{1c} , T _{2flair}	Level-set with embedded CRF	0.5–0.75 (Jaccard)		3D	FA	G
Popuri <i>et al</i> (2012)	T ₁ , T _{1c} , T ₂	Variational segmentation on a clustered feature set	0.58 (Jaccard)		3D	FA	G
Hamamci <i>et al</i> (2011)	T _{1c}	Tumor-cut	0.8–0.89 (Dice)	1 s–16 min	3D	SA	G, M, Met
<i>Classification or clustering with local constraints based on neighborhood regularization</i>							
Corso <i>et al</i> (2007)	T ₁ , T _{1c} , T ₂ , T _{2flair}	Extended graph-shift algorithm	0.87 (Jaccard)	1 min	3D	FA	HGG
Corso <i>et al</i> (2008)	T ₁ , T _{1c} , T ₂ , T _{2flair}	Segmentation by weighted aggregation	0.62–0.69 (Jaccard)	<1 min	3D	FA	HGG
Lee <i>et al</i> (2008)	T ₁ , T _{1c} , T ₂	Pseudo CRFs	0.84–0.9 (Jaccard)		2D	FA	G
Wels <i>et al</i> (2008)	T ₁ , T _{1c} , T ₂	Discriminative model-constrained graph cuts	0.78 (Jaccard)	1–2 min	3D	FA	G
Birkbeck <i>et al</i> (2009)	T _{1c} , T _{2flair}	Interactive graph cuts		2 min	2.5D	SA	
Nie <i>et al</i> (2009)	T ₁ , T ₂ , T _{2flair}	Spatial accuracy-weighted hierarchical MRF	0.72–0.76 (Jaccard)	20–25 min	3D	FA	G
Hamamci <i>et al</i> (2010)	T _{1contrast}	Cellular automata segmentation	0.74–0.87 (Dice)		3D	SA	G, M, Met
Hsieh <i>et al</i> (2011)	T ₁ , T ₂	Fuzzy clustering plus region-growing	0.73 (% match)		3D	FA	M
Bauer <i>et al</i> (2011a)	T ₁ , T _{1c} , T ₂ , T _{2flair}	Hierarchical SVM+CRF	0.77–0.84 (Dice)	<2 min	3D	FA	G
Zhu <i>et al</i> (2012)	T _{1c} , T ₂	EM + MRF + post-processing	0.25–0.81 (Jaccard)	4 min	3D	SA	HGG

on conventional MRI for screening purposes. Farjam *et al* (2012) chose a similar approach, but improved on the spherical template generation process by considering variations in tumor size, lesion shape and intensities to achieve more accurate detection rates. Although these approaches do not perform a segmentation, the tumor detection could be used for initializing a segmentation method.

2.2.5. Summary and conclusion—segmentation. Tables 1–3 present an overview of all the segmentation algorithms discussed and compare their most important characteristics and results. Most algorithms that have been suggested so far rely on multi-modal MR images for the tumor segmentation. The most promising approaches perform the fully automatic segmentation based on the voxel-wise classification in combination with spatial regularization to take the neighborhood information into account. They have the advantage of being very flexible and provide robust results within a reasonable computation time. Imposing shape or localization constraints after the previous classification is an effective approach too, but less flexible in handling different data and different kinds of tumors. However, fully automatic methods are subject to differences in MRI acquisitions, which can cause difficulties. Fewer examples rely on semi-automatic methods that incorporate user interaction. The interactive methods often rely on graph cuts or deformable models with a user-defined initialization, which makes them very flexible, but eliminates the advantage of being completely objective. It is not possible to draw general conclusions about the accuracy of different methods, because so far they have all been evaluated on different datasets.

While preparing this review, it became apparent that many papers focus on segmentation algorithms and not on the features extracted from the image. Features might be more important especially when considering the variance in appearance of different tumor types and grades. In the future, it 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 be added to improvements in pre-processing for image standardization and in constraints for increased robustness.

2.3. Registration of brain tumor images

Image registration of tumor-bearing brain images mainly focuses on two different objectives: inpatient multi-modal or longitudinal registration (alignment) of images on the one hand and interpatient spatial normalization of brain tumor images to a brain atlas on the other hand. The latter is commonly used for atlas-based segmentation purposes (Cabezas *et al* 2011) or for the statistical analysis and functional/structural mapping of brain tumor images. It can also be applied for constructing statistical tumor atlases from multiple patients (Davatzikos *et al* 2011). A diagram illustrating the major blocks of most registration pipelines is shown in figure 4. The pre-processing steps are very similar to those discussed in section 2.2.1 and are therefore not repeated here. We decided to separate registration methods and methods integrating tumor modeling with the registration. Again, both can be sub-grouped into intra- or interpatient methods, which can use either standard or tumor-specific registration algorithms. Usually, an initial rigid alignment is followed by a non-rigid transformation step (Sotiras *et al* 2012). The feature metric, which is used by most of the discussed approaches, is intensity-based registration thanks to its general applicability.

