Concurrent tumor segmentation and registration with uncertainty-based sparse non-uniform graphs

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ARTICLE INFO

ABSTRACT

In this paper, we present a graph-based concurrent brain tumor segmentation and atlas to diseased patient registration framework. Both segmentation and registration problems are modeled using a unified pairwise discrete Markov Random Field model on a sparse grid superimposed to the image domain. Segmentation is addressed based on pattern classification techniques, while registration is performed by maximizing the similarity between volumes and is modular with respect to the matching criterion. The two problems are coupled by relaxing the registration term in the tumor area, corresponding to areas of high classification score and high dissimilarity between volumes. In order to overcome the main shortcomings of discrete approaches regarding appropriate sampling of the solution space as well as important memory requirements, content driven samplings of the discrete displacement set and the sparse grid are considered, based on the local segmentation and registration uncertainties recovered by the min marginal energies. State of the art results on a substantial low-grade glioma database demonstrate the potential of our method, while our proposed approach shows maintained performance and strongly reduced complexity of the model.

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1. Introduction

Gliomas are the most common type of primary brain tumors and arise from glial cells. They are classified in 4 grades by the World Health Organization (WHO), grade I corresponding to benign tumors with excellent prognosis and Grade IV gliomas (Glioblastoma Multiforme) being the most common and lethal. WHO grade II Low Grade Gliomas (LGG) are a specific kind of glioma that represent about 30% of the brain tumors and can affect younger patients (Soffietti et al., 2010). They are characterized by a continuous slow growth and yield mild symptoms. They generally undergo anaplastic transformation into a fast growing malignant tumors and therefore have to be monitored closely via frequent MRIs. Knowing the size and extent of a brain tumor is of extreme importance in order to evaluate its growth, its reaction to therapy and for

surgery planning. Currently, the physicists compute the main tumor diameters and approximate it as an ellipsoid, a highly imprecise measure that tends to overestimate the volume of the tumor (Pallud et al., 2012). The current gold standard is manual segmentation, which on top of being a tedious and time consuming task, is also subject to a high inter and intra operator variability. Automatic tumor segmentation is thus an active research field that aims at obtaining fast and robust segmentations. It is a particularly difficult subject due to the extreme heterogeneity between the tumors in appearance, shapes and size and their overlapping intensities with the healthy tissue. LGG are diffusively infiltrative tumors with extremely irregular and fuzzy boundaries, rendering the segmentation task even more difficult.

Fuzzy clustering and knowledge based methods were amongst the first considered for tumor segmentation with limited success (Clark et al., 1998; Fletcher-Heath et al., 2001). Level sets and Active Contours have been a popular approach (Ho et al., 2002; Cobzas et al., 2007; Taheri et al., 2010), but suffer from their strong sensitivity to initialization. The idea is to model the tumor boundary as a parametric curve that evolves depending on the image

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[1] This work was carried out during the author's affiliation with Ecole Centrale Paris, INRIA Saclay, Ile de France and Intrasense from 2010 to 2013.

properties and curvature constraints. Statistical classification methods offer an efficient way of detecting tumor voxels. The voxels are treated independently and separated by a classifier that is learned from a set of training samples. Examples refer to the Support Vector Machines (SVM) (Verma et al., 2008; Zhang et al., 2004; García and Moreno, 2004), Boosting (Xuan and Liao, 2007) or the Decision Forests (Zikic et al., 2012). Despite promising performance, those methods are plagued by the i.i.d assumption that treats each voxel independently, leading to irregular segmentations. Morphological filtering (Zhang et al., 2004) or neighborhood dependent features (Zikic et al., 2012) offer limited improvement on the local consistency of the segmentation. Notable improvement is observed when coupling the statistical classification with local neighborhood dependencies (Lee et al., 2008; Görlitz et al., 2007; Wels et al., 2008; Bauer et al., 2011), modeled by a random field (Markov Random Field (MRF), Conditional Random Field (CRF)) (Wang et al., 2013) based spatial prior. In this context, the segmentation is locally smoothed by penalizing neighbors that are assigned different segmentation labels, but still lacks global information regarding the tumor's position and the brain boundaries. Stronger dependencies can be modeled via a hierarchical approach. Gering et al. (2002) proposed a multi layer MRF approach where the tumor is detected as an outlier from manually selected training voxels. At each layer, the segmentation is refined based on higher level information and the previous layer's segmentation. Corso et al. (2008) combine Bayesian classification using Gaussian Mixture Models with a hierarchical graph affinity model, where the spatial dependencies are modeled by assigning an affinity to each graph edge.

