A TRUE SPATIO-TEMPORAL TEST STATISTIC FOR ACTIVATION DETECTION IN FMRI BY PARAMETRIC CEPSTRUM

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ABSTRACT

A main purpose of data analysis in functional Magnetic Resonance Imaging (fMRI) is to determine which regions of the brain are activated by pre-specified temporal stimuli. In recent work, under the assumption of known spectra, we developed a detection statistic based on a spatially and temporally correlated noise model. In this paper, we implement the developed test statistic, which includes spatial and temporal whitening operators. For the estimation of spatial and temporal correlations, we use the parametric cepstral modeling, which allows dramatic reduction of computation in the model fitting and very simple methods to obtain spatiotemporal whitening operators. Model comparison and selection are discussed as well. We apply the developed techniques to a human dataset.

***Index Terms*—** Detection statistic, spatial and temporal correlations, and parametric cepstral modeling.

1. INTRODUCTION

Functional Magnetic Resonance Imaging (fMRI) uses Nuclear Magnetic Resonance (NMR) to investigate functional activities of human brain. Due to the difference of magnetic susceptibilities of hemoglobins with different oxygenation levels, the local change of oxygenation level in brain causes the regional change of the MR decay parameter T_2^*, leading to the change in the intensity of image. During a typical fMRI experiment, a pre-specified temporal stimulus which is a periodic pulse is given to a subject in the MR scanner. While the subject reacts to the stimulus, the scanner can capture images reflecting changes in the subject's brain in rapid succession, typically every second.

The observed fMRI signal can be represented as the superposition of the Blood Oxygenation Level Dependent (BOLD) response $s_{t,v}$ and the brain noise $w_{t,v}$, where t represents time and v means voxel position. The BOLD response $s_{t,v}$ can be thought of as a spatiotemporal response of subject's brain to a given temporal stimulus c_t. The brain noise $w_{t,v}$ consists of two factors, one of which is the hemodynamic fluctuation from unknown origins, possibly related to physiological background processes in the brain and cardiac fluctuations. The other is the thermal noise from an MR scanner. Thus, $w_{t,v}$ is spatially and temporally correlated. There may be other sources of spatial correlation. For example, techniques to reduce motion artifacts and to reconstruct images in discrete k-space can induce spatial correlation.

In the dominant current approach to construct an activation map, however, the spatial dependence has not been fully considered [1]. An activation map is just a spatial plot of a detection statistic. In our recent work [2], under the assumption of known spectra, we developed a detection statistic based on a spatially and temporally correlated noise model. In practice, since spatial and temporal correlations need to be estimated, its implementation requires non-trivial statistical model estimation. In this paper, we propose a method which is unusual and based on a truncated cepstrum expansion for the modeling of noise structure. In addition, adjustment terms to reflect the difference between estimates of spatiotemporal spectra under different hypotheses are added to the developed statistic for a more practically satisfactory detection statistic. Model comparisons to determine the order of the proposed model and to compare it with an existing model are discussed as well.

2. SIGNAL MODELING AND DETECTION

An observed fMRI signal model which is widely used has the following linear form [3]. For t = 1, …, T, v = 1, …, M, ignoring baseline and temporal drift,

$$y_{t,v} = s_{t,v} + w_{t,v} = \xi_t^T f_v + w_{t,v}, \tag{1}$$

$$\xi_t \triangleq [\xi_{1,t}, \ldots, \xi_{L,t}]^T, \quad f_v \triangleq [f_{1,v}, \ldots, f_{L,v}]^T,$$

where $s_{t,v}$ is the BOLD response and $w_{t,v}$ denotes zero mean spatiotemporally stationary Gaussian random field. The BOLD response $s_{t,v}$ models the brain reaction to a given temporal stimulus c_t in the experiment. In (1), the BOLD response is described as

$$s_{t,v} = \left(\sum_{i=1}^{L} h_{i,t} f_{i,v} \right) * c_t \triangleq \sum_{i=1}^{L} \xi_{i,t} f_{i,v}, \tag{2}$$

