Atlas-Based Segmentation of Tumor-Bearing Brain Images

14

Stefan Bauer, Roland Wiest, Johannes Slotboom, and Mauricio Reyes

Contents

Abstract

In diagnostic neuroradiology as well as in radiation oncology and neurosurgery, there is an increasing demand for accurate segmentation of tumor-bearing brain images. Atlas-based segmentation is an appealing automatic technique thanks to its robustness and versatility. However, atlas-based segmentation of tumor-bearing brain images is challenging due to the confounding effects of the tumor in the patient image. In this article, we provide a brief background on brain tumor imaging and introduce the clinical perspective, before we categorize and review the state of the art in the current literature on atlas-based segmentation for tumor-bearing brain images. We also present selected methods and results from our own research in more detail. Finally, we conclude with a short summary and look at new developments in the field, including requirements for future routine clinical use.

Introduction

Brain Tumors and Clinical Brain Tumor Imaging

Although brain tumors are not frequent (with an incidence of about 1‰ in the western population), they are among the most fatal cancers (DeAngelis 2001). Due to their different characteristics they are categorized into different classes. The most widely used grading scheme

S. Bauer (✉) • M. Reyes
Institute for Surgical Technology and Biomechanics, University of Bern, Stauffacherstrasse 78, CH-3014 Bern, Switzerland
e-mail: Stefan.bauer@istb.unibe.ch

R. Wiest • J. Slotboom
SCAN, University Institute of Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, Freiburgerstrasse, CH-3010 Bern, Switzerland

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 12*,
DOI 10.1007/978-94-007-7217-5_14,

was suggested by the World Health Organization (WHO), classifying brain tumors into grades from I to IV with increasing malignancy. Treatment for brain tumors strongly depends on the tumor classification and the rate of progression, with treatment options ranging from surgical resection to radiation therapy, chemotherapy and/or anti-angiogenic therapy.

Brain tumors are commonly diagnosed by neuro-imaging procedures, ideally by magnetic resonance imaging (MRI) (DeAngelis 2001). There is a variety of imaging sequences that provide the possibility to vary tissue contrast, thus highlighting different pathological or healthy tissue compartments. The most relevant MRI sequences in clinical practice of brain tumor imaging incorporate T_1-weighted images, T_1-weighted images with contrast enhancement (usually Gadolinium-DTPA), T_2-weighted images and T_{2Flair} images (Drevelegas and Papanikolaou 2011). Although imaging is very powerful and important in brain tumor diagnosis and treatment planning, even advanced imaging methods may fail in the delineation of the complete extent of the actual tumor.

Medical Image Segmentation

Medical images must be processed and the relevant information has to be extracted in order to provide useful information to the neuroradiologist and the clinician. This information contains tumor location and size, including a precise delineation of the tumor boundaries, but also the location of healthy tissues and subcortical structures surrounding the tumor, which is of relevance for radiotherapy and neurosurgery. Medical image segmentation (Pham et al. 2000) aims at dividing an image into several different compartments. These compartments can be chosen according to structures of interest or tissue types. In today's clinical practice, the most common approach is to perform manual segmentation by drawing the outline of the structure or tissue of interest on the patient image. The drawback of this approach is that it is very time-consuming, especially for 3D images, and it also lacks in reproducibility (Mazzara et al. 2004). Therefore, automatic methods to segment tumor-bearing brain images are promising, because they can significantly reduce segmentation time during post-processing and also offer better reproducibility with respect to their objectiveness.

Automatic segmentation methods for tumor-bearing brain images usually require some pre-processing, which may include skull-stripping (Speier et al. 2011) and the alignment of sequential or multi-modal images in a common frame of reference by image registration (Mang et al. 2008). The current segmentation methods for brain tumor images can be roughly divided into two different categories. On the one hand, there are methods that operate on multi-modal images and on the other hand, there are methods which operate on preselected mono-modal sequences only. Multi-modal approaches are commonly based on classification methods and consider several MRI modalities simultaneously (e.g. Bauer et al. 2011b). They are good at outlining the tumor including its sub-compartments, i.e. necrotic tissue, enhancing lesions and edema. These methods are not further discussed in this article. On the other hand, mono-modal approaches for segmentation of tumor-bearing brain images often rely on atlas registration. These methods, commonly referred to as "atlas-based segmentation", excel at delineating small healthy structures surrounding the tumor. Different approaches for atlas-based segmentation of tumor-bearing brain images will be discussed in more detail in the following sections. We intend to provide a short review and categorization of the state of the art of atlas-based segmentation of tumor-bearing brain images and also discuss some of our own research in more detail.

