HEMODYNAMIC TRANSFER FUNCTION ESTIMATION WITH LAGUERRE POLYNOMIALS AND CONFIDENCE INTERVALS CONSTRUCTION, FROM FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) DATA

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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 offer two contributions here. Firstly 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. Additionally we develop a procedure for providing *confidence intervals* for the *whole* HR function. This feature is completely lacking in all previous work.

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 broad statistical tasks to be carried out for analysis of the superimposed time series at a pixel can be classified into four categories 1) Modeling and estimating the HR [8], [9] that is assumed to get convolved with the stimulus input, 2) Evaluate a model selection criterion to compare the validity of the model with other models [4], 3) Make an inference on the pixel as to whether it was activated or not [9], [2], 4) Specify Confidence Intervals (CI) on the estimated parameters or a function of estimated parameters such as HR. Tasks 1 and 3 are quite standard while task 4 is not *common*. We propose new approaches in carrying out tasks 1 and 4 in this paper, while task 2 will be pursued elsewhere.

The paper is organized as follows. In section 2, we discuss the use of Laguerre polynomials in modeling the HR and the method of estimation of unknown parameters for each pixel of a slice. In section 3, we propose an approach of making an inference based on constructing *joint* CIs on the HR, while section 4 deals with results and section 5 with conclusions. The idea of constructing *joint* CIs discussed in section 3, can be extended to several other problems.

2. MODELING AND PARAMETER ESTIMATION

The approach to time series decomposition at a pixel is built on the work of several researchers [2] who used a 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 [5]. 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 [5], 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. Unfortunately a high order FIR filter is required to model the response [9]. It has been shown in [6] 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 [8], 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 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 [6] and have shape similar to the empirically assumed HR [5], [9],[8]. It is thus expected that a few basis functions will be able to characterize the HR and modeled response will have a physiological shape [5]. Thus the 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. Based on (1), if the mean value of the noisy signal at pixel P is removed then the 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,

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

For a known covariance matrix, the maximum likelihood estimate of $\boldsymbol{\beta}$ is

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

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. The is because 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.

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

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

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

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 $\mathbf{X}$. This will ensure the circular convolution involved as a result of multiplying the DFTs will not result in 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 $\mathbf{e} = \tilde{\mathbf{y}} - \tilde{\mathbf{X}}\boldsymbol{\beta}$. 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. The estimated HR is thus given by

$$\hat{h}_P(t) = \sum_{i=1}^{L} \hat{f}_{i,P} g_i^a(t) \qquad (13)$$

where $g_i^a(t)$ has been defined in (6).

3. CONFIDENCE INTERVALS CONSTRUCTION

After HR estimation [8], to the best of our knowledge no inference approaches on HR have been proposed so far. We show how to develop *joint* confidence intervals (CI) on the HR as a function of time based on Scheffe's method [7]. The estimates in (13), $\mathbf{f} = [\hat{f}_1 \ \ldots \ \hat{f}_L]$ are $\sim N(\mathbf{f}, \mathbf{V}^{-1})$ where $\mathbf{V} = \tilde{\mathbf{X}}_g^H \mathbf{C}^{-1} \tilde{\mathbf{X}}_g$, with $\tilde{\mathbf{X}}_g$ being the columnwise DFT of the matrix $\mathbf{X}$ in (9) with its first column removed. If we consider constructing joint CI on functionals of the form $h(i) = \mathbf{d}_i^H \mathbf{f}, i = 1, \ldots, N$ then a natural estimator of $h(i)$ is $\hat{h}(i) = \mathbf{d}_i{}^H \hat{\mathbf{f}}$, which is $\sim N(h(i), \mathbf{d}_i^H \mathbf{V}^{-1} \mathbf{d}_i)$. An $100(1-\alpha)$ CI on a *single* $h(i)$ is *straightforward* and given by,

$$\{\hat{h}(i) \pm Z_{1-\frac{\alpha}{2}} \sqrt{\mathbf{d}_i^H \mathbf{V}^{-1} \mathbf{d}_i}\} \qquad (14)$$

However for a *joint* CI, we need C_α such that

$$P\{\frac{|\hat{h}(i) - h(i)|}{\sqrt{\mathbf{d}_i^H \mathbf{V}^{-1} \mathbf{d}_i}} \leq C_\alpha; i = 1, \ldots N\} = 1 - \alpha \qquad (15)$$

which is equivalent to

$$P\{\max_{1 \leq i \leq N} \frac{|\hat{h}(i) - h(i)|}{\sqrt{\mathbf{d}_i^H \mathbf{V}^{-1} \mathbf{d}_i}} \leq C_\alpha\} = 1 - \alpha \qquad (16)$$

Scheffe's method for upper bounding this probability is based on the following bounding arguments

$$\hat{h}(i) - h(i) = (\mathbf{d}_i^H \mathbf{V}^{-\frac{1}{2}})(\mathbf{V}^{\frac{1}{2}}(\hat{\mathbf{f}} - \mathbf{f})) \qquad (17)$$

Then, by Cauchy-Schwartz inequality,

$$|\hat{h}(i) - h(i)| \leq \sqrt{\mathbf{d}_i^H \mathbf{V}^{-1} \mathbf{d}_i} \sqrt{(\hat{\mathbf{f}} - \mathbf{f})^H \mathbf{V} (\hat{\mathbf{f}} - \mathbf{f})} \qquad (18)$$

