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Detecting Brain Activations in Functional Magnetic Resonance Imaging (fMRI) Experiments with a Maximum Cross-Correlation Statistic

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Abstract: Various statistical models have been proposed to analyze fMRI data. The usual goal is to make inferences about the effects that are related to an external stimulus. The primary focus of this paper is on those statistical methods that enable one to detect 'significantly activated' regions of the brain due to event-related stimuli. Most of these methods share a common property, requiring estimation of the hemodynamic response function (HRF) as part of the deterministic component of the statistical model.

We propose and investigate a new approach that does not require HRF fits to detect 'activated' voxels. We argue that the method not only avoids fitting a specific HRF, but still takes into account that the unknown response is delayed and smeared in time. This method also adapts to differential responses of the BOLD response across different brain regions and experimental sessions. The maximum cross-correlation between the kernel-smoothed stimulus sequence and shifted (lagged) values of the observed response is the proposed test statistic.

Using our recommended approach we show through realistic simulations and with real data that we obtain better sensitivity than simple correlation methods using default values of SPM2. The simulation experiment incorporates different HRFs empirically determined from real data. The noise models are also different AR(3) fits and fractional Gaussians estimated from real data. We conclude that our proposed method is more powerful than simple correlation procedures, because of its robustness to variation in the HRF.

Key words: HRF, kernel, nonparametric.

1. Introduction

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Magnetic resonance imaging represents a major technological breakthrough. Unlike other medical imaging technologies that involve injecting radioactive elements into the body (e.g., PET and SPECT), MRI is non-invasive and uses the body's natural magnetic properties to produce images of any part of the body. The MRI scanner measures an intensity of a signal from resonating hydrogen atoms, as detected by receiver coils that are placed around the body. The measure used to 'quantify brain activity' is called blood oxygenation level dependent (BOLD) response.

Metabolic changes in the brain require energy that is mainly a result of oxidative metabolism. Hence, when a brain region is active, oxygen consumption increases and local oxygen demand increases. To meet this increased oxygen demand, neuronal activation is accompanied by increased local blood flow. However, not all oxygen delivered to the active area of the brain is utilized. This leads to local changes in the relative concentrations of oxyhemoglobin and deoxyhemoglobin in addition to the change in local cerebral blood flow (CBF). Hemoglobin has different magnetic properties when bound to or detached from oxygen. fMRI uses this differential magnetic susceptibility of hemoglobin to produce contrast images of the brain. The observed image intensity is proportional to the ratio of oxygenated to deoxygenated hemoglobin in the brain. Higher BOLD signal intensities arise from an increase in the concentration of oxygenated hemoglobin. In other words, increases in CBF that produce an increase in oxyhemoglobin lead to increased BOLD signal.

Functional magnetic resonance imaging designs are broadly classified as event-related or block designs based on how the stimuli are presented to subjects in an fMRI scanner and effects of interest are modeled. In event-related designs, stimuli of possibly different types are intermixed and are presented individually for short durations. Block designs on the other hand present stimuli of the same type in blocks of closely spaced repetitive stimuli, separated by periods of no stimulus or baseline condition. For block designs, effects are usually modeled with some form of boxcar regressor convolved with a hemodynamic response function (HRF). For event-related designs, effects of interest are typically modeled by convolving each stimulus onset (dyadic functions) with an HRF. The methods discussed here are mainly for event-related designs but can be readily adapted to block designs.

There are various statistical approaches for analyzing fMRI data. For an excellent survey see Lindquist (2008). One goal is to make inferences about the effects that are related to an applied external stimulus. The primary focus of this paper is on those statistical methods that enable one to detect 'significantly activated' regions of the brain due to external event-related stimuli. Most of these methods share a common property, requiring estimation of the HRF as part of the deterministic component of the statistical model. A very popular technique for

these analyses is known as a statistical parametric map (SPM). See Friston *et al.* (1995) and Bullmore *et al.* (1996). Because estimating the HRF is at the heart of these methods, a review of mathematical models used for the HRF is covered in Section 2. This is followed by a review of the commonly applied statistical methods for assessing the relationship between the observed BOLD responses and the external stimuli. In Section 4 we present our method for detecting activation without using an HRF. The results of a simulation experiment are summarized in Section 5.