Atlas-Based Segmentation of Tumor-Bearing Brain Images

Clinical Requirements

Atlas-based segmentation has been shown to be more suitable for delineating healthy tissues and

structures around the tumor than for segmenting the tumor itself. Therefore, its most important application comes from neurosurgical or radiotherapy planning, where manual delineation of the tissues and structures at risk for damage is currently state of the art. To make the transition from the current manual segmentation to a fully automatic atlas-based segmentation in a clinical environment, the methods have to fulfill certain requirements. These include proven accuracy and robustness of the segmentation result, but also a limit on the maximum computation time of the algorithm. Computation time is crucial for the productive use of a method in daily clinical practice. Another important aspect is the user-friendliness of the tool provided: Physicians are unlikely to make routine use of a new method unless it is easy to use and well-understood, to rely on it for making clinical decisions. Additionally, it would be useful if the chosen segmentation method is able to handle a large variety of different brain tumors, including multifocal lesions, without requiring too much user intervention.

The Basics of Atlas-Based Segmentation

Atlas-based segmentation performs implicit segmentation by registering an atlas to the patient image and propagating the atlas labels (Cabezas et al. 2011). In general, the method requires an atlas and a transformation model for the registration. An atlas consists of an anatomical image and the segmentation label map for the structures of interest. There are a number of publicly available single-subject atlases or average atlases derived from multiple subjects; one recent example was described by Rohlfing et al. (2010). The transformation model defines how the atlas is aligned with the patient image. Most authors follow a two-step procedure for this alignment, by first performing a rough registration of both images with an affine transformation model and then doing a refined non-rigid registration for a more precise alignment of both images (Zitova and Flusser 2003). Image alignment is usually performed by using an intensity-based cost function, which is iteratively minimized with a dedicated optimizer. Finally, the atlas label map can be transformed and warped to the patient image to be overlaid on it, using the transformation parameters obtained from the alignment of the anatomical images. This provides an implicit segmentation of the patient image. In the case of image analysis for brain tumor studies, atlas-based segmentation is mostly applied on high-resolution isotropic T_1-weighted or T_1-contrast-enhanced (CE) MR images.

The major challenge in atlas-based segmentation of tumor-bearing brain images is the missing correspondence between healthy atlas image and pathological patient image. A number of approaches have been suggested to circumvent this problem. They can be broadly separated into approaches which are purely registration-based and approaches that employ a biomechanical tumor-growth model for establishing initial correspondence between both images, before a final non-rigid registration step performs a refined alignment of brain structures.

Purely Registration-Based Approaches for Atlas-Based Segmentation

The simplest solution is to use standard registration methods without considering the fact that the patient image has been distorted by the presence of a tumor. Isambert et al. (2008) delineated organs at risk in a clinical radiotherapy context by registering a standard brain atlas to the patient image using multi-affine block-matching. Figure 14.1 shows an example of their automatic delineation in green of the optic nerves, eyes, brain stem and cerebellum for one patient, together with a manually defined ground truth in red. Deeley et al. (2011) combined multi-affine and non-rigid registration with a final level-set refinement for the segmentation of brain structures in the presence of space-occupying lesions.

Brett et al. (2001) were among the first to explicitly address the problem of missing correspondence in registration of tumor images. They suggested masking the cost function of a combined affine and non-rigid registration method.

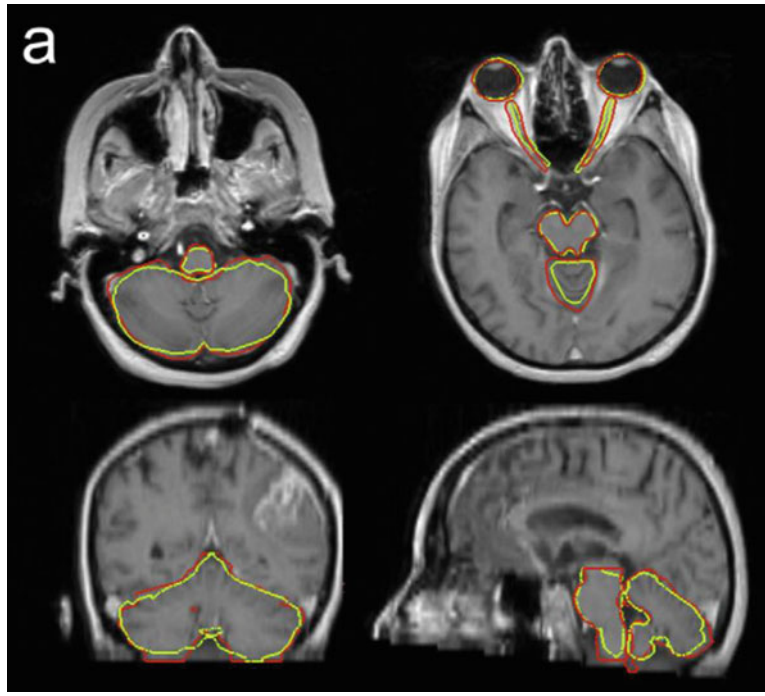

Fig. 14.1 Automatic (in *green*) and manual (in *red*) delineation of brain organs at risk in radiotherapy. The segmented structures include optic nerves, eyes, brain stem and cerebellum (From Isambert et al. (2008))