Thus,

$$\max_{1 \leq i \leq N} \frac{|\hat{h}(i) - h(i)|}{\sqrt{\mathbf{d}_i^H \mathbf{V}^{-1} \mathbf{d}_i}} \leq \sqrt{(\hat{\mathbf{f}} - \mathbf{f})^H \mathbf{V} (\hat{\mathbf{f}} - \mathbf{f})} \qquad (19)$$

So, from (16) and (19)

$$P\{\max_{1 \leq i \leq N} \frac{|\hat{h}(i) - h(i)|}{\sqrt{\mathbf{d}_i^H \mathbf{V}^{-1} \mathbf{d}_i}} \leq C_\alpha\} \leq P\{(\hat{\mathbf{f}} - \mathbf{f})^H \mathbf{V} (\hat{\mathbf{f}} - \mathbf{f}) \leq C_\alpha^2\} \qquad (20)$$

Since $V^{\frac{1}{2}}(\hat{\mathbf{f}} - \mathbf{f})$ is $N(0, I)$, then quadratic form on right hand side (RHS) of (20) will have a χ^2 distribution with L degrees of freedom. Hence, the RHS of (20) is $P(\chi_L^2 \leq C_\alpha^2)$. Thus, C_α^2 does not depend on N and is given by

$$C_\alpha^2 = \chi_{L;1-\frac{\alpha}{2}}^2 \qquad (21)$$

Then the joint $100(1-\alpha)\%$ CI of general functionals of the form $\hat{h}(i)$ defined in the beginning of this section is given by,

$$\left[\hat{h}(i) \pm C_\alpha \sqrt{\mathbf{d}_i^H \mathbf{V}^{-1} \mathbf{d}_i}\right] \qquad (22)$$

Now we construct joint CI on the real and imaginary parts of the estimated frequency domain HR using (22). From (22) joint $100(1-\alpha)$ CI on real and imaginary parts of the estimated HR at frequencies $\omega_k, k = 1, \ldots, N$ are

$$\left[[\hat{\tilde{h}}(\omega_k)]_R \pm C_\alpha \sqrt{(\mathbf{d}_{\omega_k}^H)_R \mathbf{V}^{-1} (\mathbf{d}_{\omega_k})_R}\right] \qquad (23)$$

and

$$\left[[\hat{\tilde{h}}(\omega_k)]_I \pm C_\alpha \sqrt{(\mathbf{d}_{\omega_k}^H)_I \mathbf{V}^{-1} (\mathbf{d}_{\omega_k})_I}\right] \qquad (24)$$

where C_α^2 is obtained from (21) and

$$(\mathbf{d}_{\omega_k})_R = [\tilde{g}_1^a(\omega_k) \ \ \ldots \ \ \tilde{g}_L^a(\omega_k)]_R^{'} \qquad (25)$$

$$(\mathbf{d}_{\omega_k})_I = [\tilde{g}_1^a(\omega_k) \ \ \ldots \ \ \tilde{g}_L^a(\omega_k)]_I^{'} \qquad (26)$$

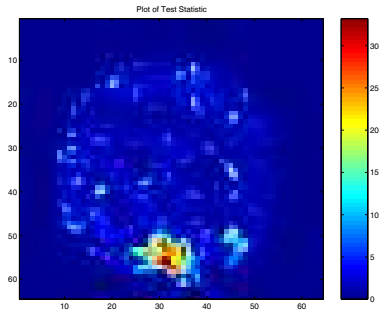
with the subscripts R and I denoting the real and imaginary parts of the vector respectively and $\tilde{g}_i^a(\omega_k)$ being the i^{th} frequency domain Laguerre polynomial at ω_k. After a joint CI has been obtained at each ω_k we compute the inverse discrete Fourier (IDFT) of the frequency domain response to obtain the CI on the time domain response.

4. RESULTS

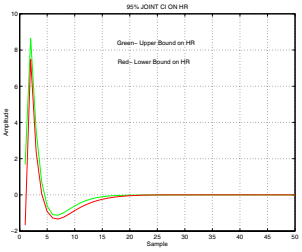
The fMRI data used in this study were collected from a visual experiment using a Siemens Allegra MR scanner, using a gradient-echo planar pulse sequence. A visual blocked design experiment was carried out in which a subject was presented with a readily recognizable stimulus present on a screen for 1700 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. 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 [5] . 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, shows the value of an intuitive test statistic which is evaluated as the ratio of estimated signal to estimated noise at each pixel of a slice. The values are not thresholded in this plot, it just shows the value of the test statistic over the whole slice. Strong activations have been observed in the visual cortex as expected. In figure 2, we plot the 95% upper and lower *joint* CI bounds on the estimated HR at an activated pixel of this slice. It can be observed that the shape of the estimated HR is similar to assessed physiological shape In figure 3, 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. Note that the smeared response also appears physiological.

5. CONCLUSIONS

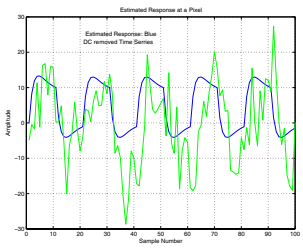
We have introduced the use of Laguerre polynomials in modeling the HR using a physiologically motivated noise model. In addition to estimating the HR, we have also constructed *joint* CI on the HR. This idea of joint CI construction could be extended in constructing it joint CI on the test statistic in a region of interest on all slices and open insights to more elaborate methods of making inferences.



(a) Plot of Test Statistic



(b) 95 % CI on HR



(c) Response at an activated pixel

Fig. 1. Test Statistic and Signal Estimation.

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