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LEVEL SET BASED CLUSTERING FOR ANALYSIS OF FUNCTIONAL MRI DATA

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Abstract

We present a level set based clustering technique to detect activation regions from functional brain images using contextual information. Earlier similar approaches have been primarily concerned with local spatial context. Our approach relies on the idea that voxels within a functional region have similar temporal behavior. Using a level set formulation, a two-dimensional curve is evolved with a speed proportional to a similarity measure between the fMRI signals of voxels lying on the curve and their neighbors in the direction of propagation. The correlation coefficient is used to quantify similarity in time series of adjacent voxels. Simulation results from synthetic images demonstrate that using spatio-temporal contextual information provides better segmentation than a context-free, voxel-wise technique. Results from a real fMRI experiment using auditory stimulation are also presented.

Keywords

Biomedical Image Processing; Clustering Methods; Image segmentation; Magnetic Resonance Imaging

1. INTRODUCTION

Functional Magnetic Resonance Imaging (fMRI) has evolved into a powerful tool to non-invasively map brain function by the blood oxygenation level dependent (BOLD) effect. Its ability to localize/characterize brain function has made it indispensable in both neuro-scientific research and clinical arenas. A crucial part in the analysis of functional brain images is to detect brain regions that are activated by input stimuli provided to the subject during a functional experiment. However, the signal change due to BOLD effect is very small, noisy and susceptible to artifacts. Hence, advanced techniques from statistics and signal/image processing are required for fMRI data analysis.

The general linear model (GLM) [1], is the most commonly used approach for classifying brain voxels into active and inactive voxels. Activation regions are found by statistically comparing fMRI signals measured at each voxel during stimulation (task) and rest (baseline). GLM is a model-driven method which generates an expected response to the stimulus and compares it with the data. Alternatively, data-driven techniques such as principal component analysis (PCA) [2] and independent component analysis (ICA) [3] attempt to derive activation information without imposing a model. However, these traditional methods evaluate the level of activation at each voxel independently.

An important aspect of fMRI data is that a single activation region typically consists of numerous voxels, i.e. clustered activations. To improve detection of activated areas, data is

often spatially smoothed. However, smoothing produces a biased estimate by displacing activation peaks and underestimating their height. Spatial modeling has been proposed [4,5] to take the spatial activation pattern into consideration. Salli *et al.* [6] use a clustering approach to incorporate contextual information in conjunction with a Markov random field (MRF) model [7]. In these techniques contextual information is primarily limited to agreement with local neighborhoods.

In this paper, we present a level set based clustering strategy to detect functional activation regions in the brain. The fundamental assumption of our technique is that voxels with similar temporal behavior belong to the same functional region of the brain. We measure similarity between time series of voxels using correlation coefficient. An initial curve is evolved with a speed proportional to the similarity metric between the time series of voxels lying on the front and their neighbors in the direction of propagation. The level set implementation of front propagation allows natural handling of topological changes and ensures stable evolution.

2. METHOD

2.1. Level Set Formulation

The level set method, introduced by Osher and Sethian [8], has been used extensively for evolving curves and surfaces that may undergo complex topological changes such as merging and splitting. The main idea is to embed the propagating interface as the zero level set of a higher dimensional function. Let ϕ be an implicit representation of the curve so that $C = \{(x, y) \mid \phi(x, y, t) = 0\}$, i.e. the zero level set of a time varying surface function $\phi(x, y, t)$. We define ϕ to be the signed distance function of the propagating curve C such that ϕ is positive inside and negative outside C . Then, evolving the curve C in the normal direction with speed F amounts to solving the differential equation:

$$\frac{\partial \phi}{\partial t} + F |\nabla \phi| = 0, \quad \phi(x, y, 0) = \phi_0(x, y) \quad (1)$$

where ϕ_0 is the initial curve. The evolution of the curve C at any time t is given by the zero level set of the function $\phi(x, y, t)$.

2.1.1. Speed Function—In designing the speed term, we follow a similar approach to that presented in [9]. As mentioned earlier, our front propagation method is based on the idea that voxels with similar temporal behavior belong to the same functional region in the brain. We use the correlation coefficient to quantify similarity in the fMRI signals of adjacent voxels. Unlike other similarity metrics such as L2-Norm which emphasize the difference in signal amplitudes, the correlation coefficient captures covariance in signals. The front propagates into a voxel with a speed proportional to the similarity between the time series of the current voxel and time series of the adjacent voxel in the direction of propagation. The front propagation speed is defined as

$$F = r(\mathbf{x}, \mathbf{y}) = \frac{\text{Cov}(\mathbf{x}, \mathbf{y})}{\sigma_{\mathbf{x}} \sigma_{\mathbf{y}}} \quad (2)$$

