A TRUE SPATIOTEMPORAL APPROACH FOR ACTIVATION DETECTION IN FUNCTIONAL MRI

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ABSTRACT

A goal in functional Magnetic Resonance Imaging (fMRI) data analysis is determining whether a certain region of brain is activated by presented temporal stimuli. Since the fMRI data is a sequence of images, spatiotemporal models are needed and spatially and temporally correlated noise plays a crucial role in the models. Until very recently, most attention has focussed on temporally correlated but spatially independent models. And spatial correlation has been dealt with in an ad hoc fashion. We develop, for the first time, a properly formulated true spatiotemporal detection statistic based on a spatially and temporally correlated noise model. Additionally, we develop a theoretical performance analysis method for comparing different test statistics through Asymptotic Relative Efficiency (ARE) for the first time in fMRI. We perform simulations for the comparison of new test statistic with a standard statistic as well.

1. INTRODUCTION

Functional Magnetic Resonance Imaging is the technique to investigate functional activity in the human brain by means of Nuclear Magnetic Resonance (NMR). NMR can capture the change of blood flow as a result of the local neuronal activity in response to a given temporal stimulus resulting in digital image contrasts. This is due to the fact that the local change of oxygenation levels of hemoglobins makes the local change of magnetic properties in the brain. In a typical fMRI experiment, a subject in the MR scanner is provided with a pre-specified temporal stimulus which is a periodic "on-off" pattern. During the experiment, images of the brain can be obtained in rapid succession. For example, to stimulate the visual cortex, a flickering checkerboard image which is on for 10 seconds and off for 15 seconds is given to a subject. The fMRI data available for analysis is spatiotemporal - a sequence of three dimensional images. For a given time point, the data consists of multiple two dimensional slices of sections of brain taken at different axial coordinates. For a given voxel, the data is one dimensional time series with a sampling interval ranging from a few hundreds of milliseconds to several seconds. The observed data at each voxel is a superposition of Blood Oxygenation Level Dependent (BOLD) response $s_{t,v}$ and the brain noise $w_{t,v}$, where t represents time index and v means voxel index. The BOLD response $s_{t,v}$ can be thought of as a spatiotemporal response of human brain to a given temporal stimulus c_t. The brain noise $w_{t,v}$ is composed of hemodynamic fluctuations from unknown origin, possibly related to physiological background processes in the brain and cardiac fluctuation, and thermal noise from MR scanner. Therefore, the noise has spatial and temporal correlations. However, the dominant current approach to modeling uses a spatial independence assumption. We review details of that in section 2. Then, we introduce our new detector statistic based on a spatially and temporally correlated noise model in section 3. In section 4, newly developed theoretical performance analysis method is provided based on ARE. We perform simulations for a comparison of our new test with the standard T test in section 5.

2. MODELING UNDER SPATIAL INDEPENDENCE

A typical fMRI signal model is

$$y_{t,v} = m_v + b_v t + s_{t,v} + w_{t,v}, \tag{1}$$

where $t = 1, \ldots, T$, $v = 1, \ldots, M$, m_v is baseline, $b_v t$ means temporal drift, $s_{t,v}$ represents BOLD response and $w_{t,v}$ represents zero mean noise [1]. The drift term $b_v t$ is necessary to model the uncorrected motion artifacts and magnetic field inhomogeneity. The BOLD response $s_{t,v}$ is to model the brain response to given temporal stimuli in the experiment. In the parametric approach [2], BOLD response can be simply represented as $s_{t,v} = f_v (h * c)_t$ with the Hemodynamic Response Function (HRF) h_t and the activation magnitude f_v. For more flexible modeling of HR, FIR model has been used [3]. The noise $w_{t,v}$ has several sources which can be the MR scanner and physiological fluctuations. Thus noise has temporal and spatial correlations. To model the temporal aspect of the noise, an AR(1) process in white Gaussian noise has been used, which is equivalent to ARMA(1,1) noise [1]. Higher order models have also been used [4]. In the past, several approaches have been proposed to model h_t. The simplest approach is a fully specified h_t, based loosely on experimental studies, namely ; $h_t = k\, t^{8.6} exp(-t/0.546)$, where k

is the scaling factor to satisfy $\sum h_t^2 = 1$. FIR approach models the response as the output of a FIR filter of a given order excited by the stimulus input. However, typically a FIR filter with a high order is required [3].

For the modeling of f_v, [5] implicitly assumed spatial continuity and proposed a Gaussian Point Spread Function (PSF). A likelihood ratio test then leads [6] to a matched filter involving spatial smoothing. This is a reason that a spatial smoothing is being used in several softwares to analyze fMRI data. For example, Statistical Parametric Mapping (SPM) is a widely used package developed by the Wellcome Department of Imaging Neuroscience in University College London.

