FMRI SIGNAL MODELING USING LAGUERRE POLYNOMIALS

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ABSTRACT

In order to construct spatial activation plots from functional magnetic resonance imaging (fMRI) data, a complex spatio-temporal modeling problem must be solved. A crucial part of this process is the estimation of the hemodynamic response (HR) function, an impulse response relating the stimulus signal to the measured noisy response. The estimation of the HR is complicated by the presence of low frequency colored noise. The standard approach to modeling the HR is to use simple parametric models, although FIR models have been used. We pursue a nonparametric approach using orthonormal *causal* Laguerre polynomials which have become popular in the system identification literature. It also happens that the shape of the basis elements is similar to that of a typical HR. We thus expect to achieve a compact and so bias reduced and low noise representation of the HR. This is not the case in FIR modeling, because a low FIR order is unable to cover the whole length of the HR over its region of support while a high FIR order results in overestimation of signal and underestimation of noise leading to misleading interpretations.

1. INTRODUCTION

Functional magnetic resonance imaging (fMRI) relates to rapid high spatial and temporal resolution imaging of ongoing functional activity in contrast to *static* structure, by means of nuclear magnetic resonance(NMR). In the context of human brain mapping, it can be considered as a technology that enables creation of images, revealing localized neural activity in human brains during sensory, motor and cognitive activity. NMR facilitates detection of changes in chemical composition or rate of blood flow as a result of the *local* neural activity in response to controlled stimuli resulting in digital image contrast. A brief readable survey of Brain Mapping with fMRI is available in [1]. In a typical fMRI experiment, a subject is presented with a stimulus or cognitive task, in a periodic "off-on" pattern, while images of the brain are taken in rapid succession. A simple example might be a flickering checkerboard visual stimulus which is on for 10 s and off for 15s (i.e a square wave stimulus). Such experiments are designed to determine and analyze regions of functional specialization within the brain that are related to stimulus presentation. The fMRI data available for analysis is *spatiotemporal*. The data consists of several two dimensional slices of sections of brain taken at different angles, with each slice containing certain *specific functional* areas. The 2 dimensional image data is recorded as a function of time, with a sampling interval ranging from a few hundreds of milliseconds to several seconds. The observed data at each pixel of a given slice is a superposition of 1) Blood Oxygenation level dependent (BOLD) hemodynamic response (HR) $s_{t,P}$ brought about by some stimulus c_t depending on the experiment, and the 2) brain noise $v_{t,P}$. The brain noise consists of hemodynamic fluctuations of unknown origin, possibly related to background processes in the brain as well as cardiac fluctuations. The two main statistical tasks carried out are estimation and inference. The most commonly adopted technique to make inferences is based on comparison of a test statistic which is a function of the estimated parameters, with a threshold and declare the pixel as active or inactive. Even though this approach has been used widely, visual observation of estimated time domain signal has been usually *neglected* even though it can provide good visual insights to the quality of estimation. In particular visual inspection at some activated pixels helps in determining whether the signal has been overestimated, is physiological or not and more. Two models may have similar kinds of test statistic maps as test statistics are generally a ratio of estimated signal to noise, while the estimated time series may be very different for two models. We illustrate this case in this paper for a real data example.

The paper is organized as follows. In section 2, we discuss the use of Laguerre polynomials in modeling the HR, in section 3 the method of estimation of both the signal and noise parameters for each pixel of a slice. In section 4, we present the results on a data set undergoing visual stimulation and compare our modeling approach with that of FIR. Section 5 deals with conclusions.

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2. MODELING

The approach to time series decomposition at a pixel is built on the work of several researchers [2] who used convolution with a Poisson shaped impulse response to relate stimulus to response, who showed that there is important low frequency colored noise; [3] who investigated the validity of linearity and convolution. The observed time series at a pixel P as discussed in previous section can be represented as

$$x_{t,P} = m_P + b_P t + s_{t,P} + v_{t,P} \tag{1}$$

where $m_P, b_P t$ are the DC levels and background drifts respectively, while $s_{t,P}$ is the response to the input given by

$$s_{t,P} = h_P(t) * c(t) \tag{2}$$

with $h_P(t)$ being the HR at pixel P, and the noise $v_{t,P}$ is modeled as an AR(1) process in white Gaussian noise, which is equivalent to ARMA(1,1) noise, [4]. Thus noise can be expressed as

$$v_{t,P} = w_{t,P} + u_{t,P} \tag{3}$$

where $w_{t,P}$ is background white Gaussian noise of the scanner with power σ_w^2 and $u_{t,P}$ is a temporally correlated noise AR(1) given by,

$$u_{t,P} = \rho_P u_{t-1,P} + \eta_{t,P} \tag{4}$$

with $\eta_{t,P}$ being Gaussian with zero mean and variance σ_η^2.