2.3.1. Standard inpatient registration. In the case of inpatient multi-modal or longitudinal registration of images, the aim is to geometrically transform the images into a common reference space for a simultaneous analysis of the different modalities, or for

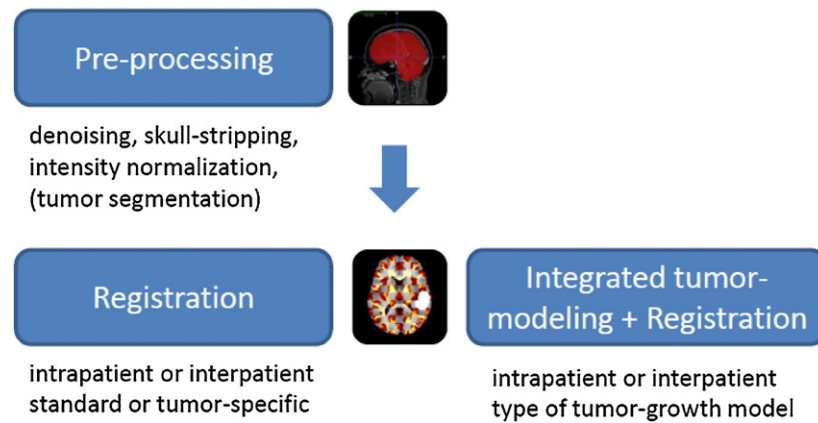


Figure 4. Illustration of the main blocks, which are used for building up the registration pipeline of most algorithms discussed in this review. We distinguish between algorithms, which are only based on registration and integrated algorithms combining tumor-growth modeling with the registration. Most algorithms perform a linear registration for an initial alignment before a non-rigid transformation is applied. The non-rigid transformation can be standard or tumor-specific.

tumor-growth monitoring over time. The problem of simply aligning the images without specifically considering any growth or deformation effects by the tumor was extensively studied by Mang *et al* (2008), who concluded that in general, the affine registration with an MI metric performed best. Another problem, which frequently occurs in the registration of tumor-bearing brain images, is the anisotropic voxel spacing. The individual modalities are usually acquired with different anisotropic resolutions, sometimes even in different orientations. The resulting interpolation problem has been addressed for the general case in Thévenaz *et al* (2000). Nevertheless, in practice, the inherent partial-volume effects still pose significant challenges for resampling all images in a common reference space. Characteristics of the method are summarized in table 4.

2.3.2. Advanced longitudinal intrapatient registration to handle resections. The problem of intrapatient registration is much more difficult when effects of surgery are considered because then nonlinear effects have to be included and in most cases it is not sufficient to apply standard registration algorithms. One application area for this is the registration of pre-operative images to intra-operative images or post-resection tumor images. Clatz *et al* (2005a) tackled the problem of non-rigidly registering intra-operative MR images to pre-operative scans. They were able to handle the mechanical brain deformation during surgery with a patient-specific finite element method (FEM) and a non-rigid block-matching method. Strict constraints on the computation time could be handled by a parallelized implementation and pre-computation of a large part of the processing pipeline. Archip *et al* (2007b) extended this approach, but they registered additional pre-operatively acquired MRI modalities, so that this information could be exploited during surgery. They achieved near-real-time computational speed and were able to provide enhanced visualization during neurosurgery. Wittek *et al* (2007) presented a patient-specific bio-mechanical model of brain deformation and its application to image registration. In their method, they were able to make use of patient-specific nonlinear bio-mechanical tissue properties for integrating the FEM analysis into the non-rigid registration of pre- and intra-operative images. Chitphakdithai and Duncan (2010) relied on the non-rigid registration

Table 4. Overview of registration methods for brain tumor images, grouped by different approaches for inpatient registration. Evaluation was performed on different datasets; empty cells indicate no reported information. Dim stands for dimensionality, S for supervision, Transf. for the transformation model. SA means semi-automatic, FA means fully automatic, L linear transformation model and NL nonlinear transformation model. Type describes the tumor type, which can be as follows: G—glioma, HGG—high-grade glioma, LGG—low-grade glioma, M—meningioma, Met—metastasis.

Authors	Method	Accuracy	Speed	Dim	S	Transf.	Type
<i>Standard inpatient registration</i>							
Mang <i>et al</i> (2008)	Consistency of parametric registration	sub-voxel accuracy		3D	FA	L	G
<i>Advanced longitudinal inpatient registration to handle resections</i>							
Clatz <i>et al</i> (2005a)	Non-rigid registration to capture brain shift	<2.5 mm	<35 s (cluster)	3D	FA	NL	
Archip <i>et al</i> (2007b)	Pre- and intra-operative alignment of MRI	<3.6 mm	179 s (cluster)	3D		NL	G
Wittek <i>et al</i> (2007)	Model of brain deformation for image registration	1–30 mm	15 min	3D		NL	
Chitphakdithai and Duncan (2010)	MAP registration estimation framework	1.3 mm (AE)		3D	FA	NL	
<i>Advanced longitudinal inpatient registration for tumor-growth monitoring</i>							
Konukoglu <i>et al</i> (2008)	Tumor monitoring	<38% (error)		3D	SA	NL	M
Niethammer <i>et al</i> (2011)	Geometric metamorphosis	0.975 (overlap)		3D	FA	NL	
Pohl <i>et al</i> (2011)	Detecting change in slowly evolving brain tumors	<23% (vol. diff.)	<5 min	3D	SA	L	M
Angelini <i>et al</i> (2012)	Differential analysis for the tumor-growth quantification	9–23% (error)		2D/3D	FA	NL	LGG

for considering changes after brain tumor treatment. They formulated the registration as a maximum *a posteriori* (MAP) problem and solved it in an EM framework. This way, the probability term of the transformation could be seen as a similarity metric for which an indicator map could model different correspondence assumptions for different tissue classes. Characteristics of each method are summarized in table 4.

