TIME-TO-ONSET LATENCY IN FMRI: FAST DETECTION OF DELAYED ACTIVATION

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ABSTRACT
A standard fMRI experiment is structured around the assumption that onset of relevant neural activity occurs almost immediately after external stimulus. Introducing deliberate lengthy delays in cognition, e.g. in problem solving tasks, necessitates adjusting the analysis model to account for any possible temporal latency. This is usually a computationally intensive task. Using Lagrange Multipliers, we develop a fast method to detect such delay in the Time-to-Onset of BOLD signal. This is conceptually different to measuring the Time-to-Peak of the BOLD Hemodynamic Response. Additionally, our method does not require prior knowledge of the length of the delay.

Index Terms— fMRI, Onset, Latency

1. INTRODUCTION

Temporal delay, or latency, in the onset of Hemodynamic Response (HR) to input stimulus in fMRI data stems from two sources:

1. Time-to-Peak of the HR, representing within-response delay
2. Time-to-Onset of the HR, as a result of extended pure delays in cognitive activity.

Time-to-Peak latency is represented directly in parameterised HR models; variations across the brain [1] are usually accounted for by including extra linear model variables such as derivatives of the estimated HR function, or using a flexible basis set, e.g. finite impulse response (FIR) model.

Time-to-Onset is traditionally accounted for in the fMRI analysis model as the input stimulus (e.g. block or event-type stimulus). Problems arise in the signal detection when some relevant neural activity (and thus BOLD response) occurs at an indeterminate time after the actual stimulus, escaping the modelling effects of the specified HR.

It would be useful to have a method to detect such activation which occurs after an unknown but significant delay, as a result of latency in the Time-to-Onset. In this paper we supply such a tool.

Other methods for detecting fMRI latency have been proposed [2, 3, 4, 5]; however these are designed for detecting the HR Time-to-Peak and require evaluation under the null and alternative hypotheses, limiting the speed of calculation since delay parameters must be estimated.

Our approach is through Lagrange multiplier (LM) tests which are well known in statistics and especially econometrics [6, 7]. The LM approach is originally due to [8]. Its popularity in econometrics is due to the fact that it does not require model fitting under the alternative but only under the null hypothesis. This leads to very fast computation and makes LM tests ideally suited to applications involving large data dimension as in fMRI. To the best of the authors’ knowledge, this is the first method designed specifically to test for significant delay in Time-to-Onset of fMRI signal.

The rest of the paper is organised as follows. In section 2 we review LM theory. In section 3 we develop a LM test for delay in fMRI data. In section 4 we show a simulation and application to real data. Conclusions are offered in section 5.

Acronyms & Notation: MLE = maximum likelihood estimator; LM = Lagrange multiplier; LS = Least squares; BOLD = Blood Oxygen Level Dependent; H = Hermitian transpose = complex conjugate transpose.

2. THEORY OF LAGRANGE MULTIPLIER TESTS

Although the LM approach is well known, we provide a brief signal-processing oriented review.

Suppose we have $n$-dimensional data $Y$ distributed according to a likelihood, dependent on a $p$-dimensional parameter $\theta$,

$$
\log \text{likelihood} = L(Y; \theta) = L(\theta) \quad \text{for simplicity.}
$$

Consider a general hypothesis, $H_0 : g(\theta) = 0$ where $g(\theta)$ is an $r$-vector of differentiable functions. We introduce the constrained MLE, $\hat{\theta}$ and the unconstrained MLE, $\tilde{\theta}$,

$$
\hat{\theta} = \arg \max_{g(\theta)=0} L(\theta), \quad \tilde{\theta} = \arg \max L(\theta), \quad \Rightarrow \frac{dL}{d\theta} = 0
$$

The LM test is developed via two Taylor series expansions applied to the log of the likelihood ratio: $L(\tilde{\theta}) - L(\hat{\theta})$, namely,

$$
L(\tilde{\theta}) = L(\hat{\theta}) + \frac{1}{2} (\tilde{\theta} - \hat{\theta})^T L_{\theta,\theta} (\tilde{\theta} - \hat{\theta}) \quad (1)
$$

$$
0 = \frac{dL}{d\theta} = \frac{dL}{d\hat{\theta}} + L_{\theta,\theta} (\tilde{\theta} - \hat{\theta}) \quad (2)
$$

where (1) is the Taylor series approximation of $L(\hat{\theta})$ around $\hat{\theta}$, and (2) is the derivative of the first-order Taylor series expansion around
where $e = e(\beta) = Y - h(\beta)$, $h(\beta)$ is the mean function and $\Omega(\alpha)$ is the noise covariance. When the constraints are on the mean parameters only, $\beta = (\pi^T, \psi^T)^T$; $g(\pi) = 0$. We then find,

$$\frac{\partial L}{\partial \pi} = Z^T \Omega^{-1} e; \quad Z^T = \frac{d h^T}{d \pi} \bigg|_{g(\pi)=0}$$