For this, a manual pre-segmentation of the lesion was required and could be used as a mask for the similarity criterion during the registration. A similar approach was chosen by Stefanescu et al. (2004). A confidence map with zero confidence for all voxels inside the pre-segmented tumor mask was used for the similarity metric during the registration process. Additionally, adaptive regularization was allowed in different tissue regions.

Dawant et al. (2002) placed small tumor seeds in the atlas at the patient's approximate tumor location. Then, a non-rigid registration was performed, which simultaneously deformed the seeds in the atlas to approximately match the pre-segmented patient tumor. Commowick et al. (2005) employed statistical measures of anatomical variability for guiding the regularization during the registration process, where regions of low variability were more strongly regularized and regions of high variability, like tumor regions, could deform more. Chitphakdithai and Duncan (2010) used an indicator map to model different correspondence assumptions for various tissue classes. Registration was regarded as a maximum a posteriori (MAP) problem and solved in an expectation maximization (EM) framework, whereas the probability term of the transformation could be seen as a similarity metric.

A different idea is to incorporate a lesion model directly into the registration method, which allows for a decoupling of the deformations due to tumor growth and inter-subject variations. In this direction, Bach-Cuadra et al. (2004) suggested a model of lesion growth for atlas-based segmentation of tumor-bearing brain images. To this end, a simplistic radial lesion growth model was incorporated 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. Despite having two distinct deformation models, this method relied on registration models only and did not include any kind of bio-mechanical

tumor-growth simulation. Later, Bach-Cuadra et al. (2006) from the same group improved their previous method by replacing the SSD-based Demons registration algorithm with an optical flow method employing the more robust mutual information similarity metric, which allowed them to drop the assumption of a linear intensity correspondence relation between the two images. Niethammer et al. (2011) proposed a metamorphosis model, which combined two distinct deformations in order to jointly estimate a deformation in space and a change in image appearance. A global geometric deformation was employed to model changes in image appearance and local matching for considering the tumor was based on an image composition model in an LDDMM framework.

Methods Combining Tumor Growth Modeling with Registration for Atlas-Based Segmentation

Another idea to circumvent the problem of a missing correspondence between the atlas image of healthy individuals and the pathological patient image is to seed the atlas with a tumor before applying the non-rigid registration. Most of the underlying approaches make use of a bio-mechanical tumor-growth model that simulates patient-specific tumor growth in the atlas image, and they finally apply a standard non-rigid registration method to the modified atlas image.

Kyriacou et al. (1999), the first ones to suggest this type of approach, assumed a uniform strain of the tumor and non-linear elastic behavior of the surrounding tissues. In a first step, they shrank the tumor in the patient image to obtain a simulated healthy patient image. Then, the tumor shrinkage process was inverted by performing tumor growth on the registered atlas using a regression method. This allowed them to obtain a patient-adapted atlas including pathology in a final step. Mohamed et al. (2006) grew the tumor in the atlas according to the pathological patient image, instead of shrinking the tumor first. The final adaptation of the modified atlas to the patient image was achieved with a non-rigid registration method. To handle the significant computational cost of the tumor growth modeling in 3D, they employed an approach based on a statistical model using principal component analysis (PCA). For each available case, they estimated the most likely parameters and applied the deformation using the pre-built statistical model. Zacharaki et al. (2008) improved this approach by implementing a multi-resolution framework for registration of brain tumor images. In their so-called ORBIT method, they also used a statistical model of tumor-induced deformation, but they embedded it into a hierarchical framework for parameter optimization. Local information was incorporated into the tumor growth model and the registration methodology was improved. In a further step, the same group improved their tumor growth model compared to the previous method (Zacharaki et al. 2009). They dropped the need for a simplified PCA-based tumor growth model while still achieving computational efficiency. To this end, they employed a piecewise Eulerian tumor mass-effect simulator with a uniform outward-pushing pressure model for the bulk tumor. Parameter optimization was parallelized for further speed improvements.