2.3.3. Advanced longitudinal inpatient registration for tumor-growth monitoring. Another area where advanced inpatient registration strategies are necessary is tumor-growth monitoring from longitudinal image acquisitions. Konukoglu *et al* (2008) suggested a registration method for monitoring slowly evolving meningiomas, which performed semi-automatic tumor segmentation, non-rigid registration and change detection consecutively. They argued that their volume-change measurements were less user-biased than manual measurements. Niethammer *et al* (2011) suggested a metamorphosis model, which jointly estimated a deformation in space and a change in image appearance for smooth transformation. Changes in image appearance were modeled by a global geometric deformation, and local matching was based on an image composition model in a large displacement diffeomorphic metric mapping framework. Pohl *et al* (2011) proposed to detect changes in slowly evolving meningiomas by semi-automatic segmentation, subsequent registration and final analysis of changes in local intensity patterns. A differential MRI analysis for the quantification of low-grade glioma growth was applied by Angelini *et al* (2012). They used a standard affine registration, but implemented a nonlinear midway-based histogram mapping, which allowed them to compare and compute intensity difference maps directly. Glioma growth was finally quantified with a statistical analysis framework of the mapped intensity distributions. Characteristics of each method are summarized in table 4.

2.3.4. Standard interpatient registration. The case of interpatient registration of tumor-bearing brain images is even more challenging than the alignment of images from the same patient because inter-subject variations have to be integrated with topological changes. Isambert *et al* (2008) circumvented this problem by using a general method for registering an atlas of a standard brain to the patient image using a multi-affine block-matching strategy. Organs at risk in a clinical radiotherapy context were delineated from the registered atlas. Later, Deeley *et al* (2011) did an extensive comparison of manual and automatic segmentation methods for brain structures in the presence of space-occupying lesions. As an automatic method, they used a combination of multi-affine and non-rigid registration with the final level-set refinement. They claimed that the accuracy of automatic and manual segmentations were in a similar range when compared against the STAPLE ground truth, but the manual segmentations were still slightly better. Characteristics of each method are summarized in table 5.

2.3.5. Interpatient registration with lesion masking approaches. In a comparison study, Andersen *et al* (2010) showed that non-rigid registration approaches which masked out the lesion area from the similarity metric achieved superior results compared to the conventional registration taking the whole image region into account. Variations of these masking methods, which gave a different weight to tumor regions, have been suggested by a number of groups.

Brett *et al* (2001) masked the cost function of a combined affine and non-rigid registration method. The lesion had to be manually pre-segmented to be used as a mask for the similarity criterion during the registration. They experimented with different thresholds for the cost function mask. Stefanescu *et al* (2004) chose a similar approach. They created a confidence map

Table 5. Overview of pure registration methods for brain tumor images, grouped by different approaches for the interpatient registration. Evaluation was performed on different datasets; empty cells indicate no reported information. Dim stands for dimensionality, S for supervision, Transf. for the transformation model. SA means semi-automatic, FA means fully automatic, L linear transformation model and NL nonlinear transformation model. Type describes the tumor type, which can be as follows: G—glioma, HGG—high-grade glioma, LGG—low-grade glioma, M—meningioma, Met—metastasis.

Authors	Method	Accuracy	Speed	Dim	S	Transf.	Type
<i>Standard interpatient registration</i>							
Isambert <i>et al</i> (2008)	Atlas-based segmentation in a radiotherapy clinical context	0.3–0.85 (Dice)	7–8 min (cluster)	3D	FA	NL	G, M
Deeley <i>et al</i> (2011)	Comparison of manual and automatic segmentation methods	0.4–0.9 (Dice)		3D	FA	NL	HGG
<i>Interpatient registration with lesion masking approaches</i>							
Brett <i>et al</i> (2001)	Cost function masking	0.5–2.6 mm (RMS)		3D	SA	NL	
Dawant <i>et al</i> (2002)	Seeded atlas deformation			3D	SA	NL	G, M
Stefanescu <i>et al</i> (2004)	Confidence map for the non-rigid registration		5–10 min (cluster)	3D	FA	NL	
Commowick <i>et al</i> (2005)	Statistical measures of anatomical variability for registration	0.84–0.94 (spec)	1 h	3D	FA	NL	
Lamecker and Pennec (2010)	Demons and deformation inpainting		9 min	3D	SA	NL	G
Li <i>et al</i> (2011)	Riemannian embedding			3D	SA	NL	M
Parisot <i>et al</i> (2011)	Graph-based spatial position mapping			3D	SA	NL	LGG
Parisot <i>et al</i> (2012)	Joint tumor segmentation and dense deformable registration	0.8 (Dice)	6 min	3D	FA	NL	LGG
<i>Interpatient registration with two distinct deformation models</i>							
Bach Cuadra <i>et al</i> (2004)	Model of lesion growth for the atlas-based segmentation	37.2 mm ³ (MSE)		3D	SA	NL	M
Pollo <i>et al</i> (2005)	Model of lesion growth for the atlas-based segmentation			3D	SA	NL	M
Bach Cuadra <i>et al</i> (2006)	Deformation field estimation for the atlas-based segmentation using MLG and MI	0.89–1.0 (TP)		3D	SA	NL	M

for the similarity metric used during the registration and assigned zero confidence to all voxels inside the pre-segmented tumor mask. Additionally, they allowed an adaptive regularization in different tissue regions.

