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Segmentation of Gliomas in Pre-operative and Post-operative Multimodal Magnetic Resonance Imaging Volumes Based on a Hybrid Generative-Discriminative Framework

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Abstract

We present an approach for segmenting both low- and high-grade gliomas in multimodal magnetic resonance imaging volumes. The proposed framework is an extension of our previous work [6,7], with an additional component for segmenting post-operative scans. The proposed approach is based on a hybrid generative-discriminative model. Firstly, a generative model based on a joint segmentation-registration framework is used to segment the brain scans into cancerous and healthy tissues. Secondly, a gradient boosting classification scheme is used to refine tumor segmentation based on information from multiple patients. We evaluated our approach in 218 cases during the training phase of the BRAIn Tumor Segmentation (BRATS) 2016 challenge and report promising results. During the testing phase, the proposed approach was ranked among the top performing methods, after being additionally evaluated in 191 unseen cases.

Keywords

Segmentation; Brain tumor; Glioma; Multimodal MRI; Gradient boosting; Expectation maximization; Probabilistic model; BRATS challenge

1 Introduction

Glioma is a common type of brain tumors that originates in the glial cells that surround and support neurons. Gliomas are divided into different types based on the degree of their growth rate and histopathology. Commonly they are classified into low- and high-grade gliomas (LGGs and HGGs). LGGs are less common than HGGs, constitute approximately 20% of central nervous system glial tumors and almost all of them eventually progress to HGGs [28]. HGGs are rapidly progressing malignancies, divided based on their histopathologic features into anaplastic gliomas and glioblastomas (GBMs) [38].

Gliomas are typically diagnosed by multimodal magnetic resonance imaging (MRI), where two main pathological regions may be identified, the tumor core and the peritumoral edematous area. The tumor core typically consists of enhancing (note that LGGs do not

always include this part), non-enhancing and necrotic parts. Edema is the response to infiltrating tumor cells, as well as angiogenic and vascular permeability factors released by the spatially adjacent tumor cells [2].

Accurate segmentation of these pathological regions may significantly impact treatment decisions, planning, as well as outcome monitoring. However, this is a highly challenging task due to tumor regions being defined by intensity changes relative to the surrounding healthy tissue, and such intensity information being disseminated across various modalities for each region. Manually delineating tumor boundaries is a highly laborious task that is prone to human error and observer bias [8]. Computer-assisted segmentation, on the other hand, has the potential to reduce expert burden and raters' variability.

The literature on computer-assisted tumor segmentation is abundant. Most methods can be categorized as being either generative or discriminative. Under a generative setting, a probabilistic model is designed for generating the underlying multimodal intensity images. The statistical model often incorporates prior knowledge of appearance and of spatial distribution of healthy brain tissues. Human knowledge for the abnormal tissues is usually encoded through tumor-specific designs (see for example [16,30,32]). Others, however, (e.g. [13,35]) choose to segment tumors as outlier classes not well represented by models for healthy tissues. In a discriminative scenario, a decision function is directly learned from manually annotated training images to characterize the difference between cancerous and normal tissues. A broad spectrum of algorithms have been used for learning the decision function (see for example [1,3,18,27,34,39]). In recent years, convolutional neural networks [1,18,20,21,34] have become an extremely popular choice as the base learner, achieving high rankings in BRATS competitions.

The method proposed in this paper is an extension of our previously published method called GLISTRboost [6,7]. When designing GLISTRboost, we restricted our attention to pre-operative baseline scans, whereas here we introduce an approach for segmenting gliomas in post-operative scans as well. Segmenting residual and recurrent tumors is a task significantly different from segmenting tumors on pre-operative baseline scans. This segmentation task is extremely challenging due to the presence of surgically-imposed cavities and non-neoplastic contrast enhancements on the cavity boundaries. These two tissue classes are not modeled in GLISTRboost. Additionally, GLISTRboost requires the manual initialization of at least one seed point where the tumor initially originated. However, such seed points cannot be identified in many post-operative scans, unless there is an apparent recurrent tumor. Lastly, the mass effect in many post-operative scans has been substantially relaxed due to the removal of the tumor bulk. Therefore, the component of GLISTRboost that models the mass effect is no longer required for segmenting post-operative scans. Due to these important differences, segmenting brain tumors in post-operative scans cannot be tackled by GLISTRboost. To address these differences, we develop here a framework that specifically targets the segmentation of gliomas in postoperative scans. The design follows the generative-discriminative principle of GLISTRboost.

