Joint fMRI brain activation detection and segmentation using Level Sets

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***Abstract*— This paper proposes a parametric, multivariate method for the joint detection and segmentation of brain activation based on fMRI data. The proposed technique uses region based level sets to separate between the activated and non-activated regions and performs, at each iteration of level set evolution, a separate multivariate linear model (MLM) analysis in each of the two regions. Simulations using synthetic data generated based on typical experimental parameters and noise levels showed a false positive rate of 6% and a false negative rate of 2% for the results obtained with the proposed technique. The performance of the level sets method was further investigated by analysing empirical fMRI data from two subjects performing a visual and a motor task. Our results indicate that the proposed technique provides brain activation results comparable to those obtained by a standard univariate approach, with the advantage that it does not require the definition of a significance threshold.**

I. INTRODUCTION

Blood Oxygen Level Dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) is a completely non-invasive tool used to identify brain regions activated in association with an experimental manipulation, such as a visual stimulus or a motor task. Although fMRI techniques have gained great popularity in the fundamental study of brain function, their translation into the clinical practice has been hindered by the lack of reliability of the results, particularly in uncooperative patients or highly pathological conditions. This is mostly due to the commonly high noise levels in the data and the requirement for multiple image pre-processing steps, followed by the statistical modeling of pre-processed images, in order to obtain the final brain activation maps [1].

The statistical analysis of fMRI data is most often carried out through a massively univariate approach, whereby a General Lineal Model (GLM) describing the experimental manipulation, as well as any confound variables, is adjusted to each voxel's time series in order to yield a 3D map of model parameter estimates. Following model estimation, the activated regions are identified by using an inference approach. Usually, *t*-tests are performed on each voxel to yield *Z* statistical maps of increased brain activity during the stimuli/task. Because it is physiologically plausible that brain activation should occur in clusters of voxels rather than at isolated voxels, the spatial correlation between neighbouring voxels should be taken into account. The theory of Gaussian Random Fields (GRF) is then employed to accomplish maximum height thresholding of the *Z*-score images at specified significance levels, *p*-value, of false-positive probabilities, corrected for multiple comparisons [2].

The final results, in terms of voxels showing significant BOLD signal changes associated with the experimental manipulation, strongly depend on the pre-processing and modeling choices, and so does the validity of the inferences made upon the statistical tests used. In particular, the choice of the significance level used for thresholding the statistical maps is associated with a certain degree of subjectivity.

On the other hand, non-parametric, multivariate methods have also been proposed for the analysis of fMRI brain activation data. These include clustering [3], independent component analysis (ICA) [4] and self-organizing mapping [5]. Both supervised and unsupervised machine learning methods, such as Support Vector Machines (SVM), have more recently been applied too [6], [7]. Although these methods do not depend on underlying model assumptions, and may therefore provide a more flexible tool in exploratory analyses, the interpretation of the results may be compromised.

In this paper, we propose a parametric, multivariate method to perform brain activation detection while simultaneously providing a segmentation of activated from non-activated regions. The proposed technique uses the region based level set method which imposes regularization and naturally takes into account the spatial correlation among neighbouring voxels. The level set method does not require the definition of a significance threshold, makes no assumption about the shape or number of clusters and is very flexible because it is able to change the topology of the detected regions since the contour automatically splits and merges. At each iteration of level set evolution, a separate multivariate linear model (MLM) analysis is performed in each of the two regions, which results in increased robustness of the parameter estimates when compared to standard univariate methods.

The remainder of this paper is organized as follows: section II describes the proposed method for fMRI brain activation detection and segmentation, section III describes the experimental results and section IV concludes the paper.

II. PROPOSED METHOD

The proposed technique uses a 3D implementation of the region based level sets method [8] to separate between the activated and non activated regions and performs, at each

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iteration of level set evolution, a separate multivariate linear model analysis in each of the two regions.