Recently, researchers from the same group built upon the previous methods by making improvements to the tumor growth model. Instead of considering only bio-mechanical mass effects with a simplified pressure model, they proposed a more sophisticated coupled physio-mechanical model. In GLISTR, Gooya et al. (2011a), employed a diffusion–reaction model for tumor growth, which was coupled with an Eulerian finite element method (FEM) for simulating the mass effect. They operated on multi-sequence images to obtain a probability map of the different tissue classes using classification techniques. In the atlas, a patient-specific tumor was grown and a Demons-like algorithm was finally used for the atlas-to-patient transformation. For this, the tissue probability map output from the classifier was used in the cost function. The process was formulated as an EM problem, which jointly estimated tumor growth parameters and the spatial transformations to adapt the atlas to the patient image. This resulted in a large

optimization problem, which had to be solved. In a next step, Gooya et al. (2011b) dropped the requirement for pre-classification and proposed a joint segmentation and registration model, which also included tumor growth. This was again formulated in an EM framework for joint estimation of tumor growth parameters and the deformation field for registration. The posterior tissue probabilities, which had been derived from the deformed atlas, yielded the segmentation of the patient image.

Our own research was inspired by methods which suggested combining tumor-growth modeling for the tumor mass effect and the establishment of initial correspondence between atlas and patient image with advanced non-rigid registration. In our method for atlas-based segmentation of tumor-bearing brain images, we explored two different lines of research: On the one hand, we worked on a simplistic but fast method for atlas-based segmentation, and on the other hand, we explored a more sophisticated but computationally more demanding approach.

For the simplistic but fast approach, in Bauer et al. (2011a), we developed a method, that segmented the healthy tissues surrounding the tumor in a brain image by atlas-based segmentation. These tissues included cerebrospinal fluid (CSF), gray matter (GM) and white matter (WM). The method used a simplistic but computationally fast bio-mechanical tumor growth method to first grow a patient-specific tumor in the atlas and then deform the modified atlas to match the patient image using a non-rigid Demons registration method. We relied on a pre-segmentation of the tumor as an input and performed automatic skull-stripping in a pre-processing step. Then, we aligned the atlas to the patient image using an affine transformation model. From there, we defined a tumor seed in the atlas which was located in the center of mass of the patient tumor. Subsequently, a mesh-free method based on Markov Random Fields (MRF) was used for modeling the tumor-mass effect. We chose a radial expansion model which was propagated by an MRF on the deformation field and which was bio-mechanically justified because it considered the Young's modulus of different brain tissues during tumor expansion. Tumor expansion was formulated as an energy minimization problem in an MRF context which was solved using the iterated conditional modes (ICM) algorithm. The ICM algorithm had the advantage that it could be parallelized very easily and it was implemented on a massively parallel graphics processing unit (GPU); this led to significant speed improvements. After tumor growth modeling, the final adaptation of the modified atlas to the patient image was done using an ITK implementation (Ibanez et al. 2005) of the Diffeomorphic Demons non-rigid registration method (Vercauteren et al. 2009). Figure 14.2 illustrates the pipeline. A tumor seed was automatically selected in the center of mass of the patient tumor and the tumor was grown in the atlas, deforming the surrounding tissues, before the final non-rigid registration was applied. The results were analyzed on four T_1-weighted images from the ContraCancrum database (Marias et al. 2011) and four synthetically generated brain tumor images with a well-defined ground truth (Prastawa et al. 2009). Quantitative evaluation was performed using the Dice similarity coefficient, which measures the overlap with the ground-truth segmentation. The Dice coefficient can range from 0 to 1, with 0 indicating no overlap and 1 indicating perfect overlap. The algorithm achieved Dice coefficients between 0.7 and 0.82 for the relevant tissue CSF, GM and WM within a total computation time of less than 30 min on a GPU.

For the biophysically more realistic approach, in Bauer et al. (2012), we explored a computationally more demanding method for multi-scale tumor growth modeling in atlas-based segmentation of tumor-bearing brain images. We chose the same pipeline as in the previous method that included automatic skull-stripping of the patient image, affine registration of the atlas, seeding the atlas with a physically realistic tumor seed in the center of mass of the patient tumor, tumor growth simulation to model the tumor mass effect, and final non-rigid registration. The difference was that, in this case, we replaced the simplified purely bio-mechanical tumor growth model with a more sophisticated tumor growth model which considered multiple scales ranging from the

