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Segmentation of Perivascular Spaces Using Vascular Features and Structured Random Forest from 7T MR Image

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Abstract

Quantitative analysis of perivascular spaces (PVSs) is important to reveal the correlations between cerebrovascular lesions and neurodegenerative diseases. In this study, we propose a learning-based segmentation framework to extract the PVSs from high-resolution 7T MR images. Specifically, we integrate three types of vascular filter responses into a structured random forest for classifying voxels into PVS and background. In addition, we also propose a novel entropy-based sampling strategy to extract informative samples in the background for training the classification model. Since various vascular features can be extracted by the three vascular filters, even thin and low-contrast structures can be effectively extracted from the noisy background. Moreover, continuous and smooth segmentation results can be obtained by utilizing the patch-based structured labels. The segmentation performance is evaluated on 19 subjects with 7T MR images, and the experimental results demonstrate that the joint use of entropy-based sampling strategy, vascular features and structured learning improves the segmentation accuracy, with the Dice similarity coefficient reaching 66 %.

1 Introduction

Perivascular spaces (PVSs) are cerebrospinal fluid (CSF) filled spaces ensheathing small blood vessels as they penetrate the brain parenchyma. The clinical significance of PVSs comes primarily from their tendency to dilate in the abnormal cases. For example, normal brains show a few dilated PVSs, while an increase of dilated PVSs has been shown to correlate with the incidence of several neurodegenerative diseases, making the research of PVS a hot topic. Since most of the current studies require the segmentation of PVS to calculate quantitative measurements, the accurate and automatic segmentation of PVS is highly desirable.

So far, there are a few studies focusing on automatic PVS segmentation from MR images. For example, Descombes *et al.* enhanced the PVSs with filters and used a region-growing

approach to get initial segmentation, followed by a geometry prior constraint for further improving the segmentation accuracy [1]. Uchiyama *et al.* adopted a gray-level thresholding technique to extract PVSs from the MR images after being enhanced by a morphological white top-hat transform [2]. However, the segmentation accuracies are often limited with these unsupervised techniques, since it is very challenging to distinguish PVSs from confounding tissue boundaries. Recently, it has been demonstrated that the supervised methods are superior on the vessel segmentation problem by learning powerful classifiers. For example, Ricci and Perfetti employed the support vector machine (SVM) for retinal vessel segmentation with a specially designed line detector [3]. Marín *et al.* adopted the neural network (NN) for retinal vessel segmentation with gray-level and moment invariants based features [4].

However, there are several challenges for directly applying these supervised learning methods to PVS segmentation: (1) Since PVSs are extremely narrow and have low contrast compared with the neighboring tissues, general features may not capture the discriminative characters of PVSs compared with confounding background. (2) Informative tubular structures of PVSs cannot be considered in the label space, thus often leading to discontinuous and unsmooth segmentations. However, using a simple global geometrical constraint may cause over-fitting, since PVSs can appear at any locations and also have large shape variations (*e.g.*, different lengths, widths and curvatures). (3) Since the number of PVS voxels is much smaller than that of background voxels and there are always a large number of uninformative voxels in the background, it is difficult to train a reliable classifier with the conventional sampling method.

To address these challenges, we propose a structured learning-based framework for PVS segmentation from high-resolution 7T MR images. We integrate three types of vascular features, based on steerable filters, optimally oriented flux (OOF), and Frangi filter, into a structured random forest for classifying voxels into positive (*i.e.*, PVS) and negative (*i.e.*, background) classes. In addition, we also propose a novel entropy-based sampling strategy to extract informative samples in the background. Since various vascular features can be extracted by these three vascular filters, even thin and low-contrast structures can be effectively extracted from the noisy background. Moreover, the continuous and smooth segmentation results can be obtained by utilizing the patch-based structured labels.