A. Level set method

In this work we assume that the fMRI image, denoted by y, is formed by two 3D regions Ω_1 and Ω_2 containing activated and non-activated voxels, respectively. These two regions are separated by a curve C, and each region Ω_1 and Ω_2 is modeled by probability density functions p_1 and p_2, respectively. The segmentation is obtained by minimizing the following energy function [8]:

$$\begin{aligned} E(C,p_1,p_2) = &-\lambda_1 \int_{\Omega_1} \log p_1(y|\theta_1) d\Omega \\ &-\lambda_2 \int_{\Omega_2} \log p_2(y|\theta_2) d\Omega + \mu\, lenght(C) \end{aligned} \tag{1}$$

The first two terms of this equation are data fitting terms and the last term is a regularizing term that depends on the length of the curve; μ, λ_1 and λ_2 are positive weighting parameters.

Using the level set formulation [9], embedding the curve C as the zero level set $C(t) = \{(x)|\phi(t,x) = 0\}$ of a higher dimensional level set function $\Phi(t,x)$ this energy function can be rewritten as:

$$\begin{aligned} E(\Phi,p_1,p_2) = &-\int_{\Omega} [H(\Phi)\log p_1(y|\theta_1) + \\ &(1-H(\Phi))\log p_2(y|\theta_2)] d\Omega + \mu \int_{\Omega} \nabla H(\Phi) d\Omega \end{aligned} \tag{2}$$

where H is the Heaviside function, $H(z) = 1$ if $z \geq 0$ and $H(z) = 0$ if $z < 0$. Function $\Phi(t,x)$ represents region Ω_1 for $\Phi > 0$ and Ω_2 for $\Phi < 0$. Therefore, the Heaviside function is used to distinguish the two regions.

In practice a regularized version of the Heaviside function is used:

$$H_\varepsilon(z) = 0.5\left[1 + \frac{2}{\pi}\arctan\left(\frac{z}{\varepsilon}\right)\right] \tag{3}$$

Keeping p_1 and p_2 fixed, Φ is evolved according to the following motion Partial Differential Equation (PDE):

$$\begin{aligned} \frac{\partial \Phi}{\partial t} = &\delta_\varepsilon(\Phi)[\mu div\left(\frac{\nabla\Phi}{|\nabla\Phi|}\right) - \lambda_1 \log p_1(y|\hat{\theta}_1) \\ &+ \lambda_2 \log p_2(y|\hat{\theta}_2)] \end{aligned} \tag{4}$$

where $\delta_\varepsilon(\Phi)$ is the Dirac delta function $\delta_\varepsilon(z) = \frac{\delta}{\delta z} H_\varepsilon(z)$.

The contour is roughly initialized by the user in the expected activation region. Then, the algorithm estimates in alternate steps the contour and the PDF's of both regions, p_1 and p_2. The way the estimates of p_1 and p_2 are updated is described in the following section.

B. Density estimation

In this work, the probability density functions p_1 and p_2 are estimated from the fMRI data in regions Ω_1 and Ω_2, respectively. In each region, we assume the multivariate linear model:

$$Y = X\beta + \varepsilon \tag{5}$$

where Y denotes the NT×1 matrix obtained by concatenating the fMRI data of N voxels with T time points, X denotes the NT×k experimental paradigm including k inputs driving brain activation and β denotes the corresponding k×1 parameter estimates. These parameter estimates are obtained by Linear Least Squares fitting of the BOLD signal, which amounts to modeling the residuals ε in each region as $N(0,\sigma_m^2)$, $m = 1,2$. Therefore, the following densities are obtained for p_1 and p_2:

$$p_m(y|\theta_m) = \frac{1}{\sqrt{2\pi}\sigma_m} \exp\left(-\frac{(y - B_m x)^2}{2\sigma_m^2}\right) \tag{6}$$

The estimation of parameters β_1 and β_2 should be performed separately for the activated and non-activated regions because the two regions will in general have different numbers of voxels.

III. Experimental Validation

This section presents results of the application of the proposed method to both synthetic and empirical fMRI data and compares them with the results obtained using a standard univariate GLM approach.

A. Synthetic Data

Synthetic data were generated based on a 3D head phantom with volume size 64×64×30, where two rectangular activation regions were defined (10×10×10 and 5×15×5 voxels, respectively). A block design paradigm alternating ten 18 *sec* periods of activation and ten 18 *sec* periods of rest, with repetition time $TR = 3000\,ms$, yielding a total of $T = 122$ time points, was considered. The simulated activation signals in each region were then created by convolving this paradigm with a canonical Gamma-variate Haemodynamic Response Function (HRF), as implemented in SPM99 (http://www.fil.ion.ucl.ac.uk.pt) [10], with $\beta = 10$. Noisy data were then obtained by adding zero mean Gaussian noise to the simulated data, such that the SNR was 0 dB. Figure 1 shows the simulated data and the results of the proposed method. In these images the initial contour is overlaid in yellow and the final contour in red.

