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Bayesian Network and Structured Random Forest Cooperative Deep Learning for Automatic Multi-label Brain Tumor Segmentation

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Abstract: Brain cancer phenotyping and treatment is highly informed by radiomic analyses of medical images. Specifically, the reliability of radiomics, which refers to extracting features from the tumor image intensity, shape and texture, depends on the accuracy of the tumor boundary segmentation. Hence, developing fully-automated brain tumor segmentation methods is highly desired for processing large imaging datasets. In this work, we propose a cooperative learning framework for multi-label brain tumor segmentation, which leverages on Structured Random Forest (SRF) and Bayesian Networks (BN). Basically, we embed both strong SRF and BN classifiers into a multi-layer deep architecture, where they cooperate to better learn tumor features for our multi-label classification task. The proposed SRF-BN cooperative learning integrates two complementary merits of both classifiers. While, SRF exploits structural and contextual image information to perform classification at the pixel-level, BN represents the statistical dependencies between image components at the superpixel-level. To further improve this SRF-BN cooperative learning, we 'deepen' this cooperation through proposing a multi-layer framework, wherein each layer, BN inputs the original multi-modal MR images along with the probability maps generated by SRF. Through transfer learning from SRF to BN, the performance of BN improves. In turn, in the next layer, SRF will also benefit from the learning of BN through inputting the BN segmentation maps along with the original multimodal images. With the exception of the first layer, both classifiers use the output segmentation maps resulting from the previous layer, in the spirit of auto-context models. We evaluated our framework on 50 subjects with multimodal MR images (FLAIR, T1, T1-c) to segment the whole tumor, its core and enhanced tumor. Our segmentation results outperformed those of several comparison methods, including the independent (non-cooperative) learning of SRF and BN.

1 INTRODUCTION

The emergence of the new field of radiomics, which addresses the conversion of medical images into mineable data through the extraction of large amounts of quantitative features (Aerts et al.,2014), has led to major advances in tumor diagnosis, phenotyping, and patient treatment planning. Notably, the reliability of radiomics fundamentally depends on the accuracy of the tumor boundary segmentation, as radiomic features are generally extracted from within and around the tumor lesion. Hence, fully automated brain tumor segmentation methods are highly desired. This will in part alleviate the burden of manually segmenting tumor lesions on brain images, as well as facilitate the task of statistically analyzing big brain tumor image datasets for clinical studies. The large variation in tumor characteristics (shape, position, texture) makes the segmentation task very challenging.

To solve this problem, several previous works considered tumor segmentation as a classification problem at the pixel, voxel, patch or region level (Havaei et al., 2017; Koley et al.,2016; Lefkovits et al.,2016; Christ at al., 2017; Folgoc et al., 2016). In particular, Random Forest (RF) was previously used for tumor segmentation, where basically each input intensity image patch is mapped to a class label at

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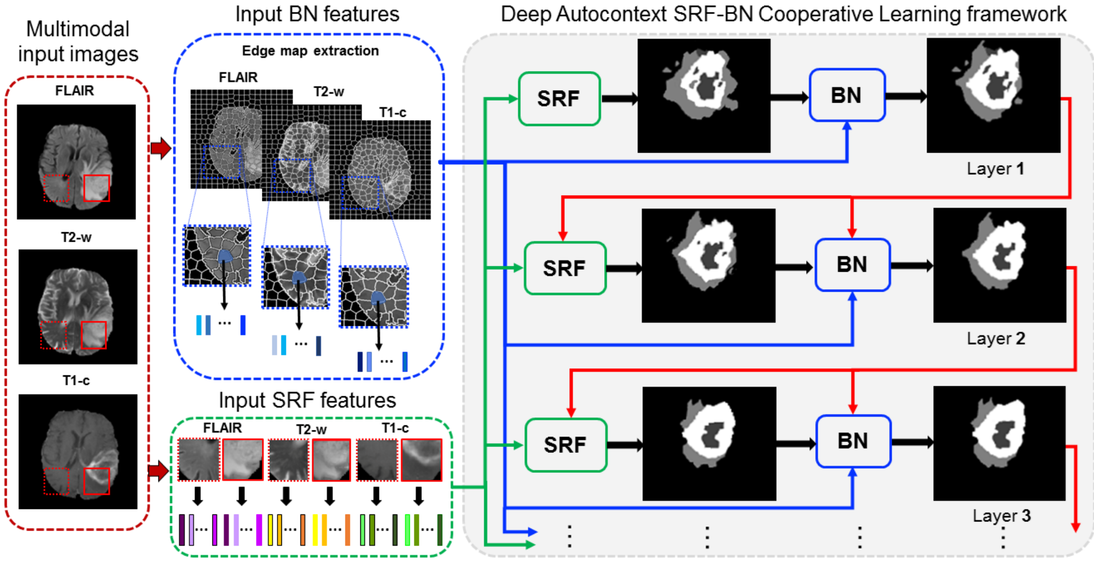