2. Hemodynamic Response Function

The hemodynamic response function models the brain's response to an impulse input. The shape of the HRF is generally characterized by a delay of four to six seconds from the onset of the stimulus until it rises to a peak or plateaus. If the stimulation is not sustained, it then drops back to baseline with a slight undershoot (Buxton and Wong, 1998). In some experiments, the BOLD signal may immediately drop after stimulation for a brief period of approximately 0.5-1 second. This is called an initial undershoot. Discussion of physiological relationships and features of the HRF can be found in Jezzard, Mathews and Smith (2004, Chapter 8).

Lange and Zeger (1997) used a simple gamma function to model the HRF but this model does not capture the small undershoot after the HRF has returned to baseline. A widely used HRF model that accounts for this undershoot is a difference of two gamma functions as proposed by Friston *et al.* (1998). The model is given by

$$h(t) = c_1 \left(\left(\frac{t}{d_1} \right)^{a_1} \exp\left(\frac{-t - d_1}{b_1} \right) - c_2 \left(\frac{t}{d_2} \right)^{a_2} \exp\left(\frac{-t - d_2}{b_2} \right) \right),$$

where $d_j = a_j b_j$ is the time to peak. For auditory stimulus, Glover (1999) gave estimates of the parameters as $a_1 = 6$, $a_2 = 12$, $b_1 = b_2 = 0.9s$, and $c = 0.35$. The above model does not account for the post-stimulus initial drop of the HRF. When the design paradigm consists of multiple episodes of the same stimulus the HRF is assumed to be a linear convolution given by,

$$y(t) = \int_0^\infty h(u)s(t-u)du,$$

where t represents time and $s(t)$ takes values 1 when the stimulus is "on" and 0 when it is "off".

Deconvolution is a method for extracting the HRF from an observed fMRI time series signal. Assuming that the system is linear, the previous equation may

be written

$$y(t) = s(t) * h(t), \tag{1}$$

where $*$ denotes the convolution operator. With the above noise-free model, and the relationship that the Fourier transform of the convolution in the time domain is a product of the Fourier transforms in the frequency domain, an obvious approximation of the HRF can be found as the inverse Fourier transform of,

$$H(w) = \frac{Y(w)}{S(w)}, \tag{2}$$

where $Y(w)$, $H(w)$, and $S(w)$ are the Fourier transforms of $y(t)$, $h(t)$, and $s(t)$, respectively. This deconvolution approach works only if none of the $S(w)$ are zero. In practice zero or near zero values for the denominator occur for periodic stimulus sequences, resulting in poor or unstable HRF estimates. For this reason, pseudo-random or other non-periodic stimulus patterns are usually used.

Glover (1999) proposed a more realistic convolution model that incorporates an error term in the model in (1) as

$$y(t) = s(t) * h(t) + n(t), \tag{3}$$

where $n(t)$ is the noise in the measurement. An approximation for the HRF can be obtained from the observed response, using a Weiner filter as

$$\hat{h}(t) = \Im^{-1} \left\{ \frac{S(w) * Y(w)}{|S(w)|^2 + |N(w)^2|} \right\}, \tag{4}$$

where, $\Im^{-1}$ denotes the inverse Fourier transform operator and $N(w)$ is the Fourier transform of $n(t)$. Here, the estimate depends on the choice and approximation of the noise term. In practice the noise spectrum can be estimated from time series measurements in nonactivated brain regions. Observe that in the absence of noise, the Weiner filter becomes an inverse filter and the result is the same as the deconvolution method discussed above.

A common problem with frequency-domain based deconvolution methods is their instability for periodic or near periodic stimuli since the Fourier transforms of the stimulus sequence yields values close to zero. A relatively easier to implement and more stable estimate of the HRF can be found in the time domain as follows. The method is based on the noise free model (1) and uses least squares to obtain an estimate of the HRF by minimizing,

$$\min_{h(t)} = \left\{ \sum \left(y(t) - h(t) * s(t) \right)^2 \right\}, \tag{5}$$

The minimization is with respect to the HRF, $h(t)$ in the time domain. The parameters in this minimization are the first m time points during which the

HRF is believed to be present. Here we assume the HRF dies out after time m, i.e., $h(t) = 0$ for $t > m$. This method is used in later sections to empirically estimate the HRF for simulation purposes.

3. Methods of Detecting Activated Brain Regions

Cross-Correlation (CC) and the General Linear Model (GLM) are the two most widely used and well established statistical methods for detecting active voxels that use some form of an estimated HRF in modeling the BOLD response. The methods provide a test statistic in the form of a correlation coefficient, a t-test, or an F-test for each voxel. A map of such univariate test statistics, commonly known as a statistical parametric map (SPM), along with an applied threshold can be used to detect active voxels and regions in the brain. Brief overviews of the CC and the GLM methods are given next. Problems with these approaches are identified and a new approach that addresses these problems is proposed and discussed in Section 4.