2 Method

As shown in Fig. 1, our method is comprised of two stages. In the *training stage*, we first extract a region-of-interest (ROI) for each MR image. Then, we sample training voxels according to the probabilities calculated with local entropies. Next, the vascular features from MR images to describe a voxel's local structure are extracted, and the patch-based structured labels are also extracted from the binary segmentation (PVS) images as multiple target labels. Finally, a structured random forest is trained. In the *testing stage*, features are similarly extracted for each voxel in the ROI, and then all voxels in the ROI are classified by the trained structured random forest model.

2.1 Region-of-Interest Generation

PVSs only appear in the white matter (WM) tissue, and T2-weighted MRI is the best modality to identify all PVSs [5]. Therefore, we extract the WM tissue in the T2-weighted image as our ROI for PVS segmentation. Since image contrast between white matter and gray matter is clearer in the T1-weighted image, rather than the T2-weighted image, we rigidly align the T1-weighted image to the T2-weighted image, and then perform skull stripping and WM tissue segmentation in the aligned T1-weighted image. Therefore, we can obtain the WM segmentation in the T2-weighted image space.

2.2 Voxel Sampling Strategy

In general, the number of PVS voxels is much smaller (*i.e.*, ranging from several thousands to tens of thousands) than the total number of voxels in the WM (*i.e.*, millions). Therefore, we select all PVS voxels as positives samples for training. On the other hand, we extract negative samples from background, whose number is several times larger than that of the positive samples. Since the background includes a large number of uninformative (or less informative) voxels from the uniform regions but a relatively small number of informative voxels, it is inappropriate to randomly sample the negative voxels from background. In order to balance the proportions of uninformative and informative voxels, we propose to sample the voxels according to the probabilities calculated with the local entropies around voxels.

Specifically, for a region around a specific voxel $\mathbf{x}$, the local entropy $E(\mathbf{x})$ is defined as

$$E(\mathbf{x}) = -\sum_i p_i(s, \mathbf{x}) \log p_i(s, \mathbf{x}), \quad (1)$$

where i is a possible intensity value, and $p_i(s, \mathbf{x})$ is the probability distribution of intensity i within a spherical region $|\mathcal{Q}(s, \mathbf{x})|$ centered at $\mathbf{x}$ with a radius of s .

Then, we sample the voxel $\mathbf{x}$ with the probability of $\mathcal{P}(\mathbf{x})$, which is defined as

$$\mathcal{P}(\mathbf{x}) = e^{-\frac{\alpha}{E(\mathbf{x})}}, \quad (2)$$

where α is a coefficient that directly affects the sampling probability and also controls the total number of sampled voxels.

2.3 Feature Extraction

For many vessel segmentation problems, the orientations of the vessels are generally irregular (*e.g.*, retinal vessels and pulmonary vessels). Therefore, the orientation invariance is an important property of features. However, unlike these vessel segmentation problems, PVSs have roughly regular orientations that point to ventricles filled with CSF, as shown in Fig. 1(b) (PVS segmentation). To consider the useful orientation information, we extract three types of vascular features based on steerable filters, OOF, and Frangi filter from T2-

weighed images. For each type of these features, we also employ multi-scale representation to capture both coarse and fine structural features.

Steerable Filter-Based Features—Since Gaussian derivative filters are steerable, any arbitrary oriented responses of the first-order and second-order Gaussian derivative filters can be obtained by the linear combinations of some basis filter responses [6], and the steerable filters have been broadly used for feature extraction [7–9]. In this paper, we extract the 3D steerable filter-based features including the responses of a Gaussian filter, 9 oriented first-order Gaussian derivative filters and 9 orientated second-order Gaussian derivative filters. Therefore, there are 19 features for each scale of steerable filters (*i.e.*, the standard deviation of Gaussian/Gaussian derivative filters).