It can be seen that, although the initial region selected by the user is quite distant from the final segmentation and does not contain the two activated regions, the algorithm is able to converge to the correct boundary. This example also illustrates the ability of the contour to split automatically into two separate regions, since the activated regions are disjoint. In this example, the proposed method obtained $\beta = 9.96$ in the activated region and $\beta = 3.2e-16$ in the non-activated regions, which is very close to the true values. The resulting

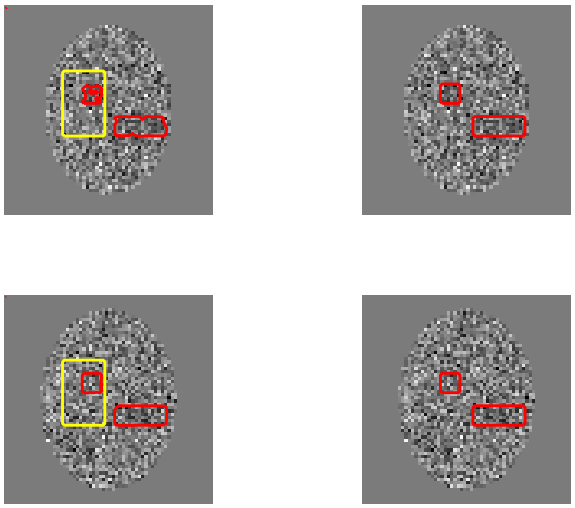

Fig. 1. Segmentation results with synthetic data. Left: Results of the proposed method shown in red and initialization shown in yellow. Right: Simulated activation regions shown in red.

segmentation had a false positive rate of 6% and a false negative rate of 2%.

B. Real Data

Empirical fMRI brain activation data from a visual stimulation experiment (*visual*) and a motor task experiment (*motor*) were used. Both datasets were collected from healthy volunteers on 1.5T MRI systems, using T_2*-weighted echo-planar imaging (EPI). In the visual experiment, 120 volumes were acquired with $TR = 3000\,ms$ and a voxel resolution of $3,5 \times 3,5 \times 4,0\,mm$. In the motor experiment, 150 volumes were acquired with $TR = 2000\,ms$ and a voxel resolution of $3,4 \times 3,4 \times 5,0\,mm$.

The visual experiment consisted in a block design alternating ten 18 *sec* periods of a visual stimulus presentation and ten 18 *sec* periods of fixation. The motor experiment consisted in a block design alternating five 30 *sec* periods of right-hand thumb-digit apposition with five 30 *sec* periods of rest.

Datasets were pre-processed and analyzed for BOLD signal change detection using the FEAT software (http://www.fmrib.ox.ac.uk/fsl). The following pre-processing steps were performed on each BOLD time series: motion correction [11]; non-brain removal [12]; mean-based intensity normalization of all volumes by the same factor; spatial smoothing (Gaussian kernel, 5 *mm* FWHM) and high-pass temporal filtering (Gaussian-weighted least squares straight line fitting, 50 *sec* cut-off).

A GLM was defined by modeling each stimulus/task period (*VisualStimulus* or *MotorTask*) as a square function of width equal to the period duration convolved with a canonical Gamma-variate HRF [10]. For the standard univariate approach, a GLM with local autocorrelation correction was used to test for stimulus/task-related activity changes [13], [14]. Linear contrasts between each stimulus/task condition and the respective control conditions were then calculated and *t*-tests were performed to yield statistical maps of increased brain activity during the stimuli/task (namely, *Visual* vs *Fixation* and *MotorTask* vs *Rest*). Finally, cluster thresholding was performed by employing the theory of Gaussian Random Fields (GRF) to accomplish maximum-height thresholding of the *Z*-score images at specified significance levels, *p*-value, of false-positive probabilities, corrected for multiple comparisons [2].