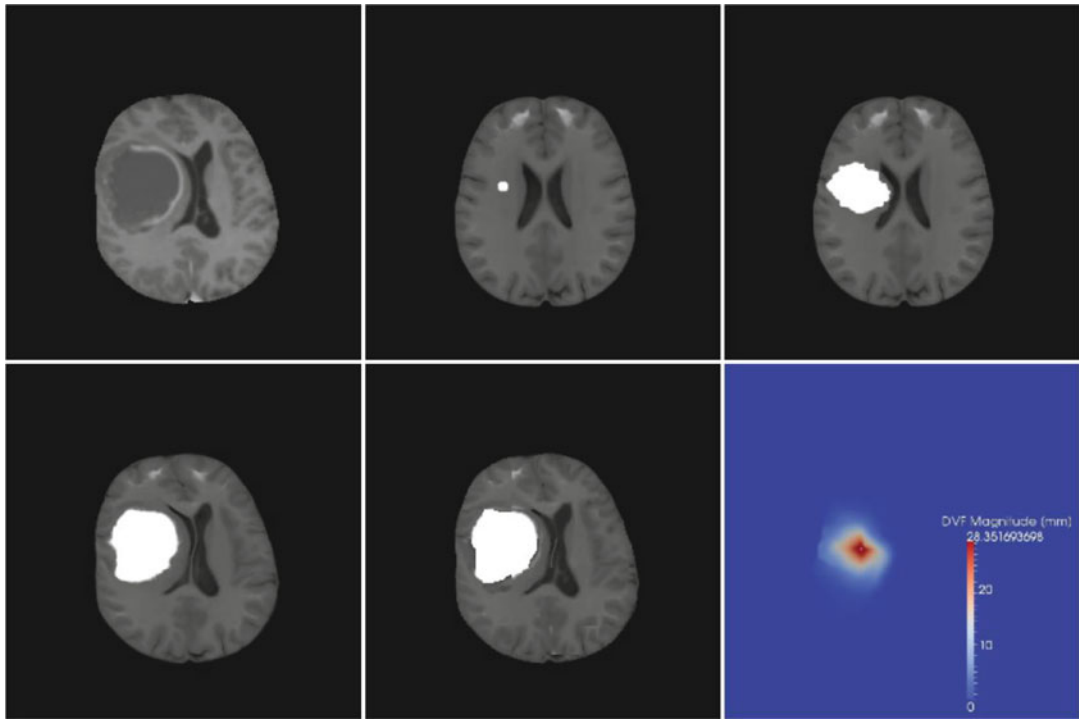

Fig. 14.2 Results of atlas-based tissue segmentation illustrated on one axial slice of a patient image. *Top row left* to *right*: patient image, seeded atlas after affine registration, deformed atlas after tumor growth. *Bottom row left* to *right*: modified atlas after final non-rigid registration, tissue checkerboard of final result and the magnitude of the displacement field resulting from the tumor mass effect simulation (From Bauer et al. (2011a))

microscopic cellular level up to the macroscopic bio-mechanical level. To this end, a discrete-entity, discrete-event cellular-level based oncosimulator (Stamatakos et al. 2010) focusing on biological phenomena like cell-cycling and apoptosis was coupled with a bio-mechanical stress/strain simulation (May et al. 2011) which could provide pressure gradient information. Since the limit of applicability of the standard Lagrangian formulation of structural mechanics was reached under large tumor-induced deformations, the linear-elastic model was solved in an Eulerian implementation of FEM. Thus, the calculation was performed on a fixed geometrical mesh and material properties were advected to neighboring elements upon deformation. Furthermore, this allowed for operating directly on the voxel mesh obtained from the image, eliminating the need for complex mesh generation procedures. The cell simulator required information on the direction into which new tumor cells would spread. This direction could be decided based on the pressure of the surrounding tissues. The pressure was obtained from the mechanical simulator which in turn required information about the expansion of each geometrical cell. This was calculated from the cellular proliferation model. The direction of least pressure $\mathbf{d}$ was calculated based on the negative gradient

$$\mathbf{d} = -\frac{\nabla p}{\|\nabla p\|}$$

whereas the pressure p was given in terms of the trace of the stress tensor $\boldsymbol{\sigma}$. A linear elastic model with Young's modulus E and Poisson ratio υ served as the governing physical law for the non-uniform stress distribution. With this approach, the tumor was grown in the atlas until the approximate volume of the patient tumor was reached, and the