where $\mathbf{x}$ is the fMRI time series at the current voxel i and $\mathbf{y}$ is the time series of the voxel behind the current voxel in the normal direction, i.e. $i - \mathbf{n}$, see Fig. 1, where $\mathbf{n}$ is the normal, given by

$$\mathbf{n} = \frac{\nabla \phi}{|\nabla \phi|} \quad (3)$$

A speed term solely based on image data could result in very jagged outlines of activation regions due to low SNR in fMRI data. To smooth the edges while evolving, front propagation is regularized by adding a curvature dependent speed term κ . The speed function now has the form $F + \kappa$ where the curvature term is obtained from the divergence of the gradient of the unit normal vector to the front, that is

$$\begin{aligned} \kappa &= \nabla \cdot \frac{\nabla \phi}{|\nabla \phi|} \\ &= \frac{\phi_{xx}\phi_y^2 - 2\phi_x\phi_y\phi_{xy} + \phi_{yy}\phi_x^2}{(\phi_x^2 + \phi_y^2)^{3/2}} \end{aligned} \quad (4)$$

2.2. Implementation Details

The proposed method has been implemented in Matlab 7.0.4 for two-dimensional images. Extension to three dimensional space can be easily handled by extending array structures and the gradient operator.

Preserving the signed distance function—As the computations for normal and curvature depend on the zero level set, it is essential that ϕ be a signed distance function throughout the evolution process. However, the solution to equation (1) often becomes very flat and/or steep at the front due to local dependence of propagation speed. Hence, the level set function is periodically reinitialized by recalculating the signed distance from each point to the zero level set by solving the following evolution equation [10]:

$$\frac{\partial \phi}{\partial t} = \text{sign}(\phi) (1 - |\nabla \phi|) \quad (5)$$

Thresholding—Unless the speed is equal to zero at a voxel, the front will eventually propagate at the voxel even if the speed is very small. To prevent unnecessary propagation, all speeds lower than a threshold are set to zero. In order to avoid causing discontinuities in the propagation, the following regularized Heaviside function [11] is used to get a smoother thresholding, where T is the selected threshold and ϵ is set to 0.1 in all the experiments.

$$H_T(x) = \begin{cases} 0 & \text{if } x < T - \epsilon, \\ 1 & \text{if } x > T + \epsilon, \\ \frac{1}{2} \left[1 + \frac{x-T}{\epsilon} + \frac{1}{\pi} \sin \left(\pi \left(\frac{x-T}{\epsilon} \right) \right) \right] & \text{if } |x - T| \leq \epsilon. \end{cases} \quad (6)$$

Weighting Parameter—The image and curvature dependent speed terms are not always of the same order. To get satisfactory regularization without inhibiting front propagation, it is important to scale these terms properly. Hence, we multiply the curvature term with weighting parameter α . The value of alpha is chosen empirically and is close 0.1 in all our experiments.

Convergence—The evolution of the curve is automatically stopped when the zero level set moves insignificantly for several consecutive iterations. If the front displacement is less than 0.1 voxels for 10 iterations, it is accepted as the solution.

Finally, the evolution of the level set function is of the form:

$$\frac{\partial \phi}{\partial t} = (H_{\tau}(F) + \alpha \kappa) |\nabla \phi| \quad (7)$$

To solve the PDE (7) numerically, we apply standard finite difference schemes for level set equations [12]. To perform clustering, a small initial curve is placed inside the activation region to be detected at a user selected location. The front is then propagated using the above equation with a speed proportional to the similarity measure defined in (2). The following section presents results of applying our model to 2-D images/slices and we are currently in the process of extending the model to handle 3-D.

3. RESULTS

3.1. Synthetic Functional Data

A two-dimensional 32×32 synthetic functional image consisting of 64 scans was simulated. Voxels in a circular blob of radius eight centered at (16,16) were selected to be active as shown in Fig. 3(a). The input stimulus was presumed to have eight cycles, each having four stimulation ON/task states followed by four OFF/rest states, and each stimulation comprised of eight scans. Box-car time series was designed for the active voxels and the inactive voxels had time series of zero amplitude. The response of the active voxels was generated by convolving the box-car time series with a gamma hemodynamic response function (HRF). Gaussian random noise was then added to the time series of both active and inactive voxels to make the data more realistic. Sample time series of active and inactive voxels is shown in Fig. 2. Spatial correlation in the scans was introduced by convolving each functional scan with a Gaussian kernel having FWHM of 3.0 and the images were then properly scaled.