where L is the number of basis functions to represent $s_{t,v}$, $h_{i,t}$ is the i-th basis function, and $f_{i,v}$ is the associated activation amplitude. Note that (2) is a generalized representation which covers various modelings of $s_{t,v}$ such as parametric modeling with the canonical Hemodynamic Response Function (HRF) [4], FIR approach [5], and Laguerre modeling [6]. The uncorrected motion artifacts and magnetic field inhomogeneity are modeled in the baseline and temporal drift. In section 5, these two terms will be removed by Ordinary Least Square (OLS) before applying the suggested techniques.

2.1. Classical Detection Statistic : GLM

The General Linear Model (GLM) used in Statistical Parametric Mapping (SPM) has a different model from (1) ;

$$y_{t,v} = s_{t,v} + \eta_{t,v} = \xi_t^T f_v + \eta_{t,v}, \tag{3}$$

where $\eta_{t,v}$ is a zero mean Gaussian noise which is spatially non-stationary, independent and temporally stationary. To be specific, it has spatially varying variance σ_v^2 and its temporal characteristic is modeled as AR(1) process with a common coefficient φ. SPM contains spatial smoothing by Gaussian amplitude kernel K_v^G and temporal filtering by ϕ_t. After spatial smoothing and temporal filtering are performed, for each voxel time course, F-statistic is built up from OLS.

2.2. New Detection Statistic : ST-LRT with Adjustment

Assuming the space-time separability, we developed a new detection statistic through Likelihood Ratio Test (LRT) in spatiotemporal DFT domain with the full consideration of spatial and temporal correlations [2]. For simplicity, we used the parametric approach for the modeling of $s_{t,v}$ (thus, $L = 1$ in (1)) and assumed spatial and temporal spectra are known. The **space-time separability** is defined as $F_{k,l} = F_k G_l$, where $F_{k,l}$ is discrete spatiotemporal Power Spectral Density (PSD), F_k means pure temporal PSD, and G_l represents pure spatial PSD. k is an index for temporal frequency and l is an index for spatial wave-number.

In practice, since the estimation of spatial and temporal spectra is needed, LRT has extra terms which induce adjustment terms in the originally proposed detection statistic in [2]. To develop an activation map, we consider the hypotheses,

$$H_0 \quad : \quad f_v = 0 \qquad for\ all \quad v, \tag{4}$$

$$H_1 \quad : \quad f_v \neq 0 \qquad for\ some \quad v. \tag{5}$$

By the same idea as in section 3 of [2], it can be shown that the spatial decomposition of LRT ($= \sum_v LRT_v$) allows the following Spatio-Temporal LRT (ST-LRT) in two pieces ; a noise piece and a signal piece,

$$LRT_v \triangleq LRT_v^N + LRT_v^S, \tag{6}$$

where LRT_v^N reflects the difference between estimates of spatiotemporal spectra under H_0 and H_1. Note that, if we know true spatial and temporal spectra, LRT_v^N term vanishes, leading to $LRT_v = LRT_v^S$ which is the same as in [2]. Here, with noticing an identity, $TM\theta_{0,0} = \sum_{k,l} \log F_k G_l$, one has

$$LRT_v^N \triangleq T \cdot \left(\widehat{\theta}_{0,0,0} - \widehat{\theta}_{1,0,0}\right) + \sum_{t=1}^{T} \left(\varepsilon_{0,t,v}^2 - \varepsilon_{1,t,v}^2\right), \tag{7}$$

$$LRT_v^S \triangleq \left(\sum_{t=1}^{T} \varepsilon_{1,t,v} \xi_t^{F\,T}\right) \left(\sum_{t=1}^{T} \xi_t^F \xi_t^{F\,T}\right)^{-1} \left(\sum_{t=1}^{T} \varepsilon_{1,t,v} \xi_t^F\right), \tag{8}$$

