Subspace Approaches for fMRI Time Series Estimation

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***Abstract*— In this paper, we present a subspace approach for functional magnetic resonance imaging (fMRI) time series analysis. The signal subspace is formed of the eigenvectors of data correlation matrix. The approach is utilized both for single-trial estimation of blood oxygenation level dependent (BOLD) responses in fMRI time series and for studying the functional connectivity of BOLD responses from different spatial areas.**

I. INTRODUCTION

Functional magnetic resonance imaging (fMRI) is a non-invasive method for studying human brain function and constructing whole brain activation maps for sensory and mental functions with relatively high spatial resolution. The most frequently used fMRI technique, the blood oxygenation level dependent (BOLD) technique, is based on different magnetic properties of oxygenated and deoxygenated hemoglobin in venous capillaries of the brain. Neuronal activity causes local increases in cerebral blood flow and cerebral blood volume. Although the neuronal activity consumes oxygen thus increasing the concentration of deoxygenated hemoglobin, the oxygen consumption is exceeded by the import of oxygenated blood. This causes a surplus of oxygenated hemoglobin which in T_2^*-weighted image is seen as an intensity increase and is called the BOLD response.

The relationship between stimulus, neural activation, and BOLD response has been studied since fMRI was introduced in 1992 [1], [2], but it is still not yet thoroughly understood. It has been found that the shape of the BOLD response varies across subjects and also within subject depending on the type of the stimulus and active cortical area [3], [4], [5]. The BOLD response is relatively slow, the peak of the response arises about 4-5 seconds after the neural activation and it may take even 10 seconds or more for the response to return to the baseline after that. For short interstimulus intervals this is problematic because the summation of the consecutive responses is highly nonlinear. However, linear deconvolution has been found to be effective, if the stimuli are separated by at least 4 seconds [3].

Normally the purpose of fMRI studies is to locate the cortical areas involved in processing the given stimulus. The analysis is done on a voxel-by-voxel basis not concentrating on the interactions or dependencies of different cortical areas. However, brain regions do not act in isolation, but are connected and they communicate with each other. The term functional connectivity is defined as the temporal correlations among neurophysiological events between spatially remote cortical areas [6]. Functional connectivity studies have, however, been mainly concentrated on block-designs [7], [8], whereas temporal dependency of event-related responses has gained less attention.

In this paper, we propose a subspace methodology for estimating the single-trial BOLD responses and their functional connectivity. For the single-trial estimation of BOLD responses a subspace regularization method is proposed. In the method, a nonlinear observation model is used for the BOLD response and the solution of the model parameters is obtained through subspace regularization. The BOLD response subspace is constructed from eigenvectors of data correlation matrix. A similar subspace can also be used for studying the functional connectivity of BOLD responses. In this approach, BOLD responses from different cortical areas are concatenated and the eigenvectors are calculated from the correlation matrix of this augmented data. The temporal correlations of BOLD responses from different cortical areas can then be determined from the eigenvector features.

II. METHODS

A. fMRI measurements and simulations

The artificial BOLD responses can be generated using a balloon model. The balloon model is a simple biomechanical model for the hemodynamic changes during brain activation [9], [10]. The central idea of the model is that the venous compartment is modeled as an expandable balloon. The neuronal activity causes an increase in cerebral blood flow (CBF) that increases the cerebral blood volume (CBV) i.e. inflates a venous "balloon". The two dynamical variables in defining the actual BOLD effect are the total deoxyhemoglobin content q and the volume of the balloon v. The time dependent changes in v and q are driven by changes in CBF, CBV, and cerebral metabolic rate of oxygen (CMRO2). The balloon model is a nonlinear model for the BOLD signal change $\frac{\Delta s}{s}$

$$\frac{\Delta s}{s} = V_0 \left[k_1 (1-q) + k_2 \left(1 - \frac{q}{v}\right) + k_3 (1-v) \right] \quad (1)$$

where V_0 represents the baseline CBV and k_1, k_2 and k_3 are dimensionless parameters that depend on the imaging parameters among other things.

Two different real fMRI measurements were acquired for this study: 1) a null data set for obtaining realistic noise and 2) a simple motor Go/NoGO task (button press for green

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squares and ignorance of red squares). Both measurements were performed in the Department of Clinical Radiology in the Kuopio University Hospital with a Siemens Magnetom Vision 1.5 T MRI scanner. During the measurement of the null data the volunteer was instructed to do nothing in order to acquire data as clean as possible with no intentional actual activations. The interscan interval in this measurement was 2.5 seconds. The gradient echo-echo planar (EP) images comprised of 16 slices with in-plane resolution of 4×4 mm. The motor task was measured with 1.5 second interscan interval and the EP images comprised of 16 slices with in-plane resolution of 3×3 mm. An anatomical T_1-image comprised of 180 sagittal slices with in-plane resolution of 1×1 mm covering the whole head was also acquired in both cases.

Both data sets were preprocessed using SPM2 (Statistical Parametric Mapping) developed by the Wellcome institute in London, UK (`http://www.fil.ion.ucl.ac.uk/spm/`). The preprocessing involved correction of movements, correction of differences in acquisition times between slices, coregistration of the EP images to the anatomical image, and normalization of the images to the SPM2 template.