The CC detection method uses the Pearson's product moment correlation coefficient between the observed response and the convolved BOLD time series model as the test statistic. This is an optimal detector when the fitted temporal model matches the true BOLD signal and the noise is independent and normally distributed (Van Trees, 1968). The basic CC approach is inflexible in the sense that it uses a single model for the hemodynamic response. However, real fMRI data exhibit variations in these functions both in time and space (Aguirre, Zarahn and D'Esposito, 1998; Grinband *et al.*, 2008).

A widely used statistical method for analyzing fMRI time series is the generalized linear model (GLM) approach. Unlike the CC approach, the GLM detection uses a linear combination of basis functions for the temporal model. The observed fMRI signals of a voxel, $\boldsymbol{Y}$, is modeled as

$$\boldsymbol{Y} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}; \quad \boldsymbol{\varepsilon} \sim N(0, \boldsymbol{V}\sigma^2), \tag{6}$$

where $\boldsymbol{V}$ is the covariance matrix of the responses. The GLM detection includes the cross-correlation approach as a special case when the design matrix, $\boldsymbol{X}$, contains only one basis function and the error is assumed to be iid Gaussian.

However, when the goal is to identify regions of the brain that responded to the stimulus sequences that were applied, simple correlation analysis between the observed fMRI signal and the estimated hemodynamic response is a reasonable approach because if the true HRF is known and the observed signal contains the true HRF plus Gaussian noise, then the Pearson's correlation coefficient is an optimal detector (Van Trees, 1968). The problem here is that the true BOLD signal is not known and has to be estimated from the data.

The convolution model given in (1) assumes that the shape of the HRF does not change over time and adds linearly for any series of stimulus activations. Moreover, most commonly used methods convolve a single estimate of the HRF to analyze the data on different regions or different subjects, thereby assuming minimal variability of HRF across subjects and brain regions. However, studies have shown that the shape of the HRF changes both spatially and across subjects (Loh, Lindquist and Wager, 2008). Using a single HRF across the whole brain and for different groups reduces detection power of the linear model and may lead to inefficiency. The proposed approach in the next section addresses this issue with a detector that imposes no HRF.

4. Maximum Cross-Correlation (r-max) Statistic

We propose and investigate a new approach that does not require HRF fits to detect 'activated' voxels. The method not only avoids fitting a specific HRF, but still takes into account that the unknown response is delayed and smeared in time. This method also adapts to differential responses of the BOLD response across different brain regions and experimental sessions. The maximum cross-correlation between the kernel-smoothed stimulus sequence and shifted (lagged) values of the observed response is proposed as a test statistic.

Let the observed fMRI signal be denoted by $y(t; \boldsymbol{s})$ and the noise process by $n(t; \boldsymbol{s})$, where time, t, is observed on a lattice and spatial locations are in three dimensions $\boldsymbol{s} = (x, y, z)$. Our model is that regions with 'inactivated' voxels contain noise only and 'activated' voxels are subject to these same noise processes plus signal, $s(t; \boldsymbol{s})$, which is an indirect response to a known sequence of stimuli as:

$$y(t; \boldsymbol{s}; \delta) = s(t; \boldsymbol{s}) + n(t; \boldsymbol{s})I, \quad t = 1, 2, \cdots, N, \tag{7}$$

where $I = 0$ if a voxel is 'inactivated' and $I = 1$ if a voxel is 'activated'.

The proposed statistic is the maximum cross-correlation between the observed response, $y(t)$, and the known sequence of spikes representing the stimulus times, $x(t)$. Because of the unknown nature and magnitudes of the delays in the HRF, the proposed method handles the nuisance lag times by maximizing these cross-correlations over lags, τ. Specifically the cross-correlation between the stimulus vector, $\boldsymbol{x}$, (smoothed or not) and a response, $\boldsymbol{y}$, at lag τ is given by

$$r_{x,y}(\tau) = \frac{\sum_{t=1}^{N-\tau}(x(t) - \bar{x})(y(t+\tau) - \bar{y})}{\sqrt{\sum_{t=1}^{N}(x(t) - \bar{x})^2 \sum_{i=1}^{N}(y(t) - \bar{y})^2}}, \tag{8}$$

The proposed statistic looks for the strongest agreement over lags up to K,

namely

$$\text{r-max} = \max_{0 \le \tau \le K < n} \{r_{x,ym}(\tau)\}. \tag{9}$$

Setting the maximum lag for the grid search, K, too large increases the chance of false positives and setting it too small decreases the power of detecting active voxels. Since the proposed statistic matches up peaks, as opposed to valleys, between the observed voxel's time course and the smoothed stimulus sequence at different lags, the time from the onset of the stimulus until the hemodynamic response rises to a peak gives relevant information in this regard. In reality the time-to-peak varies depending on the stimulus type applied (Wager *et al.*, 2005), the number of stimuli, and other unknown factors.