where, under H_j for $j = 0$ and 1, $\widehat{\theta}_{j,0,0}$ is the value of the estimated cepstrum evaluated at $(t, v) = (0, 0)$ and $\varepsilon_{j,t,v}$ are spatiotemporally whitened $y_{t,v}$. To be more specific, $\varepsilon_{j,t,v} \triangleq K_{j,v} \circledast_s (g_{j,t} \circledast y_{t,v})$, where $\circledast$ and $\circledast_s$ mean temporal and spatial circular convolution, respectively. ξ_t^F is temporally whitened ξ_t defined as $\xi_t^F \triangleq (g_{1,t} \circledast \xi_t)$ under only H_1. Under H_j, $g_{j,t}$ is a causal temporal whitening filter and $K_{j,v}$ is a spatial whitening kernel, which are given by,

$$g_{j,t} \overset{DFT}{\longleftrightarrow} \tilde{g}_{j,k}, \quad |\tilde{g}_{j,k}|^2 = \frac{1}{\widehat{F}_{j,k}}, \quad K_{j,v} \overset{DFT}{\longleftrightarrow} \frac{1}{\sqrt{\widehat{G}_{j,l}}}. \tag{9}$$

Unlike the ad hoc spatial smoothing of the classical approach, note that K_v has the relation inherently to spatial correlation and it is rather more like a spatial differentiator.

3. IMPLEMENTATION OF ST-LRT

In practice, each PSD should be estimated from a given data. Under Gaussian stationarity, a widely used method is AR-based parametric spectral estimation. Since the Fundamental Theorem of Algebra does not hold in multi dimensions (e.g., $2D$ or $3D$), the asymptotic likelihood equation to fit multi-dimensional AR or ARMA model can not be solved linearly as in one dimension. As a matter of fact, even the existence of purely spatial ($2D$) solution is not guaranteed. [7] suggested the parametric cepstrum to solve this problem. The model by parametric cepstrum allows dramatic reduction of computation in the fitting process with only FFTs and an easy description of hypothesis such as space-time separability. Here, we extend the purely spatial setup in [7] to the current spatiotemporal situation which requires temporal causality and suggest a way to obtain necessary whitening operators from estimated cepstrums. In addition to that, model comparison techniques are suggested with Akaike Information Criterion (AIC).

3.1. Parametric Cepstrum

In three dimensions, one is for time and two are for space (namely, $v \triangleq (r, s)$), the parametric cesptrum can be obtained by windowing cepstral coefficients θ_{trs},

$$\begin{aligned} \widetilde{F}_{kl_1l_2} &\triangleq \widetilde{F}(\omega_k, \lambda_{l_1}, \lambda_{l_2}) = \log F(\omega_k, \lambda_{l_1}, \lambda_{l_2}) \\ &= \sum_{t=-n}^{n} \sum_{r=-p}^{p} \sum_{s=-q}^{q} \theta_{trs} e^{-j\left(\omega_k t + \lambda_{l_1} r + \lambda_{l_2} s\right)}, \end{aligned} \tag{10}$$

at each frequency of $\omega_k = 2\pi k/T$, $\lambda_{l_1} = 2\pi l_1/M_1$, and $\lambda_{l_2} = 2\pi l_2/M_2$. Here, M_1 and M_2 mean the number of voxels along r-axis and s-axis, respectively. n represents the temporal order and (p,q) means the spatial orders. The space-time separability has the following linear condition in cepstral domain : for $\forall(t,r,s) \neq (0,0,0)$,

$$\theta_{trs} = \theta_{t00}\delta_{0rs} + \theta_{0rs}\delta_{t00}, \tag{11}$$

which means only θ_{trs}s on the central rs-plane located at $t = 0$ and along the temporal axis have non-zero values. The symmetry of cepstrum ($\theta_{t,v} = \theta_{-t,-v}$ for $\forall(t,v)$) allows a simple expression of (10), an inner product of two vectors as shown in (19). Under the space-time separability in (11), there are $R(\triangleq 2pq+p+q+n+1)$ cepstral coefficients to be estimated.