Dawant *et al* (2002) introduced small tumor seeds in the atlas at the approximate patient tumor location. Subsequently, they performed the non-rigid registration, which also deformed the seed in the atlas to match the shape of the pre-segmented tumor in the patient approximately. Commowick *et al* (2005) used statistical measures of anatomical variability to guide the regularization during the registration process. Regions of low variability were regularized more strongly. Lamecker and Pennec (2010) took up the idea of using confidence weights. They added an inpainting step to a Demons registration algorithm, which modeled a zero confidence within the pathologic region. Li *et al* (2011) chose a Riemannian embedding for their registration algorithm, which was able to handle topological changes. The method required an *a priori* estimation of topological changes as an input. Parisot *et al* (2011) did not take the tumor voxels into account for the deformable registration of a dataset of images from different patients. The registration output has been used for graph-based spatial position mapping of low-grade gliomas. Later, they proposed a graph-based joint segmentation and registration framework (Parisot *et al* 2012). In the tumor region, which was identified by an AdaBoost classifier, the registration criterion was relaxed to produce a smooth solution of the segmentation. Characteristics of each method are summarized in table 5.

2.3.6. Interpatient registration with two distinct deformation models. Another idea for the interpatient registration is to incorporate a lesion model directly into the registration method. This allows for a decoupling of the deformations due to tumor-growth and inter-subject variations, without having to model the complex tumor-growth behavior explicitly. Bach Cuadra *et al* (2004) suggested a model of lesion growth for the atlas-based segmentation of tumor-bearing brain images. They incorporated a simplistic radial tumor-growth model into a Demons-based non-rigid registration method. The lesion-growth model modified a healthy atlas and adapted it to the tumor-bearing patient image; however, the method was completely based on registration methods and did not include any kind of bio-mechanical tumor-growth simulation. Later, Pollo *et al* (2005) from the same group conducted a more qualitative evaluation of the method. Finally, they further improved it by replacing the SSD-based Demons algorithm with an optical flow method based on MI (Bach Cuadra *et al* 2006). They reported better results for this method because the assumption of linear intensity correspondence between both images could be dropped (see figure 5 for results). Characteristics of each method are summarized in table 5.

2.3.7. Summary and conclusion—registration. Most registration methods make use of a combination of rigid/affine and non-rigid registration with specific adaptations for tumor-bearing images. While non-rigid methods are obviously more accurate than the standard rigid registration, they also carry additional risks of mis-registrations, especially when topological changes due to the tumor are involved. This risk can be reduced by tumor-specific adaptations; however, these methods are in general more difficult to handle than standard registration approaches. It is not possible to draw a general conclusion about the accuracy and performance of different methods because different data have been used for validation, but we will briefly summarize the qualities of the different approaches.

The case of intra-subject alignment of longitudinal/multi-modal images can be easily solved by standard registration methods if tumor effects are neglected. The problem is much more difficult if the registration is used for longitudinal tumor-growth monitoring or when

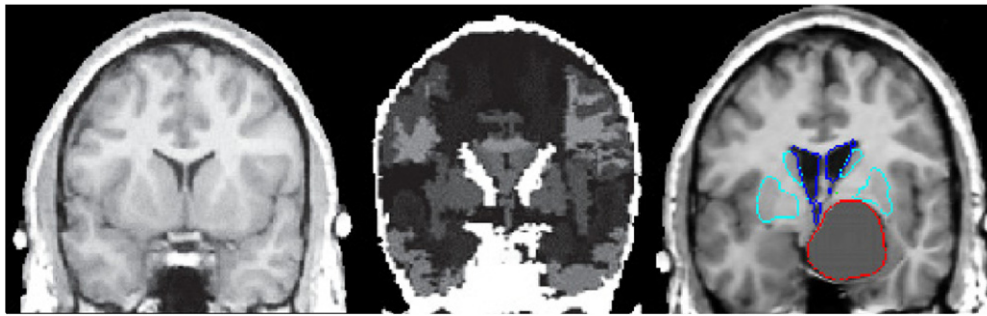


Figure 5. Registration based on two distinct deformation models. From left to right: atlas image, atlas label map and the segmented patient image (Reprinted from Bach Cuadra *et al* 2006 *Comput. Methods Programs Biomed.* **84** 66–75. Copyright with permission from Elsevier). The atlas is modified using a lesion-growth model to mimic the tumor-induced deformation and the segmented structures from the atlas are transferred to the patient image by the non-rigid registration.

registering pre- and post-resection images. Methods for registering images during surgery often make use of FEM models for considering the effect of brain shift, while in longitudinal registration methods, usually a special way of handling the tumor-induced appearance changes is employed. For intra-operative images, the computation time is crucial and therefore emphasized by all authors. An overview and comparison of the presented techniques can be found in table 4.

