USING RELATIVE CONTRAST AND ITERATIVE NORMALIZATION FOR IMPROVED PROSTATE CANCER LOCALIZATION WITH MULTISPECTRAL MRI

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ABSTRACT

In this paper, a new method that uses relative contrast is proposed for medical image segmentation problems. Generally, the absolute intensity values of different features are mapped into a comparable range with a normalization method, but the differences across patients are not considered. In order to utilize the patient-specific information from medical images, we use relative contrast between the normal and malignant tissues to perform training. The proposed relative contrast based method mimics the image segmentation procedure performed by human readers based on relative intensity values rather than absolute intensity values. The proposed method requires the knowledge of normal and malignant tissues since it is based on their relative intensities. This is known at the training stage, but unknown for the test data. Therefore, we present an iterative algorithm to estimate the relative contrast based on the current estimate of the class membership for the test data. Our experimental results show that the suggested algorithm outperforms the classical z-score normalization for prostate cancer localization with multispectral MRI images.

Index Terms— Image normalization, prostate cancer localization, MRI, SVM

1. INTRODUCTION

Medical images obtained from different modalities are widely used in many clinical and research applications. In this paper, a new normalization method using relative contrast to utilize the patient specific information is presented for medical image segmentation problems. For multispectral images, it is widely known that normalization is essential to combine the information provided from different modalities, and schemes such as z-score or energy normalization are classically applied. However, the classical normalization methods normalize different image types by transforming the intensity values into a comparable range, without taking into account the considerable differences between patients. In order to normalize across different subjects, the proposed method uses relative contrast to mimic the manual segmentation procedures that the human readers perform who are essentially comparing the contrast between two classes without being given the actual intensity values.

In practice, the relative contrast can be easily calculated for the training data, but cannot be obtained directly for the test data without the knowledge of class labels. To conquer this difficulty, we propose to apply an iterative strategy to estimate the relative contrast based on the current estimate of class membership. In this study, we use support vector machine (SVM) [1] for localization to illustrate the use of the proposed method. However, the proposed method based on relative contrast can also be applied to other classifiers.

The rest of this paper is organized as follows. In section 2, the z-score normalization is described for comparison purposes. The proposed iterative normalization method and the use of relative contrast is presented in Section 3. The visual and quantitative results of the proposed method and comparison with z-score normalization method is shown in Section 4. Last, conclusions and future work are provided in Section 5.

2. Z-SCORE NORMALIZATION METHOD

2.1. Z-score Normalization

Z-score normalization has been widely used in previous studies in many applications, including prostate cancer localization with multispectral MRI [2],[3]. This method transforms the intensity of different features into a comparable range of values which has zero mean and unit variance. The z-score normalized data is defined as:

$$x^{zs}_m = \frac{x_m - \mu_m(x_m)}{\sigma_m(x_m)},$$

where $x_m$ is the $m$th feature of multispectral image $x$, $\mu_m$ and $\sigma_m$ the mean and standard deviation of $x_m$.

In z-score normalization, the global mean and variance of the intensities of each feature are normalized. An implicit assumption is that for a certain feature, the intensity distribution from different patients are similar. This might be true in certain applications, however it will not be true for many medical images, because of the high variety between patients. The
z-score normalization induce a bias in the negative direction by shifting the data with the global mean. For a particular patient, the intensity values might be “over-shifted” by the global mean and a non-existing class may arise; or the intensity values might be “under-shifted” by the global mean and an existing class may be less likely to be detected. For real multispectral MRI images, this problem is illustrated as Fig.1. Part(b) shows the first case that intensities of a particular patient are over shifted by the global mean, and a large proportion of the pixels are shifted to have negative values. The false alarm of the segmentation result will be high in this case. In Fig.1(d), the intensities are under shifted by the global mean, so that the miss rate will be high for this patient.