The remainder of this paper is organized as follows: Sect. 2 details the provided data, while Sect. 3 presents the proposed segmentation strategy. The experimental validation setting is described in Sect. 4 along with the obtained results. Finally, Sect. 5 concludes the paper.

2 Materials

186 pre- and 88 post-operative multimodal MRI scans of patients with gliomas (54 LGGs, 220 HGGs) were provided as training images for the BRATS 2016 challenge, from the Virtual Skeleton Database [22]. Specifically, the dataset is a combination of the pre-operative baseline training set (10 LGGs and 20 HGGs) evaluated in the BRATS 2013 challenge [29], 44 LGG and 112 HGG pre-operative baseline scans provided from the National Institutes of Health (NIH) Cancer Imaging Archive (TCIA) and evaluated in the BRATS 2015 challenge, as well as 88 HGG post-operative NIH-TCIA scans evaluated in BRATS 2016. The postoperative scans describe longitudinal observations from 27 patients at multiple time points. The inclusion of these longitudinal scans will allow for the characterization of these tumors, based on expert neuroradiologists and the evaluation of the volumetric segmentations, in ‘progressing,’ ‘stable disease,’ or ‘shrinking.’

In addition to the training set, 191 multimodal volumetric images were provided as the testing set for BRATS 2016 challenge, comprising 92 pre-operative baseline and 99 post-operative scans. The partition of the testing set into pre-and post-operative was done based on visual confirmation of a surgically imposed cavity.

The data of each patient consists of native and contrast-enhanced (CE) T1-weighted, as well as T2-weighted and T2 Fluid-attenuated inversion recovery (FLAIR) MRI volumes. Finally, ground truth (GT) segmentations for the training set were also provided. Specifically, the data from BRATS 2013 were manually annotated, whereas data from NIH-TCIA were automatically annotated by fusing the approved by experts results of the segmentation algorithms that ranked high in the BRATS 2012 and 2013 challenges [29]. The GT segmentations comprise the enhancing part of the tumor (ET), the tumor core (TC), which is defined as the union of necrotic, non-enhancing and enhancing parts of the tumor, and the whole tumor (WT), which is the union of the TC and the peritumoral edematous region.

In this study, we only considered 32 out of the 88 provided post-operative HGG cases in the experiments, as labeling errors were found in the automatically generated GT for the other 56 samples. The most common mislabeling in those cases is surgically imposed cavities being segmented as part of the tumor core.

3 Methods

In this section, we describe the extended GLISTRboost segmentation framework that addresses tumor segmentation in both pre-operative baseline and postoperative multimodal volumes.

Firstly, all the provided MRI volumes are skull-stripped, co-registered and filtered to reduce intensity noise in regions of uniform intensity profile [37]. The intensity histograms of all modalities of all patients are then matched to the corresponding modality of a single

reference patient [31]. Pre-operative baseline and post-operative volumes are handled differently after the common pre-processing pipeline.

A pre-operative baseline scan is segmented by applying GLISTRboost [6,7], our previously published method that ranked 1st in the BRATS 2015 challenge. GLISTRboost is a hybrid generative-discriminative segmentation framework, in which a generative approach is used to compute probabilistic segmentations of the brain scans into cancerous, as well as healthy tissue. This generative approach is based on GLISTR [14–16,23,25], a joint segmentation-registration scheme that incorporates a glioma growth model to deal with the tumor mass effect [19]. A gradient boosting classification (discriminative) scheme is then used to refine the probabilistic segmentations based on information learned from multiple patients [10,11]. Lastly, a probabilistic Bayesian strategy, inspired by [4,5], is employed to refine further and finalize the tumor segmentation based on within-patient brain-specific intensity statistics. Interested readers are referred to [7] for detailed information on GLISTRboost.