As described in (8) and (9), the proposed test statistic can be computed using either the unsmoothed stimulus sequence (the vector of zeros and ones in which the zeros represent the time points where no stimulus occurred and the ones represent the time points for which a stimulus did occur) or a kernel-smoothed stimulus sequence. The rationale for smoothing the stimulus sequence is twofold. First, we may be able to improve the detection power if we incorporate some underlying information about the experiment and the signal we want to detect. In the present context the signal of interest is some unknown impulse response function to the stimulus sequence. If we can incorporate any major features of this unknown function into the smoothing processes, we may improve the power to detect activated voxels. Second, smoothing the stimulus sequence will enable us to search for maximum cross-correlations at non-integer lags. For a survey of kernel smoothers see Schucany (2004).

One relevant quantity for this unknown HRF is the time-to-repeat (TR) parameter, which is the time required to acquire one image volume. The TR is the sampling rate at which data are acquired throughout the life of the BOLD response. As more data are available by increasing the sampling rate, one would expect the bandwidth of the kernel smoother to increase. We want to incorporate the TR information of the experiment into selection of the bandwidth when smoothing the stimulus sequence. Maximizing the power of detecting activated voxels while controlling for false positive errors is our main goal and is used as the measure when comparing different bandwidth selection methods.

$$\text{Let} \quad x_i = \begin{cases} 1, & \text{at the time points when the stimulus is presented,} \\ 0, & \text{at the time points when the stimulus is not presented,} \end{cases} \tag{10}$$

where $i = 1, 2, 3, \cdots, n$, and the $t_i = 1, 2, \cdots, n$, represent the integer scan numbers.

Assume that the nonparametric regression model of x on t,

$$x_i = m(t_i) + \varepsilon_i \tag{11}$$

holds. The Nadaraya-Watson kernel local-constant estimator of the regression curve,

$$m(x) = E(Y|X = x) = \int y \frac{f(x,y)}{f_X(x)} dy,$$

with $E(\varepsilon|X = x) = 0$, and $V(\varepsilon|X = x) = \sigma^2(x)$ is given by,

$$\hat{m}_{NW}(x_0) = \frac{\sum_{i=1}^{n} K\left(\frac{x_i - x_0}{h}\right) y_i}{\sum_{i=1}^{n} K\left(\frac{x_i - x_0}{h}\right)}, \tag{12}$$

where K is the kernel density and h is the bandwidth. The Tukey biweight kernel,

$$K(t) = \begin{cases} \left[1 - \left(\frac{t}{h}\right)^2\right]^2, & \text{if } |t| \leq h, \\ 0, & \text{if } |t| > h, \end{cases} \tag{13}$$

is used here for compact support and some differentiability.

We experimented with empirically matching the canonical HRF used by SPM and concluded that $h \cong 1.8$ works well.

The proposed approach searches for the strongest agreement between a smoothed stimulus sequence and the observed response by taking lags only at observed sample points. If the peak of the BOLD response occurs between the observed sample points, the above approach may not optimally detect it. If the TR is large, such an approach can pose a loss in power. One solution to alleviate this problem is to use non-integer lags. This can be achieved by taking cross-correlations between the observed voxel's time course and the fractionally lagged kernel-smoothed stimulus sequence. Here we do not need to interpolate a response between the observed sample points but instead use the fact that the smoothed stimulus sequence is a continuous function and hence can be evaluated at any point within the range of the observed sample points. Figure 1 portrays our proposed smoothed $x(t)$ in (8). The vertical lines represent the time points when the stimulus is presented.