The problem of the offset induced by z-score normalization has not achieved much attention in the past. It has been discussed mainly by Strother et al and Andersson. In [4], Strother et al noticed that a large proportion of the voxels in a z-score map has negative value, consistent with the offset from the normalization process. Andersson [5] discussed and proposed a method to deal with the problem of artifactual deactivations caused by z-score normalization in PET global activity studies. However, to authors knowledge, the error induced by z-score normalization for image segmentation or classification problems has not be studied before. Also, the methods discussed in [4] and [5] could not be successfully applied to our problem. Therefore, we introduce a novel approach for iterative normalization based on fuzzy membership as explained next.

3. PROPOSED METHOD

To conquer the error caused by z-score mapping for image segmentation, we propose a new strategy to perform the normalization to mimic the manual segmentation procedure. Human readers perform image segmentation by comparing the contrast between two classes without knowing the actual intensity values. Therefore, in this paper, the idea of using relative contrast is proposed to perform the segmentation. We define the relative contrast for the i-th pixel as follows:

\[
x_{im}^{rc} = \begin{cases} x_{im}/\mu_{2m} & \text{if pixel } i \text{ belongs to class } 1 \\ x_{im}/\mu_{1m} & \text{if pixel } i \text{ belongs to class } 2 
\end{cases}
\]

(2)

where \(x_{im}\) is the intensity of the \(n\)-th feature at pixel \(i\), and \(\mu_{1m}\) and \(\mu_{2m}\) the mean intensities of the \(n\)-th feature of class 1 and 2 respectively. Note that the relative contrast value for one class depends on the mean value of the other class for a specific subject.

For the training data, the classes are known, and the relative contrast for each patient/sample can be calculated by Eq. 2. For the test data, an iterative method to estimate the relative contrast based on the current estimate of the degree of membership to the two classes is proposed. We assume all the pixels belong to a certain class (for example, class 1 or normal tissue) for the initial estimate. Then, we calculate the initial relative contrast for the i-th pixel as follows:

\[
x_{im}^{rc}(0) = \frac{x_{im}}{\mu_{2m}^{tr}}.
\]

(3)

where \(\mu_{2m}^{tr}\) is the mean intensity of the class 2 (or tumor) obtained from the training data. Then the initial estimate \(x^{rc}(0)\) is classified into two groups by the SVM classifier. After that, we calculate the fuzzy membership of each pixel to the two classes based on the SVM binary results and the posterior distribution \(p(y|x)\). The fuzzy membership \(\alpha_1\) and \(\alpha_2\) of the i-th pixel to the two classes is defined as:

\[
\alpha_{1i} = \frac{p(y_i = 1|x_i)}{p(y_i = -1|x_i) + p(y_i = 1|x_i)}
\]

\[
\alpha_{2i} = \frac{p(y_i = -1|x_i) + p(y_i = 1|x_i)}{p(y_i = -1|x_i) + p(y_i = 1|x_i)}
\]

(4)

where \(\alpha_{1i} + \alpha_{2i} = 1\), \(x_i\) is the i-th pixel of the image data, and \(y_i\) the class label obtained by SVM, \(y_i\) either 1 or -1. Depending on the choice of \(p(y|x)\), different models can be constructed. A common probabilistic model used is the Gaussian distribution, and extension to other distribution is possible by using the corresponding PDFs. For the Gaussian distribution assumption, the posterior probability \(p(y|x)\) can be expressed as:

\[
p(y = 1|x) = \frac{1}{(2\pi)^{M/2}|C_1|^{1/2}} \times \exp\left(-\frac{[x - \mu_1]^TC_1^{-1}[x - \mu_1]}{2}\right)
\]

\[
p(y = -1|x) = \frac{1}{(2\pi)^{M/2}|C_2|^{1/2}} \times \exp\left(-\frac{[x - \mu_2]^TC_2^{-1}[x - \mu_2]}{2}\right),
\]

(5)
where $M$ is the number of features of the image data, $\mu_1$ and $\mu_2$ the mean vectors of the class 1 and 2, and $C_1$ and $C_2$ the corresponding covariance matrices. Assuming independent features, we have:

$$\mu_k = \frac{1}{N_k} \sum_{x_i \in S_k} x_i, \quad C_{km} = \frac{1}{N_k} \sum_{x_i \in S_k} (x_{im} - \mu_{km})^2,$$