Under H_j for $j = 0,1$, after the estimation of cepstral coefficients is performed, it can be shown that the following relations are equivalent to (9),

$$K_{j,v} \overset{CT}{\longleftrightarrow} -\frac{1}{2}\widehat{\theta}_{j,0,v}, \qquad g_{j,t} \overset{CT}{\longleftrightarrow} \left(-\widehat{\theta}_{j,t,0}\right)^+, \tag{12}$$

where CT denotes cepstral transformation and $(\widehat{\theta}_{j,t,v})^+$ is the causal part of $\widehat{\theta}_{j,t,v}$ in cepstral domain. The causality of $\widehat{\theta}_{j,t,0}$ is required due to that of $g_{j,t}$. Thus, after estimating cepstral coefficients, we can easily obtain two whitening operators by simple algebra and FFTs under each hypothesis.

3.2. Noise Model Fitting with MLE

For three-dimensional stationary random field w_{trs} with zero mean, the periodogram is defined by $I_{kl_1l_2} \triangleq \frac{|\tilde{w}_{kl_1l_2}|^2}{TM_1M_2}$, where $\tilde{w}_{kl_1l_2}$ is the DFT of w_{trs}. By CLT, assuming all cumulants and sum of joint cumulants are bounded [8], we have the well-known asymptotic distribution, for $\forall(k,l_1,l_2) \in \Omega_h \triangleq \cup_{i=1}^3 \Omega_i$,

$$\frac{I_{kl_1l_2}}{F_{kl_1l_2}} \sim \frac{\chi_2^2}{2}, \tag{13}$$

where Ω_h denotes the half of the whole region Ω_f and Ω_h excludes the origin. Here, periodograms at different ordinates are asymptotically independent and χ_2^2 denotes chi-square distribution with two degrees of freedom. Ω_f and Ω_i have the following index regions,

$$\Omega_f = \{|k| \le k^m, |l_1| \le l_1^m, |l_2| \le l_2^m\}, \tag{14}$$
$$\Omega_1 = \{1 \le k \le k^m, -l_1^m \le l_1 \le l_1^m, -l_2^m \le l_2 \le l_2^m\}, \tag{15}$$
$$\Omega_2 = \{k = 0, 1 \le l_1 \le l_1^m, -l_2^m \le l_2 \le l_2^m\}, \tag{16}$$
$$\Omega_3 = \{k = 0, l_1 = 0, 1 \le l_2 \le l_2^m\}, \tag{17}$$

where, if T, M_1, and M_2 are all odd, $k^m = (T-1)/2$, $l_1^m = (M_1-1)/2$ and $l_2^m = (M_2-1)/2$. Note that $I_{k,l_1,l_2} = I_{k+T,l_1+M_1,l_2+M_2}$ and $F_{k,l_1,l_2} = F_{k+T,l_1+M_1,l_2+M_2}$ for any integer k, l_1 and l_2. Taking the logarithm of (13) allows

$$Y_{kl_1l_2} \triangleq \log I_{kl_1l_2} - \psi(1) = \log F_{kl_1l_2} + \epsilon_{kl_1l_2}, \tag{18}$$

where $\epsilon_{kl_1l_2}$ is an independent and identical extreme value distribution with zero mean and $\psi'(1) = 1.6449$ variance. $\psi(1) = -0.5772$ is called Euler Constant. Under the space-time separability, plugging (10) into (18) allows a classical linear regression equation,

$$Y_{kl_1l_2} = x_{kl_1l_2}^T\theta + \epsilon_{kl_1l_2}, \tag{19}$$

where $x_{kl_1l_2}^T$ is a row vector representing lexicographically ordered cosine terms in (10) and θ contains associated θ_{trs} terms. For specific expressions of these two vectors, see [7]. Note that sine terms are canceled out due to the symmetry of $\theta_{t,v}$. Although Least Square Estimate (LSE) of θ is not efficient in this case, it is unbiased and can be easily computed with a simple bias correction term in model fitting [7].