After spatial smoothing, the approach to time series decomposition at a fixed voxel called univariate analysis method is built up on the work of several researchers [7]. The assumption of a Gaussian PSF and univariate approach allow Random Field Theory (RFT) to be used to control FWE [5]. Although RFT is very complex, it gives an approximate threshold to create an activation map but sometimes shows more conservative results than Bonferroni correction in the case of t distributed field with low degrees of freedom [8]. In the above modeling of f_v, the Gaussian PSF implicitly suggests spatial continuity of the activation which is not supported by recent empirical work [9]. Besides that, the assumption of spatial white noise is not reasonable in practice.

Given these drawbacks of the previous approaches, we propose an empirically more satisfactory model considering temporal and spatial noise correlations without any specific assumption on spatial continuity of activation, i.e without a specific assumption on f_v.

3. MODELING WITH SPATIAL CORRELATION : NEW DETECTOR STATISTIC

For convenience, we ignore the drift term of (1) for a while. Thus, the model with pre-specified HRF is

$$y_{t,v} = s_{t,v} + w_{t,v} = f_v \xi_t + w_{t,v}, \tag{2}$$

where t = 1, …, T, v = 1, …, M, $\xi_t = (h * c)_t$ and $w_{t,v}$ is assumed spatiotemporally stationary Gaussian. The results from this simplest case (2) can be easily extended to two more general cases, one of which will be (1). The other extension is (1) with a FIR model of HRF. We gain considerable simplification by considering the temporal and spatial correlations of noise in the temporal frequency and spatial wave-number domains. After taking spatiotemporal DFTs in (2), we obtain following equivalent model in the DFT domains. $\tilde{\tilde{y}}_{k,l} = \tilde{f}_l \tilde{\xi}_k + \tilde{\tilde{w}}_{k,l}$, where $k = 1, \ldots, T$, $l = 1, \ldots, M$, $\tilde{f}_l$ stands for spatial DFT transformed f_v and $\tilde{\tilde{y}}_{k,l}$ represents spatiotemporal DFT transformed $y_{t,v}$. For large T and M, the DFT transformed noise $\tilde{\tilde{w}}_{k,l}$ obeys CLT [10].

$$\frac{1}{\sqrt{TM}} \cdot \tilde{\tilde{w}}_{k,l} \overset{i.d.}{\sim} N^c(0, F_{k,l}), \tag{3}$$

where N^c represents Complex Gaussian Distribution (CGD), *i.d.* means independently distributed and $F_{k,l}$ represents spatiotemporal Power Spectral Density (PSD). For simplicity, we assume **space-time separability** $F_{k,l} = F_k G_l$, where $F_k = F(\frac{2\pi k}{T})$ is discrete temporal PSD and $G_l = G(\frac{2\pi l}{M})$ is discrete spatial PSD.

We consider the hypotheses on the activation amplitudes f_v which are equivalent to following hypotheses in the temporal frequency and spatial wave-number domains.

$$H_{null} \quad : \quad \tilde{f}_l = 0 \qquad for\ all \quad l, \tag{4}$$

$$H_{alter} \quad : \quad \tilde{f}_l \neq 0 \qquad for\ some \quad l, \tag{5}$$

where $l = 1, \ldots, M$. The null hypothesis is that there are no activated voxels in Region of Interest (ROI). From the above equivalent hypotheses testing, with separability assumption and independent CGD in (3), we can develop the new detector statistic through General Likelihood Ratio Test (GLRT) in temporal frequency and spatial wave-number domains.

$$LRT = \frac{1}{TM} \sum_{l=1}^{M} \frac{1}{G_l} \cdot \left| \sum_{k=1}^{T} \frac{\tilde{\tilde{y}}_{k,l} \tilde{\xi}_k^*}{F_k} \right|^2 \cdot \left(\sum_{k=1}^{T} \frac{|\tilde{\xi}_k|^2}{F_k} \right)^{-1}, \tag{6}$$

where $\tilde{\tilde{y}}_{k,l}$ represents spatiotemporally DFT transformed $y_{t,v}$ and $\tilde{\xi}_k^*$ means the complex conjugate of $\tilde{\xi}_k$. From (6), we obtain an equivalent detector statistic for all voxels in the time and space domains through Parseval's theorem. This gives a voxel-wise statistic, $LRT = \sum_v LRT_v$,

$$LRT_v \quad = \quad \left(\frac{\sum_{t=1}^{T} (\xi_t^F)(y_{t,v}^F * K_v)}{\sqrt{\sum_{t=1}^{T} (\xi_t^F)^2}} \right)^2, \tag{7}$$

where e.g. $\xi_t^F = (g * \xi)_t$ and g_t is a causal whitening filter. g_t and K_v have the following relations with each PSD,

$$g_t \overset{DFT}{\longleftrightarrow} \tilde{g}_k, \qquad |\tilde{g}_k|^2 = \frac{1}{F_k}, \qquad K_v \overset{DFT}{\longleftrightarrow} \frac{1}{\sqrt{G_l}} \tag{8}$$