The inter-subject normalization task is also very challenging due to the effects of the tumor mass in combination with inter-subject variations. It appears that masking out the tumor area from the calculation of the similarity metric is too simplistic and more sophisticated methods, which assign different confidence weights to different areas during the registration, or which allow for a composition of two different kinds of deformations, are a more promising way to solve the problem; however, this also affects the computation time. An overview and comparison of the presented techniques can be found in table 5.

2.4. Integrated approaches for tumor-growth modeling and registration/segmentation

The major problem when registering a brain tumor image with a healthy atlas is the missing correspondence between pathologic patient image and healthy atlas. One idea to circumvent this problem is to seed the atlas with a tumor prior and simulate tumor growth in the atlas according to the patient image, followed by a final non-rigid registration step.

2.4.1. Types of tumor-growth models. Tumor-growth simulation approaches used in image-based modeling can fall into three different categories: on the microscopic level, cellular growth models are used, while on the macroscopic scale, diffusion–reaction models or bio-mechanical models are employed.

Cellular growth models focus on cell-to-cell interactions and are able to model proliferation or apoptosis of individual cells using rule-based cellular automata (Kansal *et al* 2000, Stamatakis *et al* 2007, 2010).

Reaction–diffusion models simulate the proliferation and spread of the tumor based on a reaction–diffusion partial differential equation model. The general assumption is that the cancer cells spread along the fiber direction with different diffusion coefficients in gray matter and white matter (Swanson *et al* 2000, 2002).

Bio-mechanical models take into account the mass effect of large tumors and model the deformation of the surrounding tissues based on their material properties, usually employing an FEM (Davatzikos *et al* 2001, Zacharaki *et al* 2008a, Chen *et al* 2010). For the challenge of handling the large-scale deformations occurring in brain tumor growth, it has been suggested to use a Eulerian instead of a Lagrangian formulation (Hogea *et al* 2007a).

Multi-scale models integrate the methods mentioned previously in order to gain a more precise formulation. Most models simulate proliferation based on a reaction–diffusion equation and couple this with a bio-mechanical model for the mass effect (Clatz *et al* 2005b, Hogea *et al* 2007b, 2008b, 2008a, Prastawa *et al* 2009). An exception is May *et al* (2011), where a cellular proliferation model is coupled to a Eulerian FEM model to simulate the mass effect. Marias *et al* (2011) recently made a first attempt to integrate all three levels of complexity: cellular, diffusion and bio-mechanical into one single multi-scale model.

Personalization of these models is difficult, especially for registration purposes when only limited data are available for this task. Most authors employ image-based modeling, making ad hoc assumptions about the connection between image intensities and cell densities, which again rely on segmentations of tumor and healthy tissues. Other model parameters are either initialized with standard values from the literature or optimization methods are employed for personalizing the models by choosing individual parameters.

2.4.2. Purely bio-mechanical growth models combined with the registration. Kyriacou *et al* (1999) were the first ones to introduce the concept of combining bio-mechanical tumor-growth modeling with the non-rigid registration in order to adapt a patient image to a healthy atlas. They assumed a uniform strain of the tumor and a nonlinear elastic behavior of the surrounding tissues. First, the shrinkage of the tumor in the patient image was performed to obtain an artificial healthy patient image. A healthy atlas was then registered to the tumor-free patient image with an elastic registration method. Subsequently, tumor growth was performed on the registered atlas using a regression method to invert the tumor shrinkage process from the previous step. Finally, they obtained a patient-adapted atlas including pathology. The concept was demonstrated on 2D image slices.

Later, Mohamed *et al* (2006) from the same group chose a different approach. Instead of shrinking the patient tumor, they grew the tumor in the atlas image according to the pathologic patient image and applied a non-rigid registration to adapt the modified atlas to the patient image. In order to handle the significant computational cost of the tumor-growth modeling in 3D, they employed an approach based on a statistical model of tumor-induced deformation using the principal component analysis (PCA). For each case, the most likely parameters were estimated and the deformation could be applied based on the pre-built statistical model. Zacharaki *et al* (2008b) further developed this approach as a multi-resolution framework for the registration of brain tumor images. In their approach, they also used a statistical model of tumor-induced deformation, but in a hierarchical framework for parameter optimization. Local information was incorporated into the tumor-growth model and the registration methodology was improved. In a next step, Zacharaki *et al* (2009a) improved the tumor-growth model compared to their previous method. They employed a piecewise Eulerian simulator with a uniform outward pushing pressure model for the bulk tumor, which did not require the simplified PCA model for tumor growth while still being computationally efficient. Additionally, the parameter optimization was performed in a parallelized fashion for further speed improvements.

Bauer *et al* (2011b) proposed a more simplistic model for tumor growth, which they combined with a non-rigid Demons registration. A healthy atlas was seeded automatically and bio-mechanical tumor growth was modeled assuming a radial expansion force. The expansion

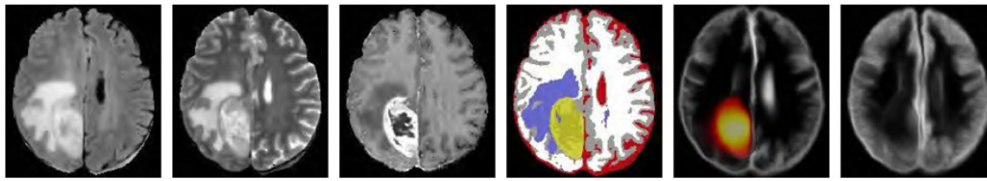


Figure 6. Integrated tumor-growth modeling and non-rigid registration. Axial slices of the three modalities (FLAIR, T_2 , $T_{1\text{contrast}}$), which were used, are shown on the left. The segmentation result of the GLISTR method is shown in the center. The images on the right depict the obtained probability maps for tumor (color), CSF and gray matter (grayscale), respectively, after the combined tumor-growth simulation and registration. Reproduced with permission from Gooya *et al* 2012 *IEEE Trans. Med. Imaging* 31 1941–54. © 2012 IEEE.

was propagated over the image by means of an MRF method on the deformation field. Characteristics of each method are summarized in table 6.