Figure 1: Proposed deep SRF-BN cooperative learning for multi-label tumor lesion segmentation. In each layer, the SRF inputs different features extracted at the 2D patch-level and generates an intermediate segmentation result, while the BN inputs different features extracted at the superpixel-level. In the next layer, SRF has two inputs: the original patch features and the output segmentation result from the previous layer; while BN has three inputs: the original patch features, the output segmentation result from the previous layer and the output SRF segmentation map in the same layer. This deep multi-layer cooperative-learning architecture provides contextual information for both classifiers through the intermediate segmentation maps to gradually improve their learning.

at the center pixel of the patch, thereby performing patch-to-pixel mapping (Breiman, 2001). As a variant of RF, Structured Random Forest (SRF) was used to take into account the image structure when producing the final segmentation maps, through estimating a patch-to-patch mapping. This allows integrating more spatial information through averaging neighboring output label patches. SRF demonstrated high-performance in different challenging classification tasks such as in (Zhang et al., 2016; Kontschieder et al., 2011; Zhang et al., 2017).

On one hand, the increasingly popular convolutional neural networks were used for tumor segmentation (Havaei et al., 2017). However, fine-tuning of an entire deep network still requires a lot of efforts and resources, and SVM-based methods also involve time consuming grid search and cross validation to identify good regularization parameters. In addition, when multiple pre-trained deep CNN models are available, it is unclear which pre-trained models are appropriate for target tasks and which classifiers would maximize accuracy and efficiency. On the other hand, among all the graphical models as Neural Networks and decision trees, Bayesian Networks (BNs) nicely overcome these limitations. Indeed, they are powerful tools in first representing probabilistic dependencies and uncertainty between different image features (Zhang and Ji, 2008), second modeling and fusing complex relationships between image features of different natures (e.g., multimodal features), and third handling noisy as well as missing signals in images. Together, these facts made

BNs well suited for multimodal image classification since they are easily adaptable for multi-label problems compared to other classifiers such as SVM, moreover they encode dependencies between the learned features of different class labels. While different object segmentation and action recognition problems in computer vision were solved based on Bayesian graphical representations (Panagiotakis et al., 2011; Zhang and Ji, 2011; Yang at al., 2015), the use of BN remains absent in tumor segmentation literature.

Although regarded as strong classifiers, both SRF and BN might suffer from a few limitations when used separately. For instance, SRF does not perform well when classifying transitions between label classes, while BN parameter learning such as prior probabilities is challenging and computationally expensive. Combining them together, may help iron out the weaknesses of each when used separately as well as leverage on their strengths (i.e., preserving the learned structural information for SRF and the integration of multimodal features for BN). Hence, we propose to combine both SRF and BN classifiers into a multi-layer deep architecture, where they can cooperate to perform joint multi-label brain tumor segmentation.

Our framework incorporates different features derived from different image components (superpixel and patch) such as intensity features. We further integrate contextual features, which capture semantic relations (i.e., label relations) between neighboring patches and enforce spatial consistency between patches within and around the tumor lesion. The proposed SRF-BN cooperative learning strategy ensures the transfer of the probability maps outputted from SRF to BN of the same layer, which enables the integration of both patch and superpixel level knowledge in a unified framework. Additionally, in the spirit of auto-context model, the output segmentation map of each layer is further aggregated with the original input features, thereby augmenting the inputs to subsequent layers. This allows boosting the classification performance of both classifiers and improving feature learning, which progressively refines the segmentation result from layer to layer.

2 DEEP COOPERATIVE LEARNING FOR MULTI-LABEL CLASSIFICATION PREPARATION

In the following, we present the main steps of our multi-label cooperative-learning based segmentation framework. Fig.1 illustrates the proposed multi-layer architecture composed of cascaded SRF-BN blocks, where each block ultimately outputs the BN posterior probability map fed as semantic context to the next SRF-BN block of the subsequent layer. Specifically, in each block excluding the first one, SRF inputs the intensity patch features of the original MR scans with the segmentation result (i.e., semantic context) of the previous layer. In turn, the prior probabilities required for BN learning are statistically computed using (1) the probability segmentation maps generated by SRF of the *same* layer and (2) the BN posterior probability of the previous layer. In the following sections, we will present the design of the two components (SRF and BN) making each block in our deep auto-context multi-label segmentation architecture.