(6)

where $k$ is the class number, either 1 or 2, $N_k$ the number of pixels in class $k$, $S_k$ the $k$th set classified by SVM, and $C_k = \text{diag}(C_{k1}, C_{k2}, ... C_{km}, ... C_{kM})$. Once the fuzzy membership of the two classes is obtained, we update the estimate of the relative contrast based on the current estimate of fuzzy membership as:

$$x^{rc}_{im}(n + 1) = \alpha_{1m}(n) \frac{x_{im}}{\mu_{2m}(n)} + \alpha_{2m}(n) \frac{x_{im}}{\mu_{1m}(n)},$$

(7)

where $\mu_{1m}(n)$ and $\mu_{2m}(n)$ are the mean intensity of the $m$th feature of class 1 and 2 at iteration $n$ respectively.

The main steps of the proposed algorithm can be summarized as:

1. Based on the given classes, the training data is normalized using the relative contrast defined by Eq.2.
2. Initialize the estimate of relative contrast for the test data by assuming all pixel belong to a certain class as expressed in Eq.3.
3. Use a segmentation method (SVM as an example) to separate the normalized test data into two groups.
4. Then update the estimate of mean and covariance matrices, and calculate the fuzzy membership by Eq.4 - Eq.6.
5. Update the estimate of relative contrast by Eq.7.
6. Repeat steps (3)-(5) until convergence.

4. EXPERIMENTAL RESULTS

4.1. Multispectral MRI data

To illustrate the performance and verify the feasibility of the proposed normalization method, we apply our method to localize prostate cancer from multispectral MRI images. The prostate MRI dataset is obtained from 20 patients with biopsy-confirmed prostate cancer. The patients underwent MRI prior to prostatectomy on a 1.5T GE Excite HD platform (GE Medical Systems, Milwaukee, WI) using a 4-channel phased-array surface coil coupled to an endorectal coil (MEDRAD, Warrendale, PA, USA). There are three different types of MRI techniques employed in this experiment: T2 weighted MRI (T2w), diffusion weighted MRI (DWI) and dynamic contrast enhanced MRI (DCE MRI).

Acquisition parameters for each dataset are as follows. Fast spin-echo (FSE) T2w: (Repetition time)/(Echo time) (TR/TE) = 6550/101.5 ms, 320 × 256 matrix, echo-train length (ETL) = 16, bandwidth (BW) = 20.83 kHz, number of excitations (NEX) = 3, field of view (FOV) = 14 cm, no phase wrap, phase encode direction left-right. Multi-echo FSE for quantitative T2: TR = 2000 ms, 10 TE(s) (9.0-90.0 ms, in 9 ms increments), 256 × 128 matrix, ETL = 10, BW = 31.25 kHz, NEX = 1, FOV = 20 cm, phase encode direction left-right. DWI: TR/TE = 4000/77 ms, 128 × 256 matrix, ETL = 144, BW = 66.7 kHz, NEX = 10, FOV = 14 cm, b = 0, 600 $s/mm^2$, phase encode direction left-right. Multi-flip fast spoiled gradient echo (FSPGR) for T1 mapping to correct DCE data: flip-angles: 2°, 5°, 10°, 20°; TR/TE = 8.5/4.2 ms; 256 × 128 matrix, ETR = 8; BW = 31.25 kHz, NEX = 1, FOV = 20 cm, phase encode direction anterior-posterior. DCE MRI: fifty phases of FSPGR MRI (flip-angle = 20°, TR/TE = 4.3/1.9 ms; 256 × 128 matrix; ETL = 8; BW = 62.5 kHz; NEX = 0.5; FOV = 20 cm; temporal resolution = 10 s, phase encode direction anterior-posterior), with two phases acquired prior to injection of 20 ml contrast agent (gadopentate-diethylene triamine pentetic acid, Magnest, Bayer Schering Pharma, Berlin, Germany) at 4 cc/s, followed by 20 ml of saline. For each patient, all MRI datasets are acquired at identical slice location with a slice thickness of 3 mm and no gap between slices.