2.4.3. Diffusion-based bio-mechanical growth models combined with the registration. Gooya *et al* (2011a) employed a more sophisticated diffusion–reaction model for tumor growth, which was coupled with a Eulerian method to simulate the mass effect. They operated on multi-sequence images to obtain a probability map of the different tissue classes using SVM classification techniques. The patient-specific tumor was grown in the atlas and a Demons-like algorithm was employed for the localized atlas-to-patient transformation for which the tissue probability maps from the multi-sequence classifier were considered for the cost function. The whole process was formulated in an EM framework to jointly estimate tumor growth and the spatial transformations for adapting the atlas to the patient image. In an extension, Gooya *et al* (2011b) dropped the requirement for a pre-classification and proposed a joint segmentation and registration model including tumor growth. To this end, they used again an EM algorithm to jointly estimate tumor-growth parameters and registration deformation field to obtain the tissue posterior probabilities in the patient image derived from the atlas. The approach was recently further improved and extended (Gooya *et al* 2012; see figure 6), where the authors also reported on employing the method for the construction of statistical atlases for gliomas. Characteristics of each method are summarized in table 6.

2.4.4. Bio-mechanical growth method based on a cellular model combined with the registration. Bauer *et al* (2012) suggested to use a bio-physio-mechanical tumor-growth model for the atlas-based segmentation of tumor-bearing brain images. They seeded the atlas with a patient-specific prior and simulated tumor growth with a cellular automaton modeling tumor cell proliferation, which was coupled to a Eulerian FEM method to handle the tumor mass effect. The modified atlas was registered to the patient image with a Demons algorithm and the label map was propagated for the segmentation. Recently, they extended this to be applicable to radiotherapy and neurosurgery (Bauer *et al* 2013). The tumor outline was defined using classification methods and important structures were segmented by warping a subcortical label map with an enhanced registration metric. Characteristics of the methods are summarized in table 6.

2.4.5. Summary and conclusion—integrated approaches. Several authors have proposed integrated approaches that combine tumor-growth modeling with segmentation methods based on the registration of an atlas (see table 6 for a summary). To this end, initial correspondence

Table 6. Overview of combined tumor-growth modeling and registration/segmentation methods, grouped by different approaches. Evaluation was performed on different datasets; empty cells indicate no reported information. Dim stands for dimensionality, S for supervision, Transf. for the transformation model. SA means semi-automatic, FA means fully automatic, L linear transformation model and NL nonlinear transformation model. Type describes the tumor type, which can be as follows: G—glioma, HGG—high-grade glioma, LGG—low-grade glioma, M—meningioma, Met—metastasis.

Authors	Method	Accuracy	Speed	Dim	S	Transf.	Type
<i>Purely bio-mechanical growth model</i>							
Kyriacou <i>et al</i> (1999)	Bio-mechanical tumor shrinkage and growth for registration	<3.5 mm	<100 min	2D	SA	NL	Met
Mohamed <i>et al</i> (2006)	Statistical model for tumor-induced deformation	<19 mm	35 min	3D	SA	NL	G
Zacharaki <i>et al</i> (2008b)	ORBIT	<42 mm	14 h	3D	SA	NL	
Zacharaki <i>et al</i> (2009a)	Non-diffeomorphic registration with tumor growth	0.67–0.74 (Dice)	<6 h (cluster)	3D	SA	NL	G, Met
Bauer <i>et al</i> (2011b)	MRF lesion-growth model	0.7–0.95 (Dice)	<30 min (GPU)	3D	SA	NL	G
<i>Diffusion-based bio-mechanical growth methods</i>							
Gooya <i>et al</i> (2011a)	Registration with the EM algorithm and diffusion modeling	0.29–0.63 (Jaccard)	6–14 h (cluster)	3D	FA	NL	G
Gooya <i>et al</i> (2011b)	Joint segmentation and registration	0.76–0.85 (Dice)		3D	FA	NL	G
Gooya <i>et al</i> (2012)	GLISTR: glioma image segmentation and registration	0.75–0.84 (Dice)	3–6 h	3D	FA	NL	G, Met
<i>Cellular-based bio-mechanical growth methods</i>							
Bauer <i>et al</i> (2012)	Multi-scale modeling for the atlas-based segmentation	0.56–0.95 (Dice)	10–36 h	3D	SA	NL	G
Bauer <i>et al</i> (2013)	Integrated segmentation for radiotherapy and neurosurgery	0.41–0.72 (Dice)	6–48 h	3D	FA	NL	G

between healthy atlas and pathologic patient image is established with the help of tumor-growth simulation. It has been observed that the initially proposed purely bio-mechanical methods, modeling the tumor-mass effect only, were not satisfactory. Therefore, the more realistic models simulate the mass effect coupled to either a microscopic cellular proliferation model or a macroscopic diffusion model. A logical next step would be to integrate all three levels: cellular, diffusion and bio-mechanical layer to obtain a more meaningful model. The non-rigid registration methods applied after tumor-growth simulation are mostly standard algorithms which are well known in the medical image analysis community. It would be interesting to see if additional knowledge about tissue distributions and characteristics in brain tumor images could be useful. However, before the approaches presented in this section can become clinically relevant, the computation time has to be drastically reduced.