Fig. 3 shows the activation detected from the synthetic image at a signal-to-noise ratio (SNR) of -7 dB. Following the general procedure for fMRI analysis, a statistical parametric map - $SPM\{t\}$ was generated by calculating the t-statistic for each voxel by comparing the fMRI signal during ON and OFF states. Thresholding $SPM\{t\}$ at a significance value of $t = 4.2$ detected activation shown in Fig. 3(b). For the level set approach, a small initial curve (a circle of radius one) was placed at the center of the circular activation blob. The front was then propagated using equation (7) with parameters: $T = 0.75$, $\epsilon = 0.1$ and $\alpha = 0.1$. The resulting clustering is shown in Fig. 3(c). The threshold values for both methods were chosen such that total errors were minimized. The percentage of false positives, false negatives and total errors (with respect to truly active voxels) incurred by these detection methods are given in Table 1. Values in the table indicate that the level set approach performs better than simple thresholding with low values for both false positives and false negatives.

3.2. Real fMRI Data

We also applied the proposed level set approach to a block-design auditory fMRI experiment available with the SPM package [13]. The whole brain BOLD/EPI images were acquired on a modified 3T Siemens Magnetom Vision system. The data set contains 96 acquisitions but the first 12 scans were discarded due to T1 effects. Each acquisition consisted of 64 contiguous slices with $64 \times 64 \times 64$ voxels of size $3\text{mm} \times 3\text{mm} \times 3\text{mm}$. The condition for successive blocks alternated between rest and auditory stimulation, starting with rest. Auditory stimulation was with bi-syllabic words presented binaurally at a rate of 60 per minute.

The top row of Fig. 4 shows the activation detected in one axial slice of the auditory fMRI data by analyzing the entire fMRI signal (all 84 scans). Fig. 4(a) outlines the region detected by the level set approach with parameters: $T = 0.7$, $\epsilon = 0.1$ and $\alpha = 0.1$. Activation within the clustered region (using t-statistic values) is shown in Fig. 4(b). Thresholding the SPM $\{t\}$ at significance value of $t = 4.2$ detected activation shown in Fig. 4(c). As expected, both methods detect significant activation in the auditory areas of the brain. Visual comparison of these activation maps reveals that the activation detected by the level set based method is more focused in the auditory cortex whereas simple thresholding of SPM $\{t\}$ resulted in a fragmented activation map.

Validation of analysis techniques for real fMRI data is complicated due to the lack of ground truth. However, to evaluate the performance of different activation detectors, we can use the activation map from entire time series as a reference and compare it to activation map from time series of reduced length. The bottom row of Fig. 4 shows the activation detected in the same axial slice by analyzing only half the fMRI signal (42 scans). Comparing activation maps from shorter time courses with their corresponding full-length references shows that voxel-wise thresholding (Fig. 4f) produces a more fragmented map due to loss of SNR from signal trimming. The level set approach generates activation map (Fig. 4e) that is reasonably similar to the full-length map (Fig. 4b). The experiments demonstrate the benefits associated with our model compared to corresponding voxel-wise approach.

4. CONCLUSIONS

Incorporating spatio-temporal contextual information in the analysis of fMRI data leads to potentially better delineation and localization of underlying spatial activation. We presented a clustering method using level set formulation to detect activation regions from functional brain images. The model incorporates context not simply in terms of local neighborhoods but in terms of similarity in temporal behavior of adjacent voxels. The experiments on real and synthetic fMRI data demonstrate the advantage of clustering using level set approach over voxel-wise thresholding in terms of its ability to (a) reduce false positive and false negative activations and (b) recover activation from significantly reduced time courses.

We are currently in the process of extending our model to handle 3-D images. Improvements to the similarity metric and algorithm implementation are also being investigated. Future work will be directed towards integrating shape prior information [14] into our level set framework to make our model more robust and assist it in achieving more accurate results in the presence of noise and other artifacts.

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Fig. 1.
Selecting the adjacent voxel by following the normal to the front.

Fig. 2.
Voxel time series in synthetic images: (Top) Active Voxel and (Bottom) Inactive Voxel

Fig. 3. Activation Detection from synthetic functional image: (a) true activation, (b) thresholding the SPM $\{t\}$ and (c) level set approach (d) colormap of t-statistics values for active voxels

Fig. 4. Real fMRI Data: (Top) Activation detected using entire time series. (Bottom) Activation detected using reduced time series. (a),(d) Outline of clustered activation region. (b),(e) Active region with t-statistic intensities. (c),(f) Thresholding the $SPM\{t\}$

Table 1

Percentage of errors incurred in detection of activation in synthetic functional image: Thresholding of $SPM\{t\}$ compared to the level set approach.

Percentage of errors	Thresholding of $SPM\{t\}$	Level-set Approach
False Positives	5.69	4.15
False Negatives	3.62	3.10
Total Errors	9.01	7.25