2.1 Structured Random Forest

SRF is a variant of the traditional Random Forest classifier, which is able to handle and preserve the structure of different labels in the image (Kontschieder et al., 2011). While, standard RF maps an intensity feature vector extracted from a 2D patch centered at pixel x to the label of its center pixel x (i.e., patch-to-pixel mapping), SRF maps the intensity feature vector to a 2D label patch centered at x (patch-to-patch mapping). This is achieved at each node in the SRF tree, where the function that splits patch features between right and left children nodes depends on the joint distribution of two labels: a first label at the patch center x and a second label selected at a random position within the training patch (Kontschieder et al.,2011). We also note that in SRF, both feature space and label space nest patches that may have different dimensions. Despite its elegant and solid mathematical foundation as well as its improved performance in image segmentation compared with RF, SRF might perform poorly at irregular boundaries separating different label classes since it is trained using regularly structured patches (Kontschieder et al., 2011). Besides, it does not include contextual information to enforce spatial consistency between neighboring label patches.

To address these limitations, we propose to embed SRF into a deep autocontext framework, where the contextual information is provided by a Bayesian network which learns to segment the image at the superpixel level, allowing to better capture irregular boundaries in the image.

2.2 Bayesian Network

Various BN-based models have been proposed for image segmentation (Zhang and Ji, 2008; Panagiotakis et al., 2011; Zhang and Ji, 2011; Guo et al., 2017). In our work, we adopt the BN architecture proposed in (Zhang and Ji, 2011). As a preprocessing step, we first generate the edge maps from the input MR image modalities (Fig. 1). The edge map consists of a set of superpixels $\{Sp_i\},i=1,..,N$ (or regional blobs) and edge segments $\{E_j\},j=1,..,L$.

We define our BN as a four-layer network, where each node in the first layer stores a superpixel. The second layer is composed of nodes each storing a single edge from the edge map. The two remaining layers store the extracted superpixel features and edge features, respectively. During the training stage, for BN parameters, we define the prior probability of $p(Sp_i)$ as a uniform distribution and then learn the conditional probability $p(MS_{pi} \mid Sp_i)$ representing the relationship between the superpixel features and their corresponding labels using a mixture of Gaussians model. In addition, we empirically define the conditional probability modeling the relationships between each superpixel label and each edge state (i.e., true or false edge) $p(E_j \mid Pa(E_j))$, where $Pa(E_j)$ denotes the parent superpixel nodes of E_j.

During the testing stage, we learn the BN structure encoding the contextual relationships between superpixels and edge segments. Specifically, each edge node has for parent nodes the two superpixel nodes that are separated by this edge. In other words, each superpixel provides contextual information to judge whether the edge is on the object boundary or not. If two superpixels have different labels, it is more likely that there is a true object boundary between them, i.e. E_j=1, otherwise E_j=0. Although automatic segmentation methods based on BN have shown great results in the state-of-the-art, they may perform poorly in segmenting low-contrast image regions and different regions with similar features (Zhang and Ji, 2011). To further improve the segmentation accuracy of BN, we propose to include additional information through cooperative learning using SRF.

2.3 SRF-BN Cooperative Learning (One Layer)

To take advantage of the strengths of both classifiers and overcome their limitations, we first propose a one-layer cooperative learning strategy, where BN benefits from the learned patch-to-patch mapping by SRF. First, the trained SRF generates the segmentation result, using the feature patches extracted from the different MRI modalities of the testing subject. Then, BN uses the SRF segmentation result to define the prior probabilities $p(Sp_i)$ for each superpixel region Sp_i. Hence, with this cooperative learning, the BN prior probabilities are estimated based on the input SRF segmentation probability maps. Such one-layer cooperative learning strategy only boosts the BN performance since it is performed in one way (from SRF to BN), while SRF does not benefit from BN learning.