Atlas-based segmentation methods rely on the registration of an annotated volume to the subject in order to segment the structures of interest. The use of a brain atlas allows for structural spatial prior information, but the task is more difficult when the structure to segment is a tumor since it cannot be matched in the atlas. That is often addressed through a model for tumor detection. Kaus et al. (2001) alternate kNN classification based on intensity and anatomical location with a registration step based on the structures' segmentation, the tumor being labeled as white matter in the registration process. In Prastawa et al. (2003) a probabilistic atlas is affinely registered to the patient, enabling to define prior probabilities on the expected intensities of the structures. The atlas is modified to account for tumor presence (detected by contrast enhancement) and edema. Similarly to Gering et al. (2002), the tumor voxels can be detected as outliers from the healthy voxels (Menze et al., 2010; Prastawa et al., 2004). The healthy structures' features are estimated from a registered healthy atlas. Additional local spatial constraints are modeled via Markov Random Fields (Menze et al., 2010) or level sets (Prastawa et al., 2004).

Atlas based methods depend on the quality of the registration. Rigid or affine registration methods are not sufficient to recover the inter patient anatomical differences, while traditional nonrigid registration methods fail in this context by attempting to find correspondences between the tumor and the healthy voxels. An efficient atlas based segmentation thus requires a registration scheme that accommodates for the presence of the tumor.

Despite extensive work in deformable image registration (Zikic et al., 2010; Ou et al., 2011; Berendsen et al., 2013; Sotiras et al., 2013), there has been limited work dedicated to registration with missing correspondences. Such a registration task is of high interest for the study of brain tumors through statistical atlases and longitudinal studies. A tumor specific probabilistic atlas, constructed through affine registration of a large database to the same reference coordinates, was notably proposed in Parisot et al. (2011). It enabled the identification of preferential locations for the tumors and could lead to unraveling position dependent behaviors and origins. Deformable registration would enable to go further and study the interactions between the tumors and the brain structures and functional areas. Understanding the tumors growth patterns and their impact on the brain's functional organization is of key importance for therapy and surgery planning.

We can distinguish two groups of methods for registration in the presence of a tumor. The first relies on modeling the tumor growth to evaluate the tumor induced deformation (Kyriacou et al., 1999; Mohamed et al., 2006; Zacharaki et al., 2008; Cuadra et al., 2004). Kyriacou et al. (1999) proposed a biomechanical finite element model to simulate the tumor induced deformation while assuming a radial uniform growth of the tumor. Using the tumor growth model, a healthy brain was simulated by contracting the tumor, allowing for a normal registration process. Cuadra et al. (2004) also assumed radial growth of the tumor. The registration is performed using the demons algorithm (Thirion, 1998) between healthy voxels and is based on the distance from a manually selected seed in the tumor area (that has been segmented prior to the registration process). Mohamed et al. (2006) decomposed the deformation as inter subject and tumor induced deformations. The latter was modeled via a biomechanical finite element model whose parameters are learned by statistical learning. The tumor growth is then simulated in the healthy atlas, enabling normal registration. This method was extended in Zacharaki et al. (2008) towards a computationally efficient biomechanical model taking into account the potential infiltrative parts of the tumor by limiting the tumor growth. Growth models require either user interaction or extensive computations to evaluate the model parameters and are mostly adapted to space occupying lesions. Low grade gliomas are infiltrative tumors with little to no mass effect and edemas. The limited amount of deformation caused by the tumors renders the use of growth model not adapted and possible prone to errors assuming the tumor pushes tissue instead of infiltrating it. The second group of methods (Brett et al., 2001; Stefanescu et al., 2004) adopts a simpler approach and masks the pathology towards excluding it during registration. The tumor area is discarded during the computation of the similarity criterion and deformed by interpolation. This kind of approach offers a better modularity with respect to the pathology since no assumption is made about the pathological area nor the progression of the tumor. Both approaches require a reliable segmentation of the tumor, making the registration dependent on the quality of the segmentation of the tumor.

Registration and tumor segmentation appear as two fundamentally correlated problems, where one could benefit from the other if performed simultaneously. The idea of coupling segmentation and registration is not a new concept. Yezzi et al. (2003) used an active contour framework, estimating the registration parameters and reference volume's segmentation curve by minimizing a joint energy depending on both images. The floating image is segmented by registering the reference's segmentation. A maximum a posteriori framework was presented in Wyatt and Noble (2003) where the segmentation and rigid registration parameters are determined alternatively. The segmentation relies on Gaussian Mixture Models coupled with an MRF prior, while the registration relies on the segmentation by minimizing the joint class histogram between both images. Mahapatra and Sun (2012) proposed an MRF based framework where each voxel of the image has to be assigned a displacement and segmentation label. The different classes are separated based on the intensities in both images while the registration relies on minimizing conventional similarity metrics. The registration and segmentation fields are smoothed by enforcing similar displacement among voxels of the same class. Ashburner and Friston (2005) proposed a statistical model, where a probabilistic atlas plays the part of a spatial prior for segmentation and bias field correction. The different classes are separated via a mixture of Gaussians, allowing for several modes per class. The atlas is globally registered by affine registration then locally deformed. Last but not least, Pohl et al.