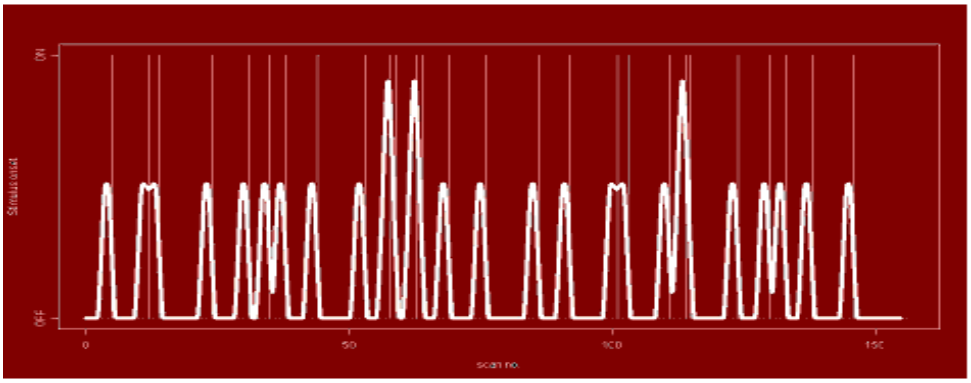

Figure 1: Kernel smoothed stimulus sequence, $h = 8$

5. Comparison of Methods by Simulation

Referring to model (7), to declare that a voxel is 'active' (i.e. contains a BOLD signal) or 'inactive', a univariate test statistic is usually computed for each voxel. The statistics to be compared are the cross correlation between the canonical HRF (Grinband *et al.*, 2008) and a voxel's time course, with the new r-max statistic proposed here. We will refer to these as the CC and r-max statistics, respectively. Based on the sampling distribution of the statistic used, a threshold is set, upon which inference will be made. We used simulation to compare the power of detecting active voxels using r-max and the CC approaches. The ROC curve, a plot of sensitivity of a test (probability of true positive rate) on the vertical versus 1 - specificity (true negative rate) on the abscissa for all possible threshold points, is used to graphically summarize the performance of the methods.

The simulations are based on the basic models (7) in which all voxels have background noise from the null distribution and only 'active' voxels also contain a known signal. Information on time to repeat, length of the time series, and the stimulus sequence are taken from a real dataset that is analyzed in Section 6. Specifically, the TR is two seconds, the length of the time series is 156 points and the region of interest (ROI) is the superior temporal gyrus. For the desired signal, we add estimated hemodynamic response functions convolved with the stimulus sequence. The hemodynamic response was empirically extracted using the simple least-squares minimization method in the time domain discussed in Section 2.

We consider two models for the background noise simulation

(1) An autoregressive model of order p, AR(p), given by

$$\tilde{y}(t) = \phi_1\tilde{y}(t-1) + \phi_2\tilde{y}(t-2) + \cdots + \phi_p\tilde{y}(t-p) + a(t); \quad t = 1, 2, \cdots, N,$$

where $\tilde{y}(t) = y(t) - \mu$; and $a(t) \overset{iid}{\sim} N(0, \sigma_a^2)$,

(2) A fractional Gaussian noise (fGn) model, which is a zero-mean stationary processes characterized by two parameters, the Hurst exponent, $H \in (0, 1)$ that measures the long-term correlation between distinct time points and the variance $\sigma^2 = \text{var}(y(t))$. The fGn distribution is completely specified by its auto-covariance function at lags $\tau \in N$ in the time domain (Beran, 1994),

$$c(\tau) = \frac{\sigma^2}{2}\left(|\tau+1|^{2H} - 2|\tau|^{2H} + |\tau-1|^{2H}\right).$$

To obtain some insight into the degree of autocorrelation in real fMRI data, we explored resting-state data. These are fMRI data taken when subjects are not doing an experimental task and are mostly used to study background noise

in fMRI experiments. These data are used in our simulations and are taken from the same subject that we analyze in Section 6. A total of 3,145 voxels in the superior temporal gyrus were considered from the resting-state data. We examined realistic values of the order of the AR model, joint distributions of the AR coefficients, Hurst exponents, and the variances of the processes to be used in our simulation. An AR(3) model was chosen for the background noise distribution. To produce sufficient variability in the simulated time series and to preserve the autocorrelation structure, resampling with replacement of the estimated AR(3) coefficients and variances were used to generate new time series. That is, estimates of coefficients of an AR(3) model fit along with the corresponding variance, $(\hat{\phi}_1, \hat{\phi}_2, \hat{\phi}_3, \hat{\sigma}_a^2)$, are sampled jointly and used for the simulation. The Hurst exponent, H, was estimated for the voxels in the ROI using Peng's variance of residuals method (Peng *et al.*, 1994). Resampling from these estimates is used to simulate a background noise process from an fGn model.