(6)

$$\frac{\partial L}{\partial \psi} = 0$$

(7)

While

$$(\tilde{\mathbf{I}}_{\pi \pi} \tilde{\mathbf{I}}_{\psi \pi} \tilde{\mathbf{I}}_{\psi \psi}) = (\tilde{\mathbf{Z}}^T \Omega^{-1} \tilde{\mathbf{Z}} \quad \tilde{\mathbf{Z}}^T \tilde{\mathbf{Z}}^{-1} \tilde{\mathbf{X}} \quad \tilde{\mathbf{X}}^T \tilde{\mathbf{Z}}^{-1} \tilde{\mathbf{X}})$$

(8)

Then using partitioned matrix inversion it can be shown that (9) becomes $V_\theta = V_\beta$ with,

$$V_\beta = \left( \sum \frac{\tilde{z}_k \tilde{z}_k^H}{F_k} \right) \left( \sum \frac{\tilde{\tilde{z}}_k \tilde{\tilde{z}}_k^H}{F_k} \right)^{-1}$$

(11)

$$Q = \left( \sum \frac{\tilde{z}_k \tilde{z}_k^H}{F_k} \right) - \left( \sum \frac{\tilde{\tilde{z}}_k \tilde{\tilde{z}}_k^H}{F_k} \right) \left( \sum \frac{\tilde{\tilde{z}}_k \tilde{\tilde{z}}_k^H}{F_k} \right)^{-1} \left( \sum \frac{\tilde{z}_k \tilde{z}_k^H}{F_k} \right)$$

(12)

where $k$ is a frequency and $F_k = \hat{F}(2\pi k)$ is the fitted noise spectrum under the null hypothesis; $n = \dim(Y)$

It is these frequency domain expressions that we will employ below.

## 3. TESTING FOR DELAY IN FMRI DATA

Here we apply the Lagrange Multiplier method to construct a test statistic for Time-to-Onset delay within the fMRI activation signal. We use the basic linear time invariant model for fMRI with time-stationary but spatially varying noise [10]. The signal model at each voxel is

$$y_t = \mu_t + v_t = m_t + s_t + v_t$$

where $m_t = d_t^T \gamma$ is baseline + drift (modeled with orthogonal polynomials) and $v_t$ is coloured noise modeled as AR (1) + white noise, $\text{var}(v) = \Omega(\alpha) \equiv \text{cov}(v_t, v_{t'}) = \delta_{t,t'} \delta_{k,k} (\alpha)$.

In the frequency domain, the voxel-wise model for activation signal is,

$$s_k = e^{-j\omega_k D} f^T \xi_k$$

where $s_k$ is the DFT of $s_t$, $D$ is temporal delay, $f$ is activation magnitude and $\xi_k$ is the DFT of the HR function convolved with input stimulus. The HR function is non-parametric and it is specified
by continuous Laguerre polynomials which have the advantages of being a linear orthogonal, causal basis set which require only 2-3 parameters; this is many fewer than FIR models which typically require \( \approx 15 \) parameters for fMRI modelling. The null hypothesis is \( H_0 : \pi = D = 0 \).

The LM test is constructed as follows.

1. Fit the model under the null hypothesis
   \[
   y_k = \tilde{\gamma}^T d_k + \tilde{f}^T \xi_k + \tilde{v}_k
   \]
   with parameter estimates under the null as \( \tilde{\gamma}, \tilde{f}, \tilde{\alpha} \). Generate the residuals,
   \[
   \tilde{v}_k = y_k - \tilde{\gamma}^T d_k - \tilde{f}^T \xi_k
   \]
2. Calculate two sets of ‘pseudo’ regressors
   \[
   X = \left[ \frac{\partial \mu_k}{\partial \tau^T} \right] = \left[ \frac{\partial \mu_k}{\partial f^T} \right] = \left[ e^{-j\omega_k D} \xi_k, d_k^T \right]
   \]
   \[
   Z = \left[ \frac{\partial \mu_k}{\partial D} \right] = \left[ -j\omega_k e^{-j\omega_k D} f^T \xi_k \right]
   \]
   and evaluating these under the null hypothesis gives
   \[
   \tilde{X} = X|_{\tau=0} = \left[ \xi_k, d_k^T \right] = \left[ \tilde{x}_k^T \right] \tag{12}
   \]
   \[
   \tilde{Z} = Z|_{\tau=0} = \left[ -j\omega_k f^T \xi_k \right] = \left[ \tilde{z}_k \right] \tag{13}
   \]
   We also need, \( \tilde{\Omega} = \Omega(\tilde{\alpha}), \tilde{F} = F(\tilde{\alpha}) \).