After the prostatectomy, each patient’s prostate was fixed into formalin for 24 hours and embedded in HistOmer gel. The gels-embedded sample was cut in 3mm sections and all sections were then prepared as haematoxylin and eosin (H&E) stained whole mount histologic slides using standard pathology techniques. The regions of tumor are outlined by a pathologist by assessing the whole mount sections. Then the pathological tumor masks are transferred to MR images by a radiologist as ground truth.

This multispectral MR dataset can both provide morphological and functional information. Three features: T2 maps, ADC and kep, derived from the T2w, DWI and DCE MRI respectively are used for segmentation. T2 maps are calculated from a series of echo time measurements and remove the variations in signal intensity as a function of proximity to the endorectal coil in T2w. ADC maps, from the DWI acquisition, can assist in differentiating between real ischemic lesions and T2 shine through effects or artifacts. kep, which is a pharmacokinetic parameter derived from DCE MRI describes the wash-in rate. Prostate cancer causes low T2 signal on T2w MRI, a low ADC on DWI, and high permeability on DCE MRI compared to normal prostatic tissues.

4.2. Experimental Results

Since our images are from three different types of MRI, a registration step is necessary before performing further procedures. In this study, the image registration is performed by an expert human reader. The prostate has several regions, such as transition zone, peripheral zone (PZ), and urethra. Most of the prostate tumor are located within PZ, therefore, only PZ region is considered in this experiment. A 5 × 5 median filter is applied to each MRI image to reduce noise.

Fig.2 and Fig.3 provide the visual and quantitative com-
Fig. 2. Comparison of SVM segmentation results of the two patients (shown as Fig.1) obtained from the proposed normalized data and the z-score normalized data. The first column are the ground truth outlined by a radiologist, the second column by the z-score normalized image, and the third column by the proposed normalized data.

Comparison between z-score normalization and the proposed method. Fig. 2 is a visual comparison obtained from two examples shown in Fig.1. It can be seen that for the first patient, the false alarm is high, and for the second patient, the miss rate is extremely large in z-score segmentation results. These results are consistent with the analysis in Section 2 and Fig.1.

In addition to the visual comparison, the dice measure (DSC) values are calculated for quantitative evaluation. The DSC is defined as:

$$DSC(A, B) = 2 \cdot |A \cap B| / (|A| + |B|),$$

where $A$ is the segmentation result, $B$ the ground truth, and $| \cdot |$ denotes the number of pixels contained in a set. Fig.3 demonstrates the improvement of DSC values by the proposed method compared with z-score normalization. It shows that for 16 of 20 patients, the DSC values are improved, and the average DSC value is increased from $\mu_{zs}(dsc) = 0.36$ to $\mu_{rc}(dsc) = 0.42$. Our experimental results show that the proposed method considerably improves the segmentation performance.

5. CONCLUSIONS

In this paper, a novel method based on relative contrast is presented for prostate cancer localization problem. Although it is well known that the normalization of different image types is a necessary step for multispectral image segmentation, the normalization of different patients for medical image processing has not been commonly studied in the past. Although the simple z-score normalization is widely applied in many applications, the offset brought by z-score mapping and the consequent error induced have not been paid much attention before.

Instead of mapping the intensities into a comparable range which has zero mean and unity variance, we use the relative contrast to normalize the image data. It mimics the human readers who utilize the brightness and darkness of the normal and tumor tissues without knowing the actual intensity values. The training data are normalized by calculating the relative contrast based on the given classes. Then an iterative method is used to estimate the relative contrast to normalize the test data with unknown labels. In this study, the SVM technique is used for the segmentation, however the proposed normalization scheme can easily be applied to other types of classifiers. The experimental results for prostate cancer localization on multispectral MRI data demonstrates the efficacy of the proposed method.

Future work includes extending our method to other segmentation methods, and applying our method to various medical image datasets.

6. REFERENCES