The results are based on simulation of 10,000 voxels, 30% of which contain one of the estimated HRF signals. The signal-to-noise ratio (SNR), defined as the ratio of the variance of the signal to the variance of the noise is 0.05. The proposed approach outperforms CC (with SPM's defaults) under both simulation scenarios as can be seen from the ROC curves shown in Figure 2. The estimated area under the curve (AUC) improves from 62.18% (sd = 0.47%) for the standard method to 81.89% (sd = 0.41%) for the new approach using integer lags, and 84.10 % (sd = 0.41%) using non-integer lags. Using non-integer lags rather than integer lags in the proposed test statistics also improved the detection power at the usual fixed levels by a similar amount.

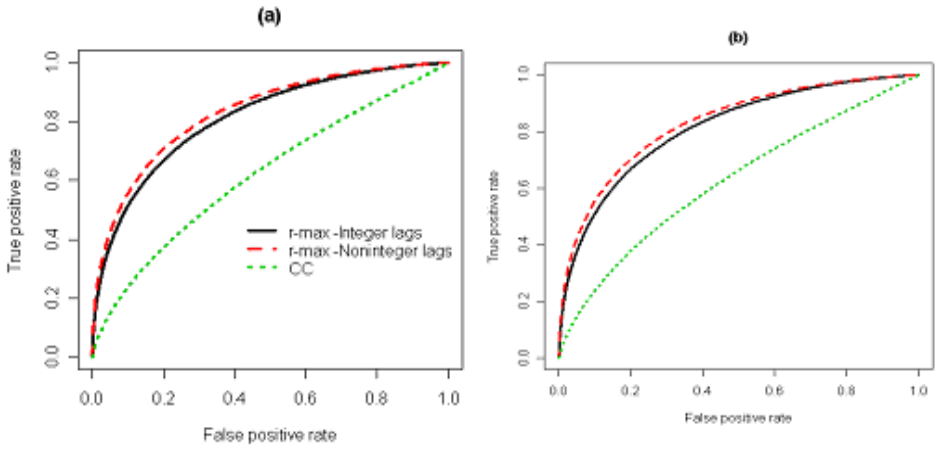

Figure 2: ROC curve comparing the proposed method using integer or fractional lag, and the correlation detection method using SPM's defaults. (a) Simulation based on AR(3) background noise models, (b) Simulation based on fGn(H) background noise models

This simulation assumes that all the voxels are acquired at the same time, i.e. no slice timing correction is necessary. Also, the simulation is based on a linear convolution model and assumes that the shape of the HRF does not change over time. However, in reality, voxels in different slices are acquired at different times. The response to closely placed stimuli may combine nonlinearly, or the HRF may change over the experimental period. The motivation is that using non-integer lags with the proposed method yields improved detection power over using integer lags and a fixed HRF in the presence of slice time differences. This obviates the need for slice timing correction, which unnecessarily smooths the data. Also, the proposed method is robust to these problems, because it does not make any of these assumptions.

6. Results from an Experiment

In this section summary results using the proposed method on an experimental dataset are presented. A typical SPM-type analysis based on CC is applied to these real data. Both sets of results are displayed on statistical parametric maps (SPM) to aid visual comparison. The fMRI dataset and the experiment that generated it are described first. It is not our intention to give a detailed fMRI data analysis in this section but only to show that the proposed method can be applied to such data.

The data for this study were obtained from a single subject, event-related, auditory fMRI experiment using a 3 Tesla Siemens Trio magnet. The stimuli are nonsense words, which a healthy volunteer repeats silently, presented through earphones semi-randomly for 300-500 ms. A total of 27 presentations of the stimuli are made. The TR is two seconds. There are 4 experimental runs each containing 156, 162, 112, 136 image volumes and one resting state run of 252 image volumes after discarding four scans in the beginning of each run while magnetization is re-equilibrating to a new steady state. Data from the first run are analyzed here. Images were acquired in coronal slices with an interleaved acquisition sequence. The voxel dimension is 3.125mm $\times$ 4mm $\times$ 3.125 mm, and there are $51 \times 48 \times 44$ voxels in x, y, and z axes, respectively. The data were preprocessed to correct for head motion correction (realignment) and normalization using SPM2 software. Images in each run were realigned to the first image in that run. Realigned images were then normalized to the EPI template. Drift was removed from each voxel by fitting a local quadratic polynomial that uses 25% of the data to obtain an estimate at a given point (span = 0.25 in loess). All the analysis was done using R software package version R 2.6.2.