The true shape of HR is only known empirically [4]. Qualitatively it can be described as a *localized hump shaped causal* function. The HR to the underlying neuronal activity and noise, will cause the HR to be a blurred, delayed and noisy version of the stimulus. The accuracy of any method proposed to detect activation will depend on the way in which these factors are accounted for, and thus, an appropriate modeling would lead to better inference. In the past, several approaches have been proposed to model $h_P(t)$. A Poisson form impulse was chosen in [2]. It is a parsimonious choice because there is only one unknown parameter involved. However since there is just one function involved, the shape becomes too constrained. In [4], a weakly nonlinear model is used involving two weighted convolution components parameterized by two time constants. The two unknown time constants are chosen empirically and the two weights computed by regression. FIR modeling has been used by [8], which models the response as the output of a FIR filter of a given order excited by the stimulus input. Choosing a low FIR order may not be able to characterize the HR well because it implies forced zeroing of response before its complete decay even if the estimation quality may be good. On the other hand choosing a higher order may be able to model the HR well but may lead to *ill determined* coefficient FIR estimates.

It has been shown in [5] that discrete Laguerre polynomials belonging to a class of orthogonal exponentials have been quite effective in reducing the model order and provide a useful low order approximation to time delay systems, if some a priori knowledge of the time constants is available. Owing to the similarity of shape of discrete Laguerre polynomials with the assessed HR shape [7], which would possibly result in estimation of *fewer* parameters and thus a reduction in bias and variance, we propose the use of these polynomials in modeling the HR. The superiority of such basis functions over FIR in modeling time delay systems has been verified [5]. The HR at pixel P will then be described as

$$h_P(t) = \sum_{i=1}^{L} f_{i,P} g_i^a(t) \tag{5}$$

where $f_{i,P}$ is the P^{th} pixel coefficient of the basis function $g_i^a(t)$ which is the inverse Z transform of i^{th} Laguerre polynomials given by

$$g_i^a(t) = Z^{-1}\left[\frac{z^{-1}}{1-az^{-1}}\left(\frac{z^{-1}-a}{1-az^{-1}}\right)^{i-1}\right] = Z^{-1}\left[\tilde{g}_i^a(z)\right] \tag{6}$$

Note that all the Laguerre polynomials of all orders and hence all the basis functions in the above equation will be characterized by the same time constant a. The basis functions are highly localized, causal [5] and have shape similar to the empirically assumed HR, [8],[7]. It is thus expected that a few basis functions will be able to characterize the HR and modeled response will have a physiological shape [4]. Thus the from (5) modeled response signal in (2) becomes

$$s_{t,P} = \sum_{i=1}^{L} f_{i,P}\left[g_i^a(t) * c(t)\right] \tag{7}$$

where L is the order of the Laguerre polynomial and $g_i(t) * c(t)$ is the convolution of i^{th} Laguerre polynomial with input stimulus.

3. ESTIMATION OF PARAMETERS

Based on (1), if the mean value of the noisy signal at pixel P is removed then the *entire* observed time series at pixel P, can be stacked and expressed in a General Linear Model (GLM) form as

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{v} \tag{8}$$

where $\mathbf{y} = [y_P(1)\ \ldots\ y_P(N)]'$ and $\mathbf{v} = [v_P(1)\ \ldots\ v_P(N)]'$ are the observed time series and noise vector at pixel P respectively and $\boldsymbol{\beta} = [b_P\ f_1\ \ldots\ f_L]'$. Also as discussed before the noise vector $\mathbf{v}$ is Gaussian ARMA(1,1) and has an unknown covariance matrix $\mathbf{C}$. The $N \times (L+1)$ matrix $\mathbf{X}$

is given by,

$$\mathbf{X} = \begin{bmatrix} 1 & (g_1(t)*c(t))_1 & \dots & (g_L(t)*c(t))_1 \\ 2 & \dots & \dots & \dots \\ N & (g_1(t)*c(t))_N & \dots & (g_L(t)*c(t))_N \end{bmatrix} \quad (9)$$

It should be noted that the *entire* available time series at a pixel is stacked above in the left side of (9) and there is no ON-OFF period delineation. The estimation of response is carried out over the whole time series in one step. For a known covariance matrix, the maximum likelihood estimate of $\boldsymbol{\beta}$ is

$$\hat{\boldsymbol{\beta}} = (\mathbf{X}^H\mathbf{C}^{-1}\mathbf{X})^{-1}\mathbf{X}^H\mathbf{C}^{-1}\mathbf{y} \quad (10)$$