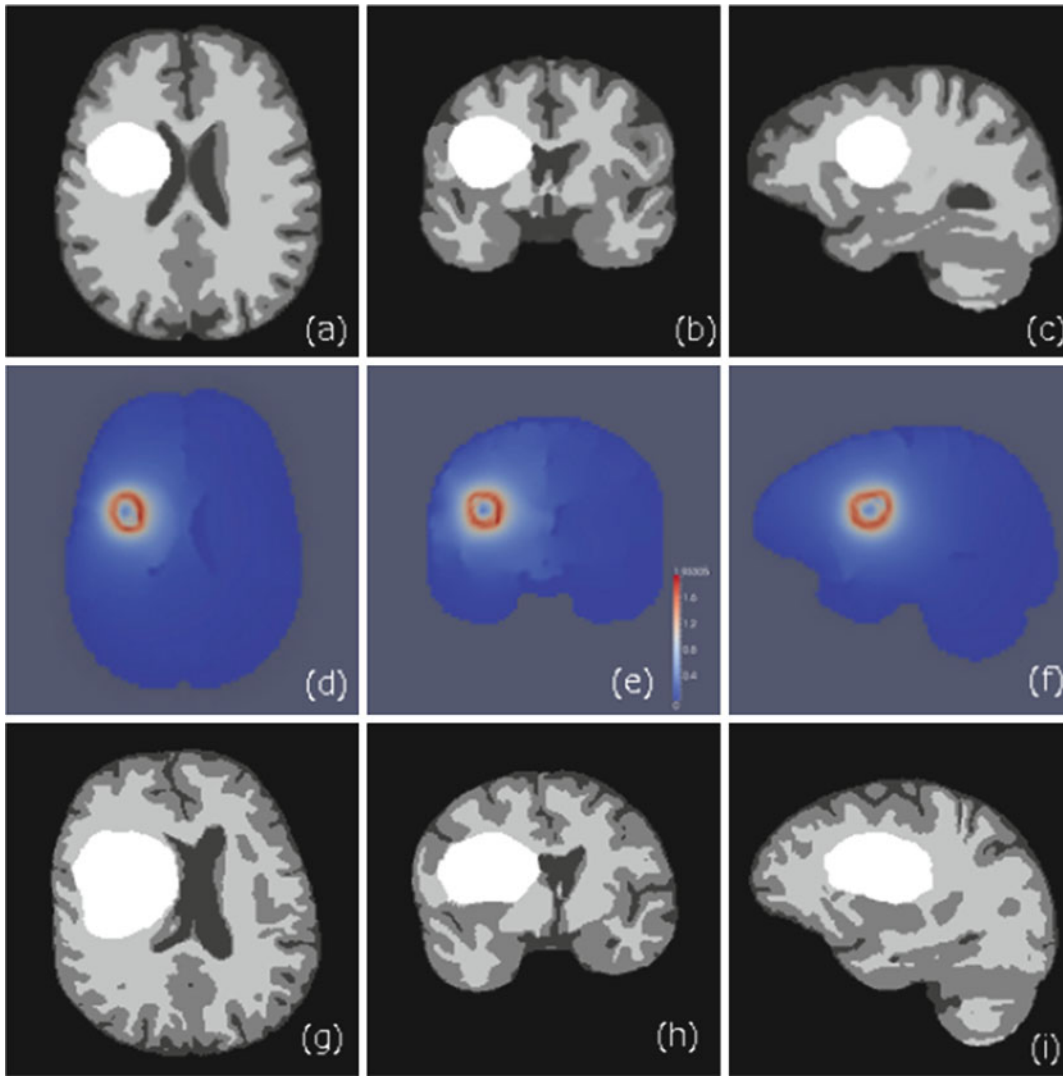

Fig. 14.3 Results of atlas-based segmentation on one slice of a patient image. *Top row*: deformed atlas label map (CSF, GM, WM, tumor) after the final tumor growth modeling step. *Center row*: magnitude of the displacement field in the final tumor growth simulation step. *Last row*: atlas label image after tumor growth and non-rigid registration. This label map forms the segmentation of the patient image. All images are shown in axial, coronal and sagittal view (From Bauer et al. (2012))

final non-rigid Diffeomorphic Demons registration (Vercauteren et al. 2009) was applied subsequently. Due to the enormous computational requirements of the multi-scale tumor growth model, simulation was performed on a coarse version of the atlas only. Figure 14.3 shows results for this approach on one patient image, including the magnitude of the displacement field. It can be inferred from the displacement field that this approach was able to account for the effect of necrosis which occurred in the tumor center. This was achieved thanks to the coupling of a cellular proliferation model with a bio-mechanical mass effect model. The method was evaluated on four synthetic datasets (Prastawa et al. 2009) and four real patient T_1-weighted datasets (Marias et al. 2011) with Dice

similarity coefficients ranging from 0.56 to 0.8 for the relevant tissues. Computation time was between 10 and 36 h depending on the size of the patient tumor.

Currently, we are exploring ways to integrate all the information available from clinical multimodal image acquisition protocols for further improving and automatizing atlas-based segmentation of tumor-bearing brain images Bauer et al. (2013). To this end, we are first performing a fully automatic segmentation of the tumor and its different layers based on the multimodal classification method presented in Bauer et al. (2011b). This serves as prior information for an atlas-based segmentation approach similar to the one presented in Bauer et al. (2012). The method allows us to segment not only tissues, but also subcortical structures. This could have important implications for planning in radiotherapy or neurosurgery.