To identify significantly activated voxels, an SPM-type analysis is to use the Pearson's cross-correlation between the observed response and a canonical HRF (using SPM defaults) convolved with the ideal stimulus sequence (CC). Figures

3 and 4 show statistical parametric maps (SPMs) of the CC statistic and r-max, respectively. It can be seen that regions of the brain that are expected to respond to an auditory stimulus show activations using the proposed r-max but no clearly activated brain regions are seen using the simple cross correlation analysis. We have also applied the proposed method to the superior temporal gyrus, the main brain structure that is expected to respond to auditory stimuli such as those in this experiment and found that the proposed method identified many voxels from this region as expected but CC identified very few voxels. Better clustering of 'activated' voxels were also observed using the proposed method.

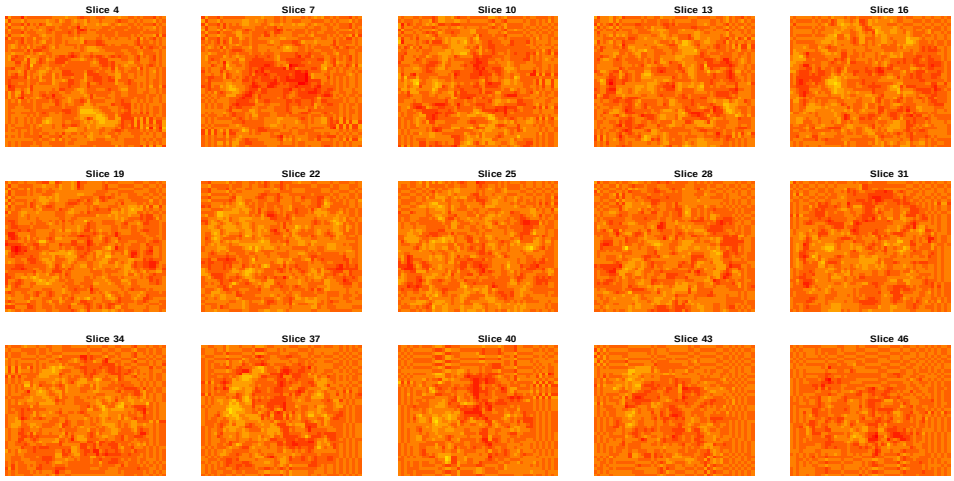

Figure 3: SPM of CC, Pearson's product moment cross-correlation coefficient between a voxel's time course and the convolved HRF, shown on coronal slices

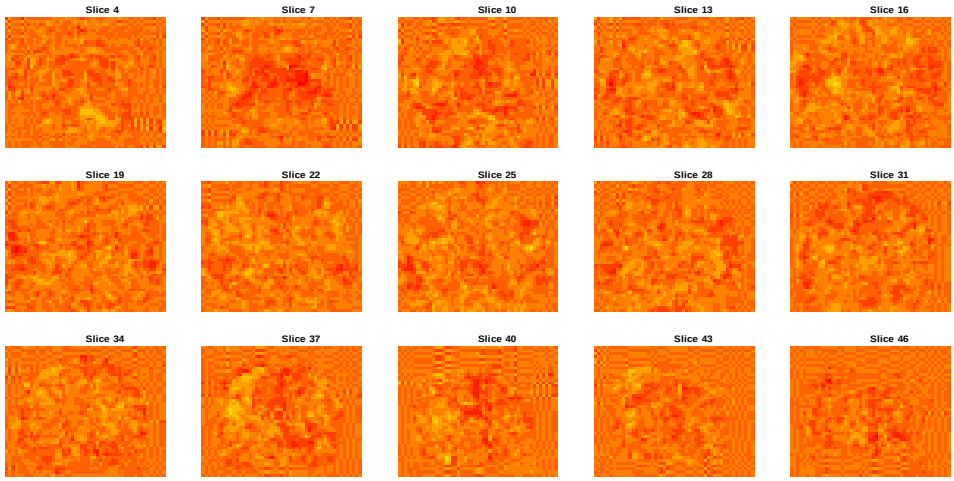

Figure 4: SPM of r-max, the maximum cross correlation between a voxel's time course and the smoothed stimulus spikes, shown on coronal slices

In summary, the classical SPM-type analysis, which uses a cross correlation between the observed voxel's time series and the HRF fitted using SPM's defaults, performed poorly for this dataset. The proposed test static was able to identify clusters of activated voxels in regions that are expected to be activated for the experiment under consideration. This observation agrees well with the conclusions obtained from the simulation experiments in the previous section.

One possible reason for the poor performance of the CC analysis is that for this dataset the time-to-peak is much longer than the SPM default of 5.4 seconds used in the default HRF. The proposed method however does not depend on an assumed HRF and hence is able to automatically adapt to such variations.