2.4 Deep SRF-BN Cooperative Learning (Two Layers)

To address the aforementioned limitation of the one-layer SRF-BN architecture, we further propose to deepen the cooperative learning between SRF and BN in the spirit of auto-context model (Tu and Bai, 2010). Basically, in the proposed deep auto-context SRF-BN cooperative learning architecture, each layer inputs the segmentation result of the previous layer to boost the per formance of both SRF and BN classifiers. In each layer, excluding the first one, SRF classifier inputs the segmentation result of the previous layer along with the original input multimodal feature patches (Fig. 1). This allows the integration of contextual features learned at both the patch level (from SRF in the previous layer) and superpixel level (from BN in the previous layer). Similarly, BN inputs the segmentation result of the previous layer along with the original input multimodal superpixel features, while adding the probability segmentation map output of the SRF in the *same* layer. In this way, BN prior probabilities are updated in each layer based on the posterior probability of the previous layer and the SRF probability map in the *same* layer.

2.5 Preprocessing and Features

To improve the performance of our segmentation framework, we perform a few preprocessing steps. Hence, we apply the N4 filter for inhomogeneity correction, and use the histogram linear transformation for intensity normalization. To train the previous models, we use conventional features (e.g., patch intensity) and we also propose a rich feature set as follows:

- **Statistical Features:** First order operators (mean, standard deviation, max, min, median, Sobel, gradient); higher order operators (laplacian, difference of gaussian, entropy, curvatures, kurtosis, skewness); texture features (Gabor filter); spatial context features (symmetry, projection, neighborhoods) (Prastawa et al., 2004).
- **Symmetric Features:** This is originally used to describe and to exploit the symmetrical properties of the brain structure. Thus, we define the symmetry descriptor characterizing the differences between symmetric pixels with respect to the mid-sagittal plane. The adopted symmetry measure is the intensity variance.

3 RESULTS AND DISCUSSION

In this section, we display the evaluation results of our proposed brain tumor segmentation framework on the Brain Tumor Image Segmentation Challenge (BRATS, 2015) dataset. It contains brain MRI scans

Table 1: Segmentation results of the proposed framework and comparison methods averaged across 50 patients.(HT: whole Tumor; CT: CoreTumor; ET: Enhanced Tumor; L=i, i=1,_,3 denotes the number of layers; * indicates outperformed methods with p-values<0.05.

Results	**Dice score**											
Features	***Intensity***			***Intensity+symmetry descriptor***			***Intensity + statistical features***			***Intensity + statisical features+symmetry descriptor***		
Methods	**HT**	**CT**	**ET**	**HT**	**CT**	**ET**	**HT**	**CT**	**ET**	**HT**	**CT**	**ET**
Deep-AC SRF-BN(L=3)	**86,8**	**75,9**	**73,8**	**87,2**	**76,3**	**75**	**89,09**	**78,4**	**78,9**	**89,1**	**80,92**	**79,2**
Deep-AC SRF-BN (L=2)*	85	73,65	70,6	85,4	74,87	73,3	88,79	77,8	78,1	88,9	78,2	78,9
SRF-BN (L=1)*	79,2	70,15	69	80	70,85	69	82,5	72,6	70	83,6	72,88	70,05
AC-SRF*	75	58	32	75,29	58,69	32,5	80	70,05	37,12	80,23	73	37,5
SRF*	72	56	31	72,9	57	31	75	60	35	75,8	61	35,2
BN*	62,96	42	30	65	43	30,8	70,8	45	32	71,3	45	33

for more than 200 patients with high-grade gliomas. For each patient, the four MRI modalities along with the corresponding manually labeled glioma's segmentation are available; they are rigidly coregistered and resampled to a common resolution.

To generate the oversegmented MR image modalities we extract the edge-map from the FLAIR MRI using SLIC oversegmentation algorithm (Achanta et al., 2010) then we apply it for the corresponding T1.c and T2 MRIs. We fix the number of superpixels to 1000 and the compactness to 10.