3. Discussion and outlook

3.1. Critical review of the current state of the art

In this review, we gave an overview of the state of the art in the MRI-based medical image analysis for brain tumor studies. The focus was on segmentation and registration, whereas some of the registration methods also included tumor-growth modeling. The first attempts in this field were made almost two decades ago, but it can be observed that in recent years, the methods are becoming mature and an increase of their use in clinical practice is expected.

The majority of segmentation approaches operate on multi-sequence MRI data, employing classification methods using different features and taking spatial information in a local neighborhood into account. The trend is not to segment the tumor only, but also to delineate tumor sub-compartments and different healthy regions on images from standard clinical acquisition protocols. This provides the physician with a more comprehensive information on which diagnosis, tumor monitoring and therapy planning can be based. Apart from the evaluation of accuracy and robustness, an important criterion is the computation time. Processing times of a few minutes are the current standard. Performing a better problem-oriented selection of the segmentation technique instead of choosing the technique first and then try to make it work on the current problem could be accomplished in the future by paying more attention to feature selection than the segmentation algorithm.

The registration methods can be separated into intra- and interpatient registration. In inpatient registration, the main challenge is to handle effects of tumor growth or resection, which is mostly done by tumor image-specific extensions to standard registration algorithms. The majority of interpatient registration approaches focus on the registration of tumor-bearing brain images with a normal atlas. This can be used for the atlas-based segmentation or for constructing statistical brain tumor atlases. One attempt to handle the missing correspondence between healthy atlas and pathologic patient image is solely based on registration methods; a different idea is to combine tumor-growth modeling with registration methods. While the registration approaches are more general, the integrated approaches tend to be more accurate; however, the tumor-growth model adds additional complexity, which also introduces additional risks. A major problem, especially for the integrated approaches, is their tremendous computation time. Therefore, these methods should be considered as pure research methods at the moment and will not reach clinical use until improvements in computational speed are attained.

Comparing the traditional segmentation techniques and the atlas-based segmentation methods, which rely on the registration, it is clear that the traditional segmentation techniques are more flexible and can be more easily adapted to handle multiple modalities simultaneously.

Additionally, it is possible to treat individual tumor sub-compartments more easily. Atlas-based methods have advantages when segmenting tissues and structures surrounding the tumor, especially subcortical structures or functional areas. These structures can be segmented more easily if there is atlas-encoded information about spatial localization available. This can have important implications for surgery or radiation therapy. However, many approaches incorporating tumor-growth modeling have difficulties in handling multifocal lesions.

While preparing this review, it became apparent that some papers in the literature lack in precision, describing what exactly is being done, what type and grade of tumor are being considered, what image data are being used or how the algorithm performs in terms of robustness, accuracy and speed. This can be easily seen from the many empty fields in the presented tables. Particularly in the case of medical image analysis for brain tumor studies, better attention should be paid not only to differences according to the tumor type and grade, but also to robustness of the algorithm. Eventually, it would be useful to test any new method on a standard database of brain tumor images to allow for a fair comparison against the state of the art. The MICCAI BraTS dataset⁵ would be one candidate for such a database (see also section 2.1).

3.2. Clinical requirements and applicability

Although a lot of research has been done in this field over the last few years, application in the clinics is still limited. Despite the huge amount of work involved and the limited objectiveness, in many cases, clinicians still rely on manual tumor delineations. This is probably mostly due to a lack of communication between researchers and clinicians. Many tools developed so far are pure research tools, which are not easy to handle for clinicians. Therefore, a major effort should be spent on embedding the developed tools into more user-friendly environments in the future. So far, in most commercial workstations, only very simple methods are implemented (e.g. thresholding). One reason for this might be that the technology transfer from the bench to the bedside is still a major challenge because the performance achieved in a well-controlled research environment can often not be reproduced in clinical routine. Recently, more researchers have tried to consider standard clinical acquisition protocols when developing their methods, instead of focusing on feasibility studies that employ pure research data as image material. This will hopefully aid in spreading the application more quickly. Another important aspect is the computation time: the real-time segmentation will be hard to achieve, but computation times which are beyond a few minutes are unacceptable in clinical routine. For everyday use, robustness is crucial. This includes robustness against slight changes in the acquisition protocol, but also the flexibility to handle new acquisition protocols. If a method tends to fail completely in some cases, doctors will lose their trust in the automatic approach and will not be willing to change their habits. Therefore, a thorough demonstration of the robustness should be one of the major steps for each new method.

Currently, image acquisition protocols are not completely standardized. In order to be able to make the best possible use of automatic methods for the medical image analysis, it is essential to have image data, which have been acquired according to a well-defined protocol across different clinical sites. We expect that such a standardization would aid significantly in improving the applicability and spread the use of automatic methods because the need for fine-tuning according to specific imaging characteristics will be eliminated.