7. Conclusions

Statistical methods typically used for fMRI analysis employ estimates of the hemodynamic response function. By adopting a single HRF model throughout the analysis, the implicit assumption is that this response does not change from subject to subject and that all brain regions respond somewhat similarly to a given impulse. An additional assumption that the HRF does not change over time is implicit in the convolution model discussed in Section 2. But different studies have shown that these assumptions are not always met and misspecifications may result in inefficiencies (Loh, Lindquist and Wager, 2008). Different solutions have been proposed to address this issue including estimating the HRF parameters individually for each voxel (Lindquist, 2008). This again depends on the general class of the HRF model selected and the quality of the estimates obtained. In this paper we addressed the issue by proposing a nonparametric methodology that avoids HRF fitting.

The maximum cross-correlation between the observed response and the kernel-smoothed stimulus at different lags is proposed as a test statistic. The proposed methodology takes into account the fact that the observed response is delayed in time. It searches for the strongest agreement between the smoothed stimulus sequence and the lagged (shifted) response. Moreover, we have shown that the proposed methodology automatically handles differential responses across brain regions and subjects. Simulation results in Section 5 showed that the proposed method outperforms the classical SPM-type analysis using the cross correlation coefficient. Using non-integer lags instead of integer lags also improves the detection power of activated voxels using the proposed r-max.

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References

Aguirre, G. K., Zarahn, E. and D'Esposito, M. (1998). The variability of human, BOLD hemodynamic responses. *NeuroImage* **8**, 360-369.

Beran, J. (1994). *Statistics for Long-Memory Processes.* Chapman and Hall, New York.

Bullmore, E. T., Brammer, M. J., Williams, S. C. R., Rabe-Hesketh, S., Janot, N., David, A. S., Mellers, J. D. C., Howard, R. and Sham, P. (1996). Statistical methods of estimation and inference for functional MR image analysis. *Magnetic Resonance in Medicine* **35**, 261-277.

Buxton, R. B., Wong, E. C. and Frank, L. R. (1998). Dynamics of blood flow and oxygenation changes during brain activation: the Balloon model. *Magnetic Resonance Imaging in Medicine* **39**, 855-864.

Friston, K. J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M. D. and Turner, R. (1998). Event-related fMRI: characterizing differential responses. *NeuroImage* **7**, 30-40.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. P., Frith, C. D. and Frackowiak, R. S. J. (1995). Statistical parametric maps in functional imaging: a general linear approach. *Human Brain Mapping* **2**, 189-210.

Friston, K. J., Josephs, O., Rees, G. and Turner, R. (1998). Nonlinear event-related responses in fMRI. *Magnetic Resonance in Medicine* **39**, 41-52.

Glover, G. H. (1999). Deconvolution of impulse response in event-related BOLD fMRI. *NeuroImage* **9**, 416-429.

Grinband, J., Wager, T. D., Lindquist, M. A., Ferrera, V. P. and Hirsch, J. (2008). Detection of time-varying signals in event-related fMRI designs. *NeuroImage* **43**, 509-520.

Jezzard, P., Matthews, P. M. and Smith, S. (2004). *Functional MRI*: *An Introduction to Methods.* Oxford University Press, Oxford.

Lange, N. and Zeger, S. L. (1997). Non-linear time series analysis for human brain mapping by functional magnetic resonance imaging. *Applied Statistics* **46**, 1-29.

Lindquist, M. A. (2008). The statistical analysis of fMRI data. *Statistical Science* **23**, 439-464.

Loh, J., Lindquist, M. A. and Wager, T. D. (2008). Residual analysis for detecting mis-modeling in fMRI. *Statistica Sinica* **18**, 1421-1448.

Peng, C. K., Buldyrev, S. V., Havlin, S., Simons, M., Stanley, H. E. and Goldberger, A. L. (1994). Mosaic organization of DNA nucleotides. *Physical Review* **49**, 1685-1689.

Schucany, W. R. (2004). Kernel smothers: an overview of curve estimators for the first graduate course in nonparametric statistics. *Statistical Science* **19**, 663-675.

Van Trees, H. L. (1968). *Detection, Estimation, and Modulation Theory.* Wiley, New York.

Wager, T. D., Vazquez, A., Hernandez, L. and Noll, D. C. (2005). Accounting for nonlinear BOLD effects in fMRI: parameter estimates and a model for prediction in rapid event-related studies. *NeuroImage* **25**, 206-218.

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