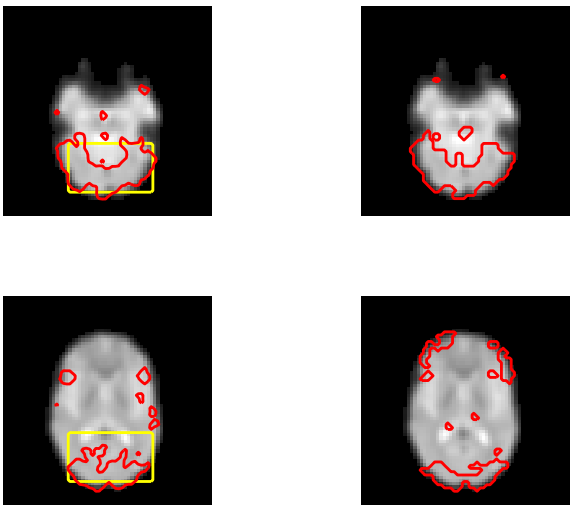

Fig. 2. Segmentation results obtained for the visual stimulation experiment. Left: Results of the proposed method shown in red and initialization shown in yellow. Right: Results of standard univariate GLM.

Figure 2 shows the results obtained for a visual stimulation experiment. It can be seen that the results of the proposed method are very consistent with the results obtained by the standard GLM technique. As expected, the visual cortex, as well as an extended network of visual processing regions, are identified. The main difference observed between the two methods is the extent of the activation in the frontal regions, which is larger for the standard technique.

Figure 3 shows the results obtained for the motor task experiment. Again, it can be seen that the results of the proposed method are very consistent with the results obtained by the standard GLM technique. Here, the left primary

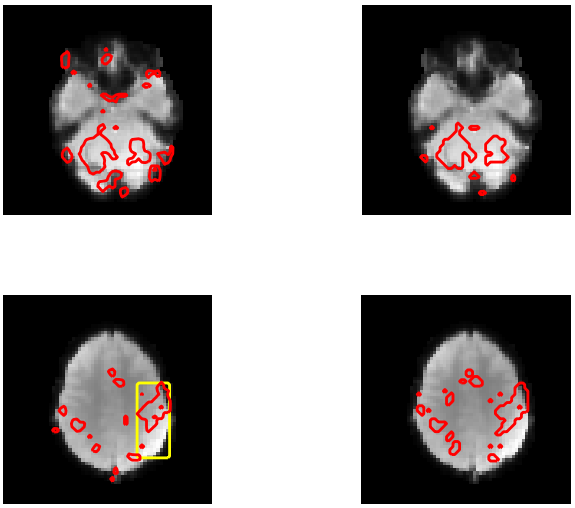

Fig. 3. Segmentation results obtained for the motor task experiment. Left: Results of the proposed method shown in red and initialization shown in yellow. Right: Results of standard univariate GLM.

motor cortex, as well as the right cerebellum, are identified, which correctly corresponds to the activity associated with the movement of the right hand.

IV. Conclusions

We proposed a method to jointly perform brain activation detection and segmentation of fMRI images. The method uses 3D region based level sets and performs a separate multivariate linear model (MLM) analysis in each region (activated and non-activated). Simulations using synthetic data produced very encouraging results, with a false positive rate of 6% and a false negative rate of 2%. We then compared our proposed technique with the standard univariate GLM approach, by using applying both to the analysis of two empirical fMRI datasets. The two methods exhibited similar performance, in terms of the localization of the detected activation areas.

The proposed multivariate method has the advantage that it does not require the definition of a significance threshold, which is implicit in the derivation of activation clusters based on univariate GLM approaches. On the other hand, the fact that a model underlies the identification of the activation brain areas avoids the interpretation limitations of non-parametric, multivariate techniques. However, one limitation of our model is the fact that it assumes that all voxels in the activated region exhibit the same level of activation (same parameter estimate β). Therefore, future work will focus on the development of a more general model accounting for different activation levels. Moreover, more comprehensive simulation studies and the application of the methods to a larger number of empirical datasets are required in order to establish the validity of the proposed methodology.

In summary, our encouraging preliminary results suggest that level sets may provide a useful parametric, multivariate tool for the automatic segmentation of brain activation regions in fMRI studies, particularly in situations where the subjective choice of significance thresholds should be avoided.

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