From (7), we can obtain important interpretations. In detail, our new test statistic shows what kind of temporal and spatial operations are needed to build up a proper detector statistic based on the spatiotemporal correlations. First, the temporal whitening of ξ_t and data $y_{t,v}$ are necessary. Second, the application of a spatial whitening kernel to temporally filtered data is needed. Third the cross correlation of spatiotemporally whitened data and temporally whitened ξ_t is required. Finally, normalization and square of normalized statistic are needed. Note that the detector is based on reducing $y_{t,v}$ to spatial and temporal white noise. Here, the idea of temporal whitening filter was suggested by several researchers in the univariate approach [8]. However, the idea of spatial whitening kernel is new. Besides that, we can easily show that spatial kernel K_v can have negative weights for a simple spatial AutoCorrelation Function (ACF). By computing (7) and thresholding using a pre-determined threshold over all voxels within

ROI, we create an activation map. Under the null hypothesis, if F_k and G_l are known, we find :

1. $(y_{t,v}^F * K_v)$ is spatially and temporally white noise and follows standard normal distribution $N(0,1)$.

2. The test statistics at different voxel locations are independent, i.e. $LRT_p \overset{ind}{\sim} LRT_q$ for all $p \neq q$.

3. Test statistic $LRT_v \sim \chi_1^2$.

Since there are many voxels in the collected data, controlling overall error rate is a multiple comparison problem. One of the widely used measures is Family-Wise Error (FWE) rate which has following definition and equivalent representations under the null hypothesis.

$$\mathit{FWE} = \mathit{Pr}\left(\bigcup_{v=1}^{M}\{LRT_v > \gamma\}\right) = \mathit{Pr}\left(\max_v LRT_v > \gamma\right), \tag{9}$$

where *FWE* is assigned to a pre-specified significant level α, typically α is set to 0.05 and γ is threshold to be determined. Since the exact distribution of our new test statistic LRT_v is known and LRT_v is spatially uncorrelated, we can determine the threshold γ analytically. We can obtain following theoretical threshold for a level α and number of voxels M.

$$\gamma(\alpha) = \Psi(\chi_1^2)^{-1}\left(\sqrt[M]{1-\alpha}\right), \tag{10}$$

where $\Psi(\chi_1^2)(t)$ is Cumulative Density Function (CDF) of χ_1^2. We assumed that F_k and G_l are known in this paper. In practice, however, these are needed estimated based on collected data. Estimations of F_k and G_l will be covered elsewhere.

In comparison with existing methods, our test statistic includes a spatial kernel determined by the spatial correlation. This is totally different from the ad hoc approach of spatial smoothing with a Gaussian amplitude kernel. In fact, our spatial kernel K_v is more like spatial differentiator, not smoother.

4. ASYMPTOTIC RELATIVE EFFICIENCY

To compare the performance of our new test statistic LRT_v with the standard T test statistic based on voxel time series in the univariate analysis method, we use Asymptotic Relative Efficiency (ARE), which is a standard method for comparing competing test statistics [11]. ARE compares two tests by measuring the relative sample sizes needed to achieve the same power given the same significant level. This application of ARE is novel in fMRI. Specifically, to test two different tests, Pitman's ARE is used with the assumption of fixed Signal to Noise Ratio (SNR) which is a reasonable in practice. From model (2), SNR has the following form, $\mathit{SNR} = (f_v/\sigma_v)\sqrt{\sum_{t=1}^{T}(\xi_t^F)^2}$, where σ_v^2 represents the variance of noise. For a fixed SNR, ξ_t and σ_v, f_v is shrinking toward 0 as T increases. By plugging (2) into (7), we obtain the following expression for our test statistic which has a non-central χ_1^2 under the alternative hypothesis.

$$LRT_v = \left((K * f)_v \cdot \sqrt{\sum_{t=1}^{T}(\xi_t^F)^2} + N(0,1)\right)^2 \tag{11}$$

where K_v is spatially whitening kernel. Applying General Linear Model (GLM) to (2) gives the standard T test statistic,

$$T_v = \frac{\sum_{t=1}^{T}(\xi_t^F)(y_{t,v} * K_v^G)^F}{\widehat{\sigma_v^S} \cdot \sqrt{\sum_{t=1}^{T}(\xi_t^F)^2}}, \tag{12}$$

where $\xi_t^F = (g * \xi)_t$ is temporally whitened ξ_t, K_v^G means a Gaussian amplitude kernel and σ_v^S represents the standard deviation of noise spatially smoothed by K_v^G. By plugging (2) into (12), we obtain the following form which follows a non-central t_{T-1} under the alternative hypothesis.