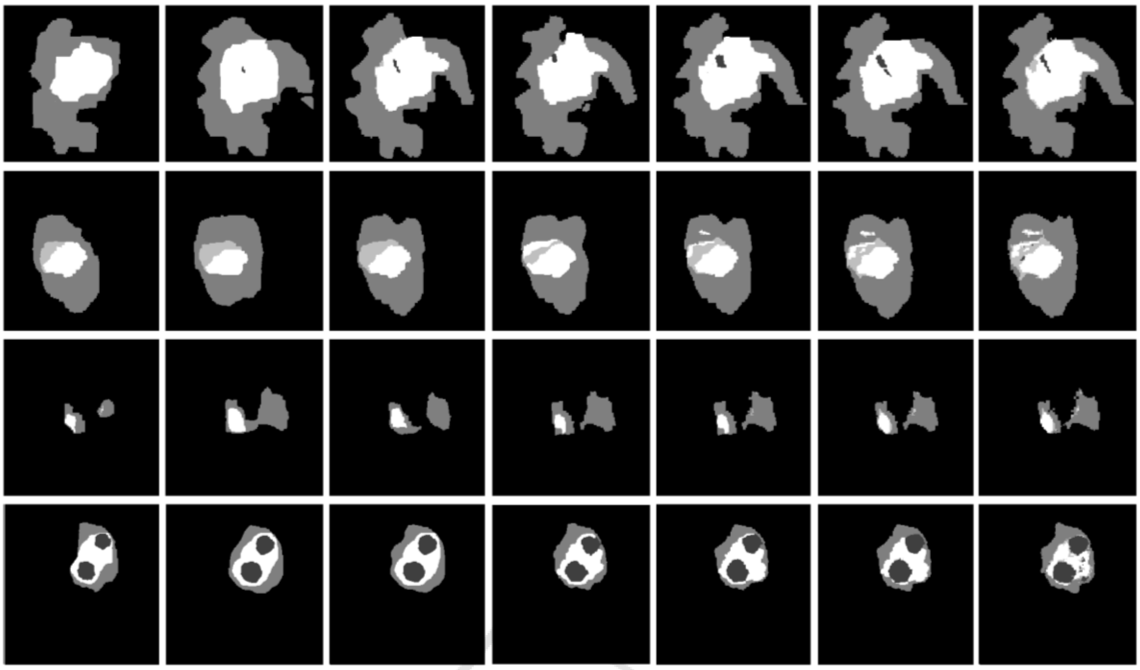
For the BN model, the conditional probabilities modeling the relationships between the superpixel labeling and the edge state are fixed as follows: $p(E_j \mid Pa\ (E_j\ )\ ) = 0.8$ if the parent region nodes have different labels and 0.2 otherwise. For the SRF, we use a 10x10 feature patches and a 7x7 label patches to train 15 trees using 500 iterations for the node tests.

In our experiments we show a comparison to several baseline methods: SRF and BN used solely, the auto-context SRF (AC-SRF) and SRF-BN cooperative learning approach (SRF-BN (L=1)). Besides, we test the influence of the layer's number on our deep auto-context SRF-BN framework. The classifiers were trained using leave-one-patient cross-validation experiments. The quality of the obtained segmentation was evaluated on the basis of the manually annotated ground truth using the well-known Dice index. In Fig. 2, we show some qualitative segmentation results and in Table. 1 and Fig. 3 we provide the mean Dice index over 50 testing subject randomly taken from the Brats dataset.

According to the qualitative and quantitative results, the proposed segmentation approach clearly outperforms the baseline methods, independently of the number of layers, with highly statistical significance (p_value <0.05). This proves that (1) leveraging the two classifiers does alleviate their limitations (2) the integration of the superpixel features and patch features in a deep manner boosts the performance of the segmentation framework (3) the information fusion of multiple image modalities.

The feature set highly influences the classification results of our framework as well as the baseline methods. In this respect, the weak effect of the symmetry descriptor can be explained by the miss-detection of the mid-sagittal plane for some subjects.

In addition, we have performed 5-cross validation on the whole dataset (220 subjects) to benchmark our results against (Zhao et al., 2016) which integrated a Fully Convolutional Neural Network and Conditional Random Fields for BRATS 2015 segmentation. Our deep SRF-BN cooperative learning still outperformed all comparison methods (p-value <0.05) and in particular the proposed method in (Zhao et al., 2016): 0.88 *vs* 0.8 for whole, 0.78 *vs* 0.68 for core, and 0.68 *vs* 0.65 for enhanced tumor. Although our results slightly dropped using using 5-fold cross-validation, they still achieve the best performance.



(a) (b) (c) (d) (e) (f) (g)

Figure 2: Qualitative segmentation results for four representative subjects using different segmentation methods: (a) the BN segmentation result; (b) the SRF segmentation result, (c) the auto-context SRF; (d) SRF+BN segmentation result; (e) our method (2 layers); (f) our method (3 layers); (g) the ground truth segmentation map.

Also, all proposed and comparison methods significantly improved when using 3 modalities compared with 1 by 8-9%. The training time took about 5 hours and testing on one image took about 4 minutes.

We would like to note that the use of the term learning 'transfer' and 'deep' learning was meant in the broad sense of both words: (1) mutual autocontext information (semantic map) transfer between BN and SRF classifiers for progressively improving their performances, and (2) 'deepening' our SRF-BN architecture to gradually improve their cooperative learning differs from deep neural networks, although both architectures can go deeper. However, unlike deep one-step CNN architectures, our method is able to consider appearance and spatial consistency between neighboring superpixels and patches via the gradual autocontext feed between SRF and BN. We also stopped at layer (L=3) in depth since the improvement became negligible at L>3.