3. The test statistic is calculated in the normalised frequency domain as,
   \[
   V_\beta = \left( \sum \frac{\tilde{v}_k \tilde{z}_k^H}{F_k} \right) Q^{-1} \left( \sum \frac{\tilde{x}_k \tilde{x}_k^H}{F_k} \right) \tag{14}
   \]
   \[
   Q = \left( \sum \frac{\tilde{z}_k \tilde{z}_k^H}{F_k} \right) \left( \sum \frac{\tilde{x}_k \tilde{x}_k^H}{F_k} \right)^{-1} \left( \sum \frac{\tilde{x}_k \tilde{z}_k^H}{F_k} \right)
   \]
   Note the nice structure; the test correlates residuals with the input signal. If delay is present there is large correlation; if not, there is small correlation.

The test statistic of (14) is applied individually to each voxel time-series in an fMRI data set. The resulting statistic is plotted spatially as a map of Time-to-Onset delay in BOLD activation. Applying a Bonferroni-corrected threshold to the test statistic based upon the \( \chi^2_{\beta-\nu} \) distribution shows significant areas of delayed BOLD activation signal.

4. RESULTS

Analysis was performed with simulated and real data.

Simulation involved embedding block- and event-type input stimulus signals into real resting state fMRI data. Results for block-type stimulus with typical SNR 1.2 are shown in Fig. 1. True positive rate of detection is shown for LM Delay algorithm (solid line) and conventional Least Squares (LS) test statistic (dotted). The LM test statistic effectively finds delayed activation where the LS statistic does not; in particular the LS algorithm is only effective when the measured and stimulus signals are completely in or out of phase, whereas the LM delay algorithm detects activation with a Time-to-Onset falling outside that narrow range, so long as it is sufficiently delayed. False positive rate is comparable with the LS test statistic. Results are consistent for event-type input stimulus and under variation of model parameters. Applying this algorithm to simulated fMRI data which does not contain temporal delay gives a null result as expected.

Real fMRI data is from a combined visual/motor experiment solving simple mathematical calculation. Four-digit numbers were presented on a screen until the subject indicated a response (sum of two numbers being higher/lower than a third) by pressing one of two buttons, at which point the visual stimulus was removed. The experiment was designed specifically to incorporate lengthy but varying delays in Time-to-Onset of cognitive activity between stimuli (observing numbers) and making a decision (button press). Data was acquired using a 3T Philips ‘Achieva’ MRI scanner with 2.000s TR; voxel size (3.125 × 3.125 × 5) millimetres, volume dimensions 61 × 50 (×82 slices); 335 temporally sampled volumes. Data was preprocessed using SPM8 (www.fil.ion.ucl.ac.uk/spm/) without spatial or temporal smoothing.

The input stimulus is modeled as an impulse at the time of button press and the noise is modeled as a first-order auto-regressive process.

Fig. 2 shows a spatial map of the LM test statistic of (14) where a significant amount of delayed activation is detected in the areas of visual and motor cortices. The threshold is applied to the test statis-
Fig. 3. The map of significant activation delay (a) reveals significantly more activated voxels than the conventional Least Squares (LS) test statistic (b), which assumes no Time-to-Onset delay. (c) shows activated voxels detected by the Lagrange Multiplier (LM) delay test statistic but not the LS test, whereas (d) shows voxels detected by the LS test but not the LM test.

stimulation) give a null result.

5. CONCLUSION

In this paper we have posited Lagrange Multiplier (LM) tests as an economical way of investigating characteristics of fMRI data. The cheap computational cost of LM tests comes from the fact that they only require model fitting under the null hypothesis. Further, LM tests are easily constructed for any kind of model deviation or model alternative. We have illustrated by constructing a test to detect experiment-related Time-to-Onset delay in fMRI Hemodynamic Response and shown its utility successfully on real data. The algorithm testing for signal delay does not require any prior knowledge or assumption in the model about the length of delay before commencement of BOLD response. The LM method testing for delay is therefore a flexible tool for detecting activation responses in fMRI data when the exact timing of the activation is completely unknown.

6. REFERENCES