$$T_v = t_{T-1}\left(\frac{(K^G * f)_v \cdot \sqrt{\sum_{t=1}^{T}(\xi_t^F)^2}}{\sigma_v^S}\right), \tag{13}$$

where the term inside the parenthesis means non-centrality parameter. Based on (11) and (13), it can be shown following the procedure in [11] that Pitman's AREs $e(T_v, L_v)$, where $L_v = \sqrt{LRT_v}$, have the following forms under the assumption of voxel-wise activation and known σ_v,

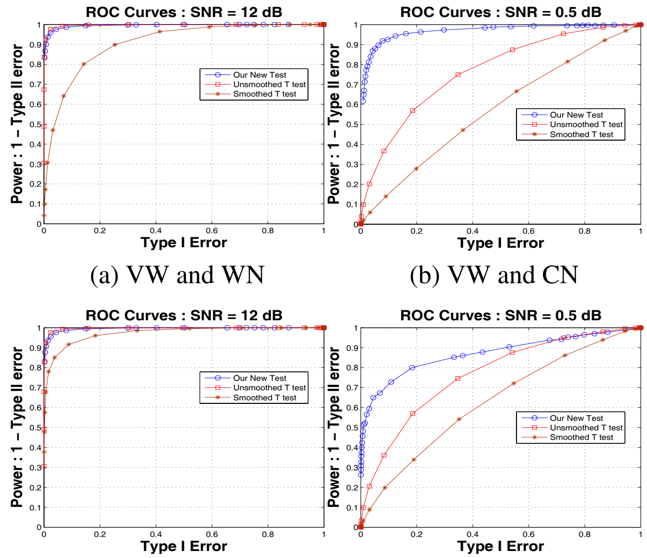
$$e(T_v, L_v) = \left(\frac{K_0^G}{\sigma_v K_0}\right)^2 \frac{1}{V_G}, \tag{14}$$

where $V_G = Var(K_v^G * w_{t,v})/\sigma_v^2$. Based on the setup of the simulations given in section 5, the following evaluations can be shown. In the case of spatially white noise with $\sigma = 1$, we can obtain $e(T_v, L_v) = 0.2824$. In the case of spatially colored noise with a known Gaussian ACF, namely $\gamma_v = exp(-v^2/2.254)$, we can obtain $e(T_v, L_v) = 0.0181$. In the case of spatially white noise and two dimensional slices, the interpretation of (14) is that asymptotically the standard T_v test requires about $3.5 (= 1/0.2824)$ times as many samples as does the new test LRT_v. In the case of spatially colored noise, T_v test requires about $55 (= 1/0.0181)$ times as many samples as does the new test LRT_v. These values of $e(T_v, L_v)$ support the results of simulations performed under several conditions in Figure 1.

5. SIMULATION RESULTS

A simulation study was carried out to compare the two test statistics. We use well known Receiver Operating Characteristic (ROC) curves as the performance measure. To specify the real activation amplitude, voxel-wise activation and random shaped region activation with fixed amplitude are used.

The real random shape activation maps are generated from two dimensional colored noise. To specify the spatial structure of noise, both spatially white noise and spatially colored noise with a known Gaussian ACF are used. Since temporal whitening is standard in the univariate approach, we assume the noise is temporally white for simplicity. Two dimensional slices are considered for convenience. 100 time points and 64×64 voxels are used. A pre-specified HRF and spatiotemporally stationary Gaussian noise are used. The width of Gaussian amplitude kernels for spatial smoothing are determined as 2.5 times of voxel size as recommended in SPM. The threshold for our test statistic is determined by (10) and the threshold for T statistic is determined by the RFT based on the above settings. In Figure 1, the new test shows better performance than T test for all cases and the new statistic is much better for spatially colored noise case. These are matched to ARE in section 4. In each graph, the results of T statistic without spatial smoothing are provided as well. Note that, since the sufficient smoothness is not guaranteed without spatial smoothing, we can not control FWE rate with unsmoothed T test statistic.



(a) VW and WN (b) VW and CN

(c) RS and WN (d) RS and CN

Fig. 1. ROC curves of new test statistic and T test statistic with and without spatial smoothing using Gaussian amplitude kernel under the assumptions of Voxel-Wise (VW) and Random Shape (RS) activations with spatially White (WN) and Colored Noise (CN).

6. CONCLUSION

We have built up a new detector statistic considering temporal and spatial correlations of background noise without any specific spatial assumption on the real activation amplitude. Using our new test statistic, we controlled FWE exactly and obtained higher power, which was verified by the analytical (ARE) and empirical (ROC) comparisons. This idea of considering the spatial information of noise for building up a detector statistic gave us insights and advantages. In future work, we will develop techniques for estimating F_k and G_l as well as for testing for space-time separability.

7. REFERENCES

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