Although GLISTRboost performs well on segmenting pre-operative baseline scans, it is not applicable to the task of segmenting post-operative volumes. Specifically, GLISTR is not designed to handle the two extra tissue classes present in post-operative scans, namely surgically-imposed cavities and non-neoplastic contrast enhancement on cavity boundaries. Moreover, it requires manual initialization of at least one seed point to approximate the center of the tumor, and such points cannot be identified in many post-operative scans unless there is an apparent recurrent tumor. Lastly, the mass effect, modeled by a computationally demanding tumor growth model in GLISTR, is expected to be substantially relaxed in most post-operative scans, where the tumor bulk is resected.

The generative part of GLISTRboost is adjusted accordingly to address these differences. Specifically, two additional classes, namely non-enhancing cavity and enhancing cavity, are introduced to the Gaussian mixture model within the joint segmentation-registration scheme to address the presence of surgically-imposed cavities and non-neoplastic enhancement on their boundaries. We have also removed the requirement for at least one manually placed tumor seed point and introduced a new option for specifying approximately the center and radius of the cavity. Lastly, the glioma growth model is taken out of the joint segmentation-registration scheme due to the absence of severe mass effect. We note that the time required for the joint segmentation-registration scheme to converge is substantially reduced after removing the computationally intensive growth model [19]. These modifications were also previously considered as a subcomponent of a registration framework that aligns pre-operative to post-recurrence brain scans of glioma patients [24,26].

We continue using the gradient boosting machine to learn a classifier for the discriminative step. The predictor variables proposed in GLISTRboost, augmented with two additional features, are used to learn the classifier. The original feature set considered in GLISTRboost comprises five components; image intensity, image derivative, geodesic information [12], texture features, and the GLISTR posterior probability maps. The intensity component includes the raw intensity value of each voxel, as well as inter-modality differences. The image derivative component consists of image gradient magnitude and the Laplacian of Gaussian. The geodesic information at a given voxel v_i was computed as its geodesic

distance to the tumor center v_s manually seeded for running GLISTR. Specifically, the geodesic distance between v_i and v_s was defined as $\min_{\gamma} \int P(\gamma(s))ds$, where γ can be any path connecting v_i to v_s . We set the weight P at each voxel to be proportional to its gradient magnitude, and the optimization was solved using the fast marching method [9,36]. Furthermore, the texture features describe the first and second order texture statistics computed from a gray-level co-occurrence matrix [17]. Two additional features have been included specifically for segmenting post-operative volumes, namely the geodesic distance of every voxel to the center of the cavity and the posterior probability of a voxel in the image being cavity (as computed by the generative step).

Finally, it should be noted that separate models have been trained for preoperative baseline and post-operative scans.

4 Experiments and Results

To assess the segmentation performance of our method on the provided training data, we evaluated the overlap, both qualitatively and quantitatively through the Dice coefficient, between the tumor labels computed by the proposed method and the GT in three regions, *i.e.*, WT, TC, and ET, as suggested in [29]. Figure 1a showcases examples of the provided multimodal pre-operative baseline scans, along with their corresponding GT and their segmentation labels as computed by our method, for four patients (two HGGs and two LGGs). We visually note the highest overlap in the edematous region while observing some disagreement in the enhancing and non-enhancing parts of the tumor between the suggested segmentations and the GT. Figure 1b illustrates representative post-operative examples of two patients with resection cavities and two with recurrent tumors. We note in the resection cases that the cavity itself and its enhancing boundary have almost identical intensity characteristics with the non-enhancing and enhancing parts of the tumor, respectively. As a result, they were partially mis-classified as cancerous regions they resemble by the proposed method.