Standard therapeutic procedures for brain tumors include resection, followed by fractionated radiation therapy combined with temozolomide chemotherapy (Stupp *et al* 2009). Due to recent changes in glioma treatment, the traditional Macdonald criteria (Macdonald

⁵ www2.imm.dtu.dk/projects/BRAITS2012/.

et al 1990) for the tumor response evaluation are increasingly recognized to be not adequate any more, as effects of pseudo-progression and pseudo-response are not covered by these criteria. Since the formulation of the Macdonald criteria, many novel MR techniques have become available, now widely used in clinical routine, that allow for the non-invasive retrieval of morphological, functional and metabolic properties of brain tumors (e.g. diffusion weighted imaging, dynamic susceptibility contrast-enhanced perfusion imaging, MRS). These techniques may be able to fill the gap in the proper evaluation of tumor progression in the future, together with improvements in the tumor volume estimation from the medical image analysis by forming an integrated platform for advanced tumor assessment.

Eventually, a dialogue should be initiated to convince practitioners that although a software tool might lack in accuracy compared to the manual method in certain cases, it offers more objectiveness, which is very important in longitudinal studies. However, while being objective, the automatic segmentation obviously has to be sufficiently close to what a radiologist perceives as the correct tumor segmentation. If this cannot be achieved by fully automatic methods, it might be worthwhile to consider an interactive method that is initialized or corrected by the user. In practice, the variability introduced by interactive user input is usually much smaller than the variability of completely manual segmentation results. In this case, ease of use for the clinician is crucial for any method to be accepted. It should also not be neglected that for automatic tumor image analysis methods to be used as a routine diagnosis tool, the certification is mandatory. This probably means that the application will not reach a breakthrough in the clinics before commercial software packages are being offered. Current clinical viewing systems are often not even well equipped yet for visualizing changes in multiple image classes over time.

3.3. Publicly available toolboxes

Only very few implementations of the presented methods are publicly available. This impedes a comparison of new methods to existing approaches and also hinders a large-scale evaluation with clinical data from different sites. To the best of our knowledge, at the moment, there are only three methods publicly available for download, which are dedicated to the analysis of brain tumor images:

Prastawa *et al* (2009) provide their ‘TumorSim’ software for the simulation of synthetic brain tumor images⁶. Bauer *et al* (2011a) offer the ‘DoctorNo’ suite of tools (Bauer and Reyes 2011) as a plug-in for the GUI-based ‘DoctorEye’ software platform (Skounakis *et al* 2010) for download⁷. Gooya *et al* (2011a) provide the ‘GLISTR’ toolkit on their website⁸.

3.4. Future directions and trends

It can be expected that the current efforts for registration and segmentation of tumor-bearing brain images on standard MRI protocols will enter routine clinical procedures in the next years (Levy and Rubin 2011). In order for this to occur, the proof of robustness and sufficient speed of the methods is mandatory, as outlined before. This development is likely to be pushed with the anticipated shift from the diameter-based MacDonald (Macdonald *et al* 1990) and RECIST (Therasse *et al* 2000) criteria to volume-based criteria for the assessment of tumor response to treatment as suggested by the RANO group (Wen *et al* 2010). However, it remains to be investigated how well automatic methods can handle the impact of treatment effects

⁶ www.nitrc.org/projects/tumorsim.

⁷ www.istb.unibe.ch/content/research/medical_image_analysis/software.

⁸ www.rad.upenn.edu/sbia/software/glistr.

and related pseudo-progression or pseudo-response on the segmentation outcome, which will also be interesting for clinical trials (Henson *et al* 2008). Nevertheless, the objectiveness of automatic methods in the tumor segmentation is undisputed and Angelini *et al* (2012) have made use of this in a first comprehensive study on longitudinal brain tumor data. It is likely that this line of research will be exploited more in the future.

Apart from the standard imaging methods, recently more advanced MRI modalities such as perfusion imaging, DTI and MRS are getting more attention (Cha 2006, Law 2009) in the brain tumor analysis. These modalities are mostly used for tumor grading and for the localization of the most active areas of the tumor. Researchers have started to apply machine learning approaches for tumor grading from perfusion images (Slotboom *et al* 2008, Zacharaki *et al* 2009b, Emblem *et al* 2009, Zöllner *et al* 2010, Zacharaki *et al* 2011) and also for the analysis of combined MRI/MRS data (Luts *et al* 2007, Fayed *et al* 2008, Georgiadis *et al* 2011). PET imaging has the potential to provide better prognostic information and distinguish recurrent tumor from radiation necrosis (Chen 2007, Dhermain *et al* 2010).

Another area, which is likely to get increased attention, is patient-specific image-based modeling of brain tumor growth (Konukoglu *et al* 2010, Menze *et al* 2011). This research could help to predict tumor progression and optimize treatment options on an individual basis.

Acknowledgments

The authors would like to acknowledge fruitful discussions within the ContraCancrum consortium. This research was partially funded by the European Union within the framework of the ContraCancrum project (FP7 - IST-223979). It was also partially funded by the Swiss National Science Foundation within the framework of the NCCR Co-Me and by the Bernese Cancer League.

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