Since, the matrix $\mathbf{C}$ is a function of the three unknown noise parameters $\boldsymbol{\alpha} = [\sigma_w^2,\, \sigma_\eta^2,\, \rho]$, closed form joint ML estimation of $\boldsymbol{\beta}$ and $\boldsymbol{\alpha}$ is difficult. Hence we carry out the estimation of $\boldsymbol{\beta}$ and $\boldsymbol{\alpha}$ *iteratively*. Instead of carrying out the estimation in the time domain we carry out the estimation in frequency domain. In frequency domain, the covariance matrix of the noise becomes approximately diagonal whose (k,k) element is given by the spectrum of the noise at frequency ω_k.

$$\tilde{\mathbf{C}}(k,k) = \frac{\sigma_\eta^2}{1 - 2\rho_P\cos(\omega_k) + \rho_P^2} + \sigma_w^2 \quad (11)$$

If $\tilde{\mathbf{y}}, \tilde{\mathbf{X}}, \tilde{\mathbf{v}}$ are the column wise Discrete Fourier Transform (DFT) of $\mathbf{y}, \mathbf{X}$ and $\mathbf{v}$ respectively, then GLM in frequency domain can be expressed as

$$\tilde{\mathbf{y}} = \tilde{\mathbf{X}}\boldsymbol{\beta} + \tilde{\mathbf{v}} \quad (12)$$

Since the time domain matrix $\mathbf{X}$ has its L columns which are computed by linear convolution, it is necessary to pad zeros to the time domain data before computing the column wise DFT of $\mathbf{y}$ and $\mathbf{X}$ to to prevent time domain aliasing. The estimation procedure can then be summarized as follows 1) Start with an initial guess of $\boldsymbol{\alpha}$ and hence $\tilde{\mathbf{C}}$. 2) Estimate the signal parameters using weighted least squares $\hat{\boldsymbol{\beta}} = (\tilde{\mathbf{X}}^H\tilde{\mathbf{C}}^{-1}\tilde{\mathbf{X}})^{-1}\tilde{\mathbf{X}}^H\tilde{\mathbf{C}}^{-1}\tilde{\mathbf{y}}$. 3)Obtain the residuals $\mathbf{e} = \tilde{\mathbf{y}} - \tilde{\mathbf{X}}\hat{\boldsymbol{\beta}}$. 4) From the residuals obtain the estimate of the noise parameters $\boldsymbol{\alpha}$ using Expectation Maximization (EM) algorithm. The complete EM algorithm details for ARMA(1,1) are provided in [4]. 5). Feed the new estimates of $\boldsymbol{\alpha}$ in (2) and repeat steps 2-4 till convergence. After performing the estimation, we need to carry out inference and declare a pixel as active or inactive. If the matrix $\tilde{\mathbf{C}}$ is known then the following test statistic (TS)

$$TS = \left(\mathbf{R}\hat{\boldsymbol{\beta}} - \mathbf{r}\right)^T [\tilde{s}^2\tilde{\mathbf{X}}^H\tilde{\mathbf{C}}^{-1}\tilde{\mathbf{X}}]^{-1}\left(\mathbf{R}\hat{\boldsymbol{\beta}} - \mathbf{r}\right) \quad (13)$$

where $\tilde{s}^2$ is given by

$$\tilde{s}^2 = \left(\tilde{\mathbf{y}} - \tilde{\mathbf{X}}\hat{\boldsymbol{\beta}})\right)^T\tilde{\mathbf{C}}^{-1}\left(\tilde{\mathbf{y}} - \tilde{\mathbf{X}}\hat{\boldsymbol{\beta}}\right) \quad (14)$$

will be such that $\frac{TS(N-k)}{m}$ will have a $F(m, N-k)$ distribution [6], with k corresponding to the number of columns in matrix $\mathbf{X}$. The condition $\mathbf{R}\hat{\boldsymbol{\beta}} = \mathbf{r}$ corresponds to the null hypothesis and m is the rank of $\mathbf{R}$. Note that in (13) and (14) we replace the covariance matrix $\tilde{\mathbf{C}}$ by its estimate as $\tilde{\mathbf{C}}$, as it is unknown for our case. Since the actual fMRI signal activation parameters dealing with the BOLD signal is $\mathbf{f} = [f_1\, \dots\, f_p]$ if $\mathbf{X}_g$ is the matrix formed by removing the first column from the matrix $\tilde{\mathbf{X}}$ then the test statistic defined in (13) becomes

$$TS = \left(\mathbf{R}\hat{\mathbf{f}} - \mathbf{r}\right)^T [\tilde{s}^2\tilde{\mathbf{X}}_g^H\tilde{\mathbf{C}}^{-1}\tilde{\mathbf{X}}_g]^{-1}\left(\mathbf{R}\hat{\boldsymbol{\beta}} - \mathbf{r}\right) \quad (15)$$

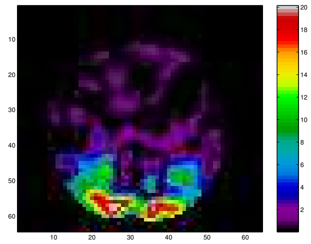
We consider the null hypothesis condition as $\mathbf{f} = \mathbf{0}$ which equivalently corresponds to the condition $\mathbf{R}$ being a $p \times p$ identity matrix and $\mathbf{r} = \mathbf{0}$. From the computed value of TS in (15), we obtain the p-values at each pixel and produce a map of p-values for each slice. Typically in fMRI problems p-values below 0.001 are declared as activated pixels.