Then, to obtain Maximum Likelihood Estimate (MLE) of θ, this LSE is used as an initial value in an iterative method based on Whittle's asymptotic log-likelihood equation and scoring algorithm, in which cepstrum allows a simple form. Details of model fitting are discussed in section III of [9].

4. MODEL SELECTION AND COMPARISON

Using AIC, we can not only compare models with different structures such as ST-LRT model and GLM but also models with the same structure to determine a proper order. First, a model selection for ST-LRT is considered in this section. Then, we move our discussion to the model comparison.

To select a proper model order for ST-LRT, i.e., to determine (L,n,p,q), a four-dimensional search is necessary. By CLT in DFT domain [2], we obtain the following AIC and the minimization of $J_{R,L}(\triangleq\text{AIC})$ gives (L,n,p,q).

$$J_{R,L} = \sum_{k,l} \log \widehat{F}_{1,k,l} + \frac{\left|\tilde{y}_{k,l} - \tilde{\xi}_k^T \widehat{\tilde{f}}_l\right|^2}{TM \cdot \widehat{F}_{1,k,l}} + 2(R+L), \tag{20}$$

where all estimates are MLEs and R is the number of cepstral coefficients. Here, with Parseval's relation, the spatial decomposition of $J_{R,L}$ allows the following AIC map for ST-LRT model :

$$AIC_v^{LRT} = T\cdot\widehat{\theta}_{1,0,0} + \sum_t \left(K_{1,v} \circledast_s g_{1,t} \circledast e_{t,v}\right)^2 + \frac{2(R+L)}{M}, \tag{21}$$

where $e_{t,v} \triangleq y_{t,v} - \xi_t^T \widehat{f}_v$ is residual and $\widehat{\theta}_{1,0,0}$ is the value of estimated cepstrum at the origin under H_1.

The spatial stationarity is assumed for the comparison of ST-LRT model and GLM. After spatial smoothing and temporal filtering are performed in (3), we obtain the equation : $\bar{y}_{t,v} = \bar{\xi}_t^T \bar{f}_v + \bar{\eta}_{t,v}$, where, e.g., $\bar{y}_{t,v} \triangleq \phi_t * (K_v^G *_s y_{t,v})$, K_v^G is a Gaussian amplitude kernel and ϕ_t is a temporal filter. For OLS, one minimizes the following function J to find $\widehat{\bar{f}}_v$:

$$J = \sum_{t,v} \left(\bar{y}_{t,v} - \bar{\xi}_t^T \bar{f}_v\right)^2 = \sum_{k,l} \frac{\left|\tilde{y}_{k,l} - \tilde{\xi}_k^T \tilde{f}_l\right|^2 \left|\tilde{\phi}_k\right|^2 \left|\tilde{K}_l^G\right|^2}{T \cdot M}, \tag{22}$$

where $\tilde{\phi}_k$ and $\tilde{K}_l^G$ are the DFTs of ϕ_t and K_v^G. Note that linear convolution is approximated by circular one with zero padding. If we compare this with $J_{R,L}$, the simplest interpretation of $\tilde{\phi}_k$ and $\tilde{K}_l^G$ is that they are whitening operators. Thus, $|\tilde{\phi}_k|^2$ and $|\tilde{K}_l^G|^2$ take the place of $1/\widehat{F}_{1,k,l}$ in (20). If ϕ_t is a temporal whitening filter, following the same idea to obtain (21) from $J_{R,L}$, we arrive at an AIC map for GLM,

$$AIC_v^{GLM} = \sum_k \log \widehat{\bar{F}}_k - 2T \cdot \theta_0^G + \sum_t \bar{e}_{t,v}^2 + \frac{2(n_p + L)}{M}, \quad (23)$$

where θ_0^G is the value of the cepstrum of K_v^G at the origin and $\bar{e}_{t,v} \triangleq \bar{y}_{t,v} - \xi_t^T \widehat{\bar{f}}_v$. For AR(1) fitting of $\bar{\eta}_{t,v}$, we have the number of parameters $n_p = 2$ and $\bar{F}_k = \frac{\bar{\sigma}^2}{|1-\varphi e^{-j\omega_k}|^2}$, where $\bar{\sigma}^2 = var(\bar{\eta}_{t,v})$ and φ is a common AR(1) coefficient.