To further evaluate the performance of the proposed method, we quantitatively validated the per-voxel overlap between the GT and the proposed segmentation using the Dice coefficient. Figure 2 summarizes the distributions of the cross-validated Dice coefficient scores for each region of interest (WT, TC, and ET) and across patients of the training set while using only the generative step, as well as the complete method. The results are presented for four different groupings of the data, comprising all pre-operative baseline scans, the pre-operative baseline HGGs, the pre-operative baseline LGGs and the post-operative HGGs. We note a definite improvement after application of the discriminative step in both the mean and median Dice coefficient values for all tissue labels and data groupings. Furthermore, it is observed that the segmentation results for the ET label vary significantly between LGGs and HGGs, with the former showing lower and less consistent results. We hypothesize that segmenting enhancing tumor is more challenging in LGGs because they are characterized by a distinct pathophysiological phenotype that often manifests as small ill-defined areas of enhancement or absence of it altogether. Nevertheless, the segmentation of the WT label in the LGGs is comparable to that of the HGGs.

One may also notice that the segmentation quality for post-operative HGG volumes is inferior to and less consistent than that for pre-operative baseline HGG volumes. Such phenomenon is in line with the visual inspections in Fig. 1, again highlighting the challenging nature of segmenting post-operative scans. It is also worth noting that we have excluded 56 out of the 88 post-operative scans for validation purposes due to labeling errors in their GT. Therefore, we believe that the difference in the number of training scans available (32 vs. 132) also affects the segmentation accuracy, and we expect to obtain improved performance by increasing the number of post-operative training samples.

A software implementation of the proposed method is available in www.cbica.upenn.edu/sbia/software/glistrboost through the Imaging Processing Portal (IPP) of Center for Biomedical Image Computing and Analytics (ipp.cbica.upenn.edu). The Cancer and Phenomics Toolkit (CapTk) [33] (www.cbica.upenn.edu/sbia/software/CAPTk) is used for the manual initialization of the proposed method. It showcases some of the highlight applications from CBICA along with advanced visualization and interactive capabilities to make it a complete radiological tool. CapTk is available in www.nitrc.org/projects/captk.

5 Conclusion

We presented a semi-automated approach based on a generative-discriminative framework towards providing a reliable and highly accurate segmentation of gliomas in both pre- and post-operative multimodal MRI volumes. The first step in the proposed approach is to compute a probabilistic segmentation for the given patient by a generative joint segmentation-registration scheme. This probabilistic segmentation is subsequently refined by a discriminative approach, taking into account population-wide tumor label appearance statistics that are learned by employing the gradient boosting machine.

The proposed method was validated on the BRATS 2016 training dataset, which is a mixture of pre-operative baseline HGG and LGG scans, as well as postoperative HGG scans. For all scan types and all regions of interests (WT, TC, and ET), the coupled generative-discriminative framework significantly improves the segmentation generated by the generative approach alone, achieving higher Dice coefficients with a clear margin in all cases.

The generative-discriminative method segmented whole tumor and tumor core with consistently high accuracy for both pre-operative baseline HGGs and LGGs. However, the difference between the performances on HGGs and LGGs is more pronounced in the enhancing tumor region, with the segmentation accuracy on LGGs being lower and less consistent. Such difference in performance suggests that segmenting enhancing tumor is much more challenging in LGGs than in HGGs, possibly because the former is characterized by a distinct pathophysiological phenotype that often manifests as small ill-defined areas of enhancement or absence of enhancement altogether while the HGGs often feature clearly defined enhancing regions. One may also note that the segmentation accuracy of the post-operative HGGs was inferior to that for the pre-operative baseline HGGs in all three areas of interests, due to their more challenging nature and fewer available training samples. Overall,

the proposed method produced high-quality segmentations for whole tumor, tumor core and enhancing tumor on the full dataset.

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Fig. 1.

Representative example segmentation results for four pre-operative baseline and four post-operative multimodal scans. Green, red and blue masks denote the edema, the enhancing tumor and the union of the necrotic and non-enhancing parts of the tumor, respectively. (Color figure online)

Fig. 2.

Distributions of the Dice coefficient across patients for each step of the proposed method, each tissue label and different groupings of data. The different steps are described by the boxes colored in green and yellow for the generative only step (G) and the complete generative-discriminative method (GD), respectively. The dot and the line inside each box denote the mean and median values, respectively. (Color figure online)