Discussion and Outlook

Atlas-based methods for segmentation of tumor-bearing brain images usually operate on monomodal high-resolution isotropic T_1-weighted magnetic resonance images. They can be broadly classified into methods employing standard registration models and methods which combine standard registration with patient specific tumor-growth modeling. Both approaches have their advantages and disadvantages: While pure registration methods are in general faster and more versatile, integrated simulation and registration methods are generally more realistic and accurate. After having moved from purely bio-mechanical tumor-growth simulation models for establishing initial correspondence between atlas and patient image to more sophisticated coupled diffusion-bio-mechanics or coupled cellular-bio-mechanics models, an obvious next step would be to integrate all three levels of complexity to model tumor behavior. These levels would include the microscopic level for modeling cell proliferation, the macroscopic level for modeling the diffusion of cancer cells along the fiber directions in the brain and finally the bio-mechanical level modeling the tumor mass-effect, as initially proposed in Marias et al. (2011). Additionally, it would be interesting to see if additional prior knowledge from multimodal structural images could be incorporated in a meaningful way in order to allow for better segmentations and more accurate predictions. Another option would be to rely on crisp multi-channel atlases similar to (Prastawa et al. 2009) to increase the amount of prior information obtained from the atlas.

However, from the clinical perspective, a major problem of most current approaches is still the tremendous computational requirements, which are mostly due to the multi-scale tumor growth models employed in atlas-based segmentation. This is also the main reason why most of the current methods are in favor of pure research explorations so far and will not reach routine clinical use before significant improvements in computational speed are being made. In daily practice, computation times on the order of a few minutes at most are required.

Validation is another critical issue. It is doubtful whether the currently used global evaluation schemes that mostly measure volumetric overlap of individual structures, are the best choice. Especially in neurosurgery and radiotherapy, it is of utmost importance to accurately delineate healthy tissues and subcortical structures in close proximity of the tumor tissue instead of more distant tissues and structures; but so far there exists no well-accepted evaluation method to make this distinction.

Acknowledgements This work was partially funded by the European Union within the framework of the ContraCancrum project (FP7 – IST-223979).

References

Bach-Cuadra M, Pollo C, Bardera A, Cuisenaire O, Villemure JG, Thiran JP (2004) Atlas-based segmentation of pathological MR brain images using a model of lesion growth. IEEE Trans Med Imaging 23:1301–1314

Bach-Cuadra M, De Craene M, Duay V, Macq B, Pollo C, Thiran JP (2006) Dense deformation field estimation for atlas-based segmentation of pathological MR brain images. Comput Meth Progr Biomed 84:66–75

Bauer S, Nolte LP, Reyes M (2011a) Segmentation of brain tumor images based on atlas-registration combined with a Markov-Random-Field lesion growth model. Int Symp Biomed Imaging 8:2018–2021

Bauer S, Nolte LP, Reyes M (2011b) Fully automatic segmentation of brain tumor images using support vector machine classification in combination with hierarchical conditional random field regularization. Lect Notes Comput Sci 6893:354–361

Bauer S, May C, Dionysiou D, Stamatakos G, Büchler P, Reyes M (2012) Multi-scale modeling for image analysis of brain tumor studies. IEEE Trans Biomed-Eng 59:25–29

Bauer S, Lu H, May CP, Nolte L-P, Büchler P, Reyes M (2013) Integrated segmentation of brain tumor images for radiotherapy and neurosurgery. Int J Imaging Syst Technol 23(1):59–63

Brett M, Leff AP, Rorden C, Ashburner J (2001) Spatial normalization of brain images with focal lesions using cost function masking. Neuroimage 14:486–500

Cabezas M, Oliver A, Lladó X, Freixenet J, Bach-Cuadra M (2011) A review of atlas-based segmentation for magnetic resonance brain images. Comput Meth Progr Biomed 104:58–77

Chitphakdithai N, Duncan JS (2010) Non-rigid registration with missing correspondences in preoperative and postresection brain images. Lect Notes Comput Sci 6361:367–374

Commowick O, Stefanescu R, Fillard P, Arsigny V, Ayache N, Pennec X, Malandain G (2005) Incorporating statistical measures of anatomical variability in atlas-to-subject registration for conformal brain radiotherapy. Lect Notes Comput Sci 3750:927–934

Dawant BM, Hartmann SL, Pan S, Gadamsetty S (2002) Brain atlas deformation in the presence of small and large space-occupying tumors. Comput Aided Surg 7:1–10

DeAngelis LM (2001) Brain tumors. N Engl J Med 344:114–123

Deeley MA, Chen A, Datteri R, Noble JH, Cmelak AJ, Donnelly EF, Malcolm AW, Moretti L, Jaboin J, Niermann K, Yang ES, Yu DS, Yei F, Koyama T, Ding GX, Dawant BM (2011) Comparison of manual and automatic segmentation methods for brain structures in the presence of space-occupying lesions: a multi-expert study. Phys Med Biol 56:4557–4577

Drevelegas A, Papanikolaou N (2011) Imaging modalities in brain tumors. Imag Brain Tumors Histol Corr 13–34