Although the proposed framework showed good segmentation results thanks to the deep cooperation between the two classifiers (BN and SRF); a few limitations can be pointed out for further improvements:

(1) Edge-map estimation. The considered edge-map is estimated from a single modality (i.e., FLAIR), which limits the learned Bayesian mapping to one type of imaging data.
Estimating edge-maps from different modalities (e.g., T1.c and T2 MRIs) will help capture different radiomic properties of the tumor lesion especially around its boundary.
(2) Unidirectional flow between classifiers. The learning transfer between the classifiers of the same block as well as through the pipeline is unidirectional, which means it can only go from one classifier to the next one. Hence there is no mutual benefit between the classifiers of the same block.
(3) Hemispheric brain symmetry detection. The brain symmetry method that we used (Loy and Eklundh, 2006) fails in detecting the mid-sagittal plane in a few cases. This might produce unreliable symmetric features.

We anticipate that addressing these limitations will further boost up the performance of our proposed framework. We plan to investigate these in our future work on a larger dataset.

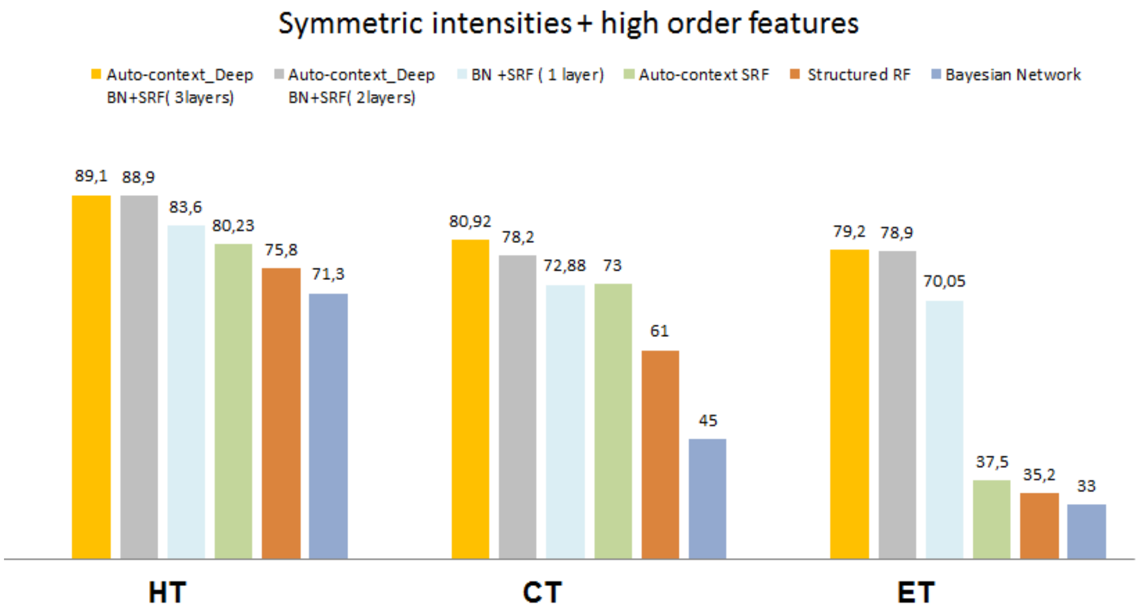


Figure 3: Average Dice index across 50 subjects using our proposed framework and all comparison methods for the three tumor tissue classes (whole:HT, core:CT, and enhanced:ET).

4 CONCLUSIONS

In this paper, we proposed an automatic brain tumor segmentation method based on a cooperative learning between two classifiers, Structured RF and BN, embedded within a deep auto-context architecture. The experimental results prove the efficiency of our proposed concept. Thus, SRF-BN cooperative learning method outperforms the two classifiers used solely, which proves that their combination alleviates their limitations. Moreover, the application of the deep auto-context architecture has shown better performances for both the quantitative and the qualitative results demonstrating its effectiveness to boost the two classifiers and to improve the feature learning.

Since the obtained results showed the effectiveness of stacking SRF and BN within a multi-label segmentation framework, we intend to explore other architectures composed of these two classifiers while addressing the limitations of our proposed framework. Besides we will compare our method with deep learning methods using multiple BRATS testing datasets, including BRATS 2013.

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