4. RESULTS

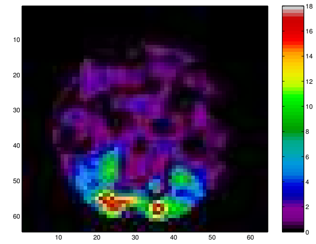
The fMRI data used in this study were collected from a visual experiment using a 3T Siemens Allegra MR scanner, using a gradient-echo planar pulse sequence. A visual blocked design experiment was carried out in which a subject was presented with a readily recognizable stimulus present on a screen for 1700 ms. Each condition included forty different pictures that were presented three times. Blocks of experimental images were separated by 20 second interval of rest during which a fixation dot was presented. Each block consisted of ten consecutive presentations of different pictures within a specific experimental condition appearing in a random order. The total block duration was 20 seconds. The data has been presmoothed. We carried out the modeling of HR at each pixel, by Laguerre polynomials of order 2 and time constant a=2/3 chosen from blood flow parameters in [4] . This order was determined by a criterion developed in [4] after testing orders 1, 2 and 3 (full details for choosing order and optimal time constant a will be pursued elsewhere). Figure 1 a), shows the value of negative logarithm of the p-values computed from the test statistic in (15) for the proposed method. Strong activations have been observed in the visual cortex as expected. Figure 1 b) shows the same statistics using 6^{th} order FIR modeling with identical noise model assumption. This plot also shows activity in the visual cortex as expected. However the maps are inferior compared to the case of Laguerre modeling (figure 1 a). The merit of the proposed method becomes more obvious if one examines the estimated time domain waveforms. In figure 1 c, we plot the noisy time series (green color) after eliminating the DC value and slope at the pixel and the estimated signal (blue color) overlaid. Figure d) shows the same using FIR orders 4,6 and 11. It can be observed from figure 1 c) that the smeared response appears physiological if Laguerre model is used. However this is not the case for FIR as can be seen clearly from figure 1 d). The estimated signal appears noisy, which is *not expected* as a convoloution of a typical smooth HR curve with a square wave should not contain high frequency components. It can be observed that the response gets noisier if the FIR order is increased. This is possibly due to improper estimation as a result of increase in the number of unknown parameters. Higher order FIR would possibly fit well only if the length of the time series was large. Thus careful examination of time series in conjunction with p-value activation maps reveals the superiority of one technique over another. Most fMRI techniques usually ignore the issue of examining the estimated time series.

5. CONCLUSIONS

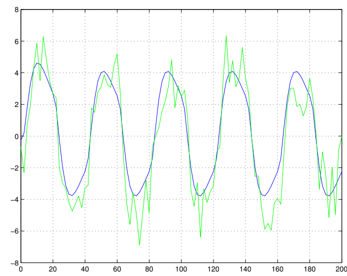
We have introduced the use of Laguerre polynomials in modeling the HR using a physiologically motivated noise model. It must be concluded that for this class of problems dealing with real physiological data, conclusions should not be drawn merely on the basis of computed test statistics which many of the proposed methods do. A close look at the estimated time series should be carried out to see the inherent physiology in the estimated waveforms. The FIR approach produces a noisy estimate of the signal which does not appear physiological and possibly underestimates the noise leading to a test statistic which is not much different from the proposed method. This is because by taking a close look at the expression for the test statistic it can be observed that it is a ratio of the estimated signal to noise. Thus incorrectly overestimating the signal and underestimating the noise may lead to higher values of test statistic and one may conclude that the method is superior over another.



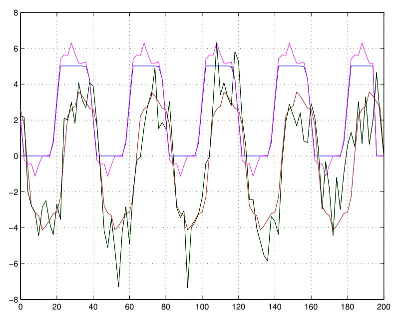
a) P Value Map- Laguerre



b) P Value Map- FIR



c) Response- Laguerre



d) Response - FIR orders 4,6, 11

Fig. 1. P Value Maps and Estimated Time Series Plots.

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