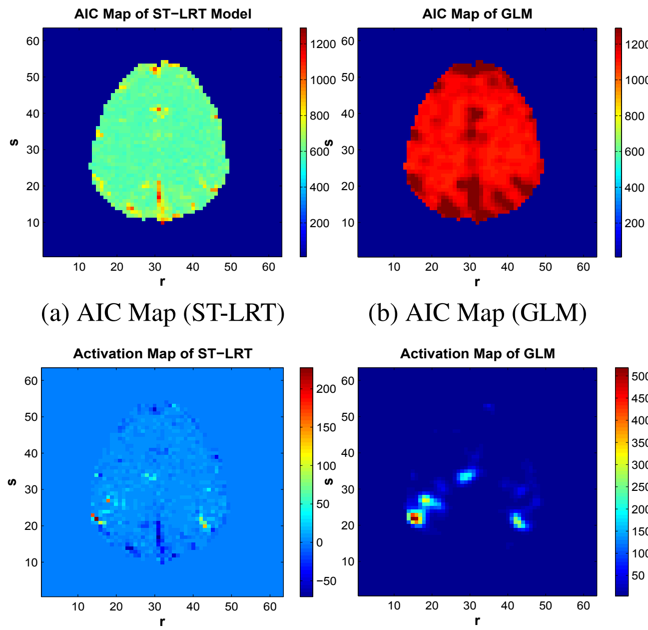
5. APPLICATION TO A REAL DATA

We apply the developed ST-LRT to a real dataset from AFNI homepage (http://afni.nimh.nih.gov/afni/). A human subject performs right-hand sequential finger-thumb opposition in the presence of a given motor stimulus. The experiment is done under 3T MRI scanner and TR is 2 secs. For simplicity, we consider a two-dimensional axial slice where motor responses are expected. $T = 99$, $M = 63^2$, and voxels have the size of $3.125 \times 3.125 \times 5mm^3$. A spatial mask to remove signals from the outside of brain and a spatiotemporal taper (Tukey-Hanning window) to reduce the edge effect are applied to the original data on the motor slice.

AIC maps and unthresholded activation maps associated with the motor responses are given on Fig.1. For ST-LRT, Laguerre functions whose orders are up to 3 are used in the modeling of $s_{t,v}$. For discussions about thresholding of ST-LRT with a given significance level, refer to the companion paper of [9]. For GLM, the FWHM of Gaussian amplitude kernel is set as 2.5 times of the voxel size. On AIC maps, AIC values for ST-LRT model are substantially lower than those for GLM, indicating ST-LRT model is on average closer to the unknown underlying true model than GLM. Activation map from ST-LRT shows sharper or more well-defined activated regions than that from GLM in the whole brain. In addition, in the right hemisphere, the new ST-LRT provides a stronger spot than does GLM, suggesting activation. It turns out that a model by BIC shows the similar results to those by AIC.

6. CONCLUSION

With the parametric cepstrum, we implemented the recently developed ST-LRT. The estimation of spatial and temporal spectra induced adjustment terms in the original ST-LRT. The parametric cepstrum allowed dramatic reduction of computation in the model fitting. A method for model comparison and model order selection was suggested using AIC. The obtained activation map from ST-LRT showed well-defined activation regions. The AIC map indicated that ST-LRT model was on average closer to the underlying truth than GLM.



(a) AIC Map (ST-LRT) (b) AIC Map (GLM)

(c) Activation Map (ST-LRT) (d) Activation Map (GLM)

Fig. 1. AIC Maps and Activation Maps.

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