OOF-Based Features—The OOF has been proven to be effective for enhancing the curvilinear structures by quantifying the amount of projected image gradient flowing in or out of a local spherical region [10]. We extract 4 features based on the first two eigenvalues (λ_1, λ_2) of OOF Hessian matrix, which are $(\lambda_1, \lambda_2, \sqrt{\max(0, \lambda_1 \lambda_2)}, \lambda_1 + \lambda_2)$. Moreover, we extract 2 orientation features based on the eigenvector (x_1, y_1, z_1) corresponding to the maximum eigenvalue λ_1 , which are $(\arccos(\frac{|z_1|}{\sqrt{x_1^2 + y_1^2 + z_1^2}}), \arctan(\frac{y_1}{x_1}))$. Therefore, there are 6 features for each scale of spherical region (*i.e.*, the radius of spherical region for calculating the flux).

Frangi-Based Features—The Frangi vesselness measurements are extracted based on the Hessian matrix of second order Gaussian derivative filter responses [11]. In our study, we extract 3 features based on the eigenvalues $(\gamma_1, \gamma_2, \gamma_3)$ of the Hessian matrix, which are $(\frac{|\gamma_1|}{|\gamma_2|}, \frac{|\gamma_1|}{\sqrt{|\gamma_2 \gamma_3|}}, \sqrt{\gamma_1^2 + \gamma_2^2 + \gamma_3^2})$. We also extract 2 orientation features based on the eigenvector (x'_1, y'_1, z'_1) corresponding to the maximum eigenvalue γ_1 , which are $(\arccos(\frac{|z'_1|}{\sqrt{x'^2_1 + y'^2_1 + z'^2_1}}, \arctan(\frac{y'_1}{x'_1}))$. Therefore, there are 5 features for each scale of Gaussian derivative filters (*i.e.*, the standard deviation of Gaussian derivative filters).

2.4 Structured Random Forest

Random forest classifier is a combination of tree predictors [12]. For a general segmentation task, the input space corresponds to the extracted features of each voxel, and the output space corresponds to the label of that voxel. As a matter of fact, the PVSs have line-like structures such that the neighborhood labels have certain structured coherence. Therefore, we perform the structured learning strategy in our task, which addresses the problem of learning a mapping where the input or output space may represent complex morphological structures.

In our task, the output space is structured, so that we utilize the structured patch-based labels (*i.e.*, the cubic patch with a size of $n \times n \times n$) in the output space. Specifically, in the training stage, we first extract vascular features for each voxel sampled from T2-weighted image, as well as a corresponding cubic label patch from manually segmented binary image. Then, a

structured random forest (multi-label) model is trained using the features and labels. In the testing stage, we similarly extract the respective features for all voxels in the WM tissue from the testing T2-weighted images. Then, the features are fed to the trained model, and each voxel outputs a label patch. By assigning the patch-based labels to the neighboring voxels, each voxel receives n^3 label values, and we take the majority value as the label for each voxel. Eventually, by using the structured labels, the local structural constraint of PVSs in the label space can be naturally added to the random forest model.

As we know, most of PVSs point to the ventricles, thus PVSs within each hemisphere have roughly statistical regularity of orientations. Therefore, we separately train one model for the left hemisphere and another model for the right hemisphere, to reduce the divergence of PVSs' orientations. Finally, voxels from each hemisphere of the testing image are fed to the corresponding trained model for prediction.

3 Experiments, Results and Discussions

A 7T Siemens Scanner with a 32-channel head coil and a single-channel volume transmit coil (Nova Medical, Wilmington, MA) was used during our data acquisition. Both T1- and T2-weighted images were scanned for each subject with the spatial resolution of $0.65 \times 0.65 \times 0.65 \text{ mm}^3$ and $0.5 \times 0.5 \times 0.5 \text{ mm}^3$ (or $0.4 \times 0.4 \times 0.4 \text{ mm}^3$), respectively. In total, there were 19 subjects. The manual labels of PVSs were generated from the T2-weighted images using a thresholding-based semi-automatic method, and then manually corrected by two experts.