Gooya A, Biros G, Davatzikos C (2011a) Deformable registration of glioma images using EM algorithm and diffusion reaction modeling. IEEE Trans Med Imaging 30:375–390

Gooya A, Pohl K, Bilello M, Biros G, Davatzikos C (2011b) Joint segmentation and deformable registration of brain scans guided by a tumor growth model. Lect Notes Comput Sci 6892:532–540

Ibanez L, Schroeder W, Ng L, Cates J (2005) The ITK software guide 2nd ed., Kitware

Isambert A, Dhermain F, Bidault F, Commowick O, Bondiau PY, Malandain G, Lefkopoulos D (2008) Evaluation of an atlas-based automatic segmentation software for the delineation of brain organs at risk in a radiation therapy clinical context. Radiother Oncol 87:93–99

Kyriacou SK, Davatzikos C, Zinreich SJ, Bryan RN (1999) Nonlinear elastic registration of brain images with tumor pathology using a biomechanical model. IEEE Trans Med Imaging 18:580–592

Mang A, Schnabel JA, Crum WR, Modat M, Camara-Rey O, Palm C, Caseiras GB, Jäger HR, Ourselin S, Buzug T, Hawkes DJ (2008) Consistency of parametric registration in serial MRI studies of brain tumor progression. Int J Comput Ass Radiol Surg 3:201–211

Marias K, Dionysiou D, Sakkalis V, Graf N, Bohle RM, Coveney PV, Wan S, Folarin A, Büchler P, Reyes M, Clapworthy G, Liu E, Sabczynski J, Bily T, Roniotis A, Tsiknakis M, Kolokotroni E, Giatili S, Veith C, Meese E, Stenzhorn H, Kim YJ, Zasada S, Haidar AN, May C, Bauer S, Zhao Y, Karasek M, Grewer R, Franz A, Stamatakos G (2011) Clinically driven design of multi-scale cancer models: the ContraCancrum project paradigm. J R Soc Interface Focus 1:450–461

May CP, Kolokotroni E, Stamatakos GS, Büchler P (2011) Coupling biomechanics to a cellular level model: an approach to patient-specific image driven multi-scale and multi-physics tumor simulation. Prog Biophys Mol Biol 107:193–199

Mazzara GP, Velthuizen RP, Pearlman JL, Greenberg HM, Wagner H (2004) Brain tumor target volume determination for radiation treatment planning through automated MRI segmentation. Int J Radiat Oncol 59:300–312

Mohamed A, Zacharaki EI, Shen D, Davatzikos C (2006) Deformable registration of brain tumor images via a statistical model of tumor-induced deformation. Med Image Anal 10:752–763

Niethammer M, Hart GL, Pace DF, Vespa PM, Irimia A, van Horn JD, Aylward SR (2011) Geometric metamorphosis. Lect Notes Comput Sci 6892:639–646

Pham DL, Xu C, Prince JL (2000) Current methods in medical image segmentation. Annu Rev Biomed Eng 2:315–337

Prastawa M, Bullitt E, Gerig G (2009) Simulation of brain tumors in MR images for evaluation of segmentation efficacy. Med Image Anal 13:297–311

Rohlfing T, Zahr NM, Sullivan EV, Pfefferbaum A (2010) The SRI24 multichannel atlas of normal adult human brain structure. Hum Brain Mapp 31:798–819

Speier W, Iglesias J, El-Kara L, Tu Z, Arnold C (2011) Robust skull stripping of clinical glioblastoma multiforme data. Lect Notes Comput Sci 6893: 659–666

Stamatakos GS, Kolokotroni E, Dionysiou D, Georgiadi E, Desmedt C (2010) An advanced discrete state-discrete event multiscale simulation model of the

response of a solid tumor to chemotherapy: mimicking a clinical study. J Theor Biol 266:124–139

Stefanescu R, Commowick O, Malandain G, Bondiau PY, Ayache N, Pennec X (2004) Non-rigid atlas to subject registration with pathologies for conformal brain radiotherapy. Lect Notes Comput Sci 3216: 704–711

Vercauteren T, Pennec X, Perchant A, Ayache N (2009) Diffeomorphic demons: efficient non-parametric image registration. Neuroimage 45:S61–S72

Zacharaki EI, Shen D, Lee SK, Davatzikos C (2008) ORBIT: a multiresolution framework for deformable registration of brain tumor images. IEEE Trans Med Imaging 27:1003–1017

Zacharaki EI, Hogea CS, Shen D, Biros G, Davatzikos C (2009) Non-diffeomorphic registration of brain tumor images by simulating tissue loss and tumor growth. Neuroimage 46:762–774

Zitova B, Flusser J (2003) Image registration methods: a survey. Image Vision Comput 21:977–1000