Two-fold cross validation is used to evaluate the segmentation performance. In order to expand the training dataset, each training image is further left-right flipped to generate one more training image. The parameters are set as follows: For extracting multi-scale steerable filters-based features, the standard deviations of Gaussian filters are set as [0.5, 1.5, 2.5, 3.5], thus obtaining 76 features in total. For extracting multi-scale OOF-based features, the flux radii are set as [0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4], thus obtaining 48 features in total. For extracting Frangi-based features, the standard deviations of Gaussian filters are set as [0.5, 1, 1.5, 2, 2.5, 3, 3.5], thus obtaining 35 features in total. Here, we select slightly denser scales for generating OOF and Frangi-based features than steerable filter-based features, to decrease the imbalance for the numbers of different types of features. For extracting patch-based labels, the patch size is set as $3 \times 3 \times 3$. For voxel sampling, the radius s is set as 10, and the coefficient parameter α is set as 15 to keep the proportion between positive voxels and negative voxels to be roughly 1:5. For training the structured random forest, 10 independent trees are trained and the depth of each tree is set as 20.

In our experiment, the segmentation performance is measured by Dice similarity coefficient (DSC). As a comparison, the results of Frangi [11] and OOF [10] with the thresholding strategy are reported in Fig. 2(a). As can be seen, our method achieves the best result as compared to these two thresholding methods, thus demonstrating the effectiveness of our learning-based framework. Figure 2(a) also shows the results by random forest (not structured) and the vascular features. It can be seen that the use of structured random forest

achieves roughly 6 % improvement in terms of DSC as compared to the standard random forest.

Sampling Strategy

In our method, we sample voxels from background with the probabilities in proportion to their local entropies. For comparison, we also show the result of random sampling voxels from background. As shown in Fig. 2(b), the proposed sampling strategy improves the segmentation performance by more than 8 % in terms of DSC for both random forest and structured random forest strategies. Figure 3(a) also shows an example of PVS segmentation of using different sampling strategies. As indicated, random sampling strategy has potential risk of wrongly classifying the confounding edge voxels as PVS. Specifically, if we sample the background voxels randomly, many voxels that are similar to PVS may not be sampled for training, since there are millions of uninformative voxels in background. The use of redundant unrepresentative sampled voxels for training may adversely affect the accuracy of classification model. As shown in Fig. 3(a), our method can distinguish the voxels that are similar to the PVS, but not PVS, compared with random sampling strategy.

Structured Random Forest

Figure 3(b) also compares a pair of segmentation results between random forest and structured random forest. As can be seen, the result by the random forest model is discontinuous and unsmooth, while the structured random forest improves such circumstance due to the use of local structural constraint in the label space.

Feature Scale Selection

One important parameter for feature extraction is the scale range for multi-scale representation. In our experiment, we define the scales of vascular features by their frequencies of being selected in all split nodes of a trained classification model. Specifically, we feed redundant features with many scales to train a classification model. Then, we count the frequencies of selected features in terms of scales. As shown in Fig. 3(c), the distribution demonstrates the importance of each scale in extracting vascular features. Finally, we only use the scales in the reasonable range for each feature type, as introduced in our parameter setting part.

4 Conclusion

In this paper, we propose a PVS segmentation method based on vascular features and structured random forest. In the input feature space, the vascular features can distinguish the PVSs from complex background. In the output label space, the patch-based structured labels preserve the local structure of PVS. Moreover, a novel voxel sampling strategy is also proposed to further improve the segmentation performance. The superior segmentation performance demonstrates the effectiveness of our structured learning-based framework for PVS segmentation.

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Fig. 1. Schematic diagram of the proposed method. (a) Training stage. (b) Testing stage.

Fig. 2. Quantitative evaluation of segmentation results. (a) Results of different methods. (b) Results of using different voxel sampling strategies.

Fig. 3.

Analysis of PVS segmentation. (a) Qualitative comparison between random sampling and our proposed sampling for obtaining the training voxels. (b) Qualitative comparison between random forest and the structured random forest. (c) Frequency of features being selected at each spatial scales.