B. Subspace methodology

This section describes the subspace methodology for estimating the single-trial BOLD responses and their functional connectivity. The subspace in both cases is constructed from the eigenvectors of data correlation matrix. Let us denote a single BOLD response measurement with a column vector

$$z(t) = [z(1), \ldots, z(N)]^T \tag{2}$$

and an ensemble of M measurements with a matrix

$$Z = \begin{pmatrix} z_1(1) & \cdots & z_M(1) \\ \vdots & \vdots & \vdots \\ z_1(N) & \cdots & z_M(N) \end{pmatrix} \tag{3}$$

where $z_m(t)$ is the m'th BOLD response measurement and N is the length of each measurement. The correlation matrix of the BOLD response measurements can then be estimated as

$$R_Z = \frac{1}{M} Z Z^T. \tag{4}$$

The eigenvectors u and the corresponding eigenvalues λ can be solved from the eigendecomposition

$$R_Z u = \lambda u. \tag{5}$$

Quantitatively, the first eigenvector u_1 (corresponding to the largest eigenvalue) is the best mean square fit of a single waveform to the set of BOLD response measurements. Thus, the first eigenvector is often similar to the mean of the measurements. In case the BOLD response measurements are otherwise similar but there is some time variation in response onsets, the second eigenvector tends to cover this latency variation, and thus, is often similar to the first derivative of the response [11].

1) Subspace regularization approach for single-trial BOLD response estimation: The subspace regularization method has been previously used in the single-trial estimation of evoked potentials [12]. Let us assume a nonlinear observation model

$$z = s + v = h(\theta; t) + v \tag{6}$$

where z is the sampled measurement, s is the BOLD response, $h(\theta; t)$ is some nonlinear model for the BOLD response, and v is the measurement noise.

The ordinary least squares (LS) solution for parameters θ is obtained by minimizing the functional

$$l(\theta) = \|z - h(\theta; t)\|^2. \tag{7}$$

Parameters θ can be solved e.g. by using the iterative Levenberg-Marquad algorithm

$$\hat{\theta}_{i+1} = \hat{\theta}_i + \kappa \left(J_h^T J_h + \lambda I\right)^{-1} \left[J_h^T \left(z - h(\hat{\theta}_i)\right)\right] \tag{8}$$

where κ defines the length of the iteration step, J_h is the Jacobian determinant of the nonlinear model $h(\theta)$, and λ is a positive constant.

The subspace regularized modification of the LS functional can be written in the form [12]

$$l = \|z - h(\theta)\|^2 + \alpha^2 \|(I - H_S H_S^T) h(\theta)\|^2 \tag{9}$$

where α is the regularization parameter. H_S is consisted of the eigenvectors of data correlation matrix and forms an orthonormal basis for a signal subspace. The distance of $h(\theta)$ from this subspace is $\left(I - H_S H_S^T\right) h(\theta)$. The Levenberg-Marquad algorithm for the subspace regularized solution becomes

$$\begin{aligned} \hat{\theta}_{i+1} \quad = \quad & \hat{\theta}_i + \kappa \left(J_h^T J_h + \alpha^2 J_h^T (I - H_S H_S^T) J_h + \lambda I\right)^{-1} \cdot \\ & \left[J_h^T \left(z - h(\hat{\theta}_i)\right) + \alpha^2 J_h^T \left(I - H_S H_S^T\right) h(\hat{\theta}_i)\right]. \end{aligned} \tag{10}$$

2) Subspace approach for functional connectivity estimation: Let us consider two different cortical areas. The voxel time series from both areas are divided into adequate BOLD response measurements. Let us denote the m'th such response from area 1 with $z_m^1(t) = \left[z_m^1(1), \ldots, z_m^1(N)\right]^T$ and that from area 2 with $z_m^2(t)$ correspondingly. An augmented $2N \times M$ data matrix is then formed as

$$Z = \begin{bmatrix} z_1^1(t) & \cdots & z_M^1(t) \\ \\ z_1^2(t) & \cdots & z_M^2(t) \end{bmatrix} \tag{11}$$

where M is the number of responses and N is the length of responses.

The subspace for the augmented data matrix is then constructed from the eigenvectors of the data correlation matrix. The correlation matrix of the augmented BOLD responses can be estimated by using (4) and the eigenvectors u and the corresponding eigenvalues λ can be solved from the eigendecomposition (5).

In the augmented data case, the first eigenvector u_1 (corresponding to the largest eigenvalue) is expected to be similar

to the mean BOLD responses in the two different areas. The next few eigenvectors will cover the latency variations of the BOLD responses. If the latency variation of the BOLD responses in areas 1 and 2 are independent, then at least two separate eigenvectors are needed to cover these latency variations. If, on the other hand, there is strong functional connectivity between the two areas, the latency variations are expected to be mainly covered by a single eigenvector.

The significance of each eigenvector is described by the corresponding eigenvalue. Information about the trial-to-trial responses can be obtained from the coefficients

$$\hat{\theta}_j = u_j^T Z, \quad j = 1, \ldots, K \tag{12}$$

where K is the number of eigenvectors and $\hat{\theta}_j = [\hat{\theta}_j(1), \ldots, \hat{\theta}_j(M)]$. That is, the m'th element of $\hat{\theta}_j$ describes the contribution of the j'th eigenvector to the m'th augmented response.

III. Results and Discussion

The proposed subspace methodology was tested with both simulated and real fMRI data. In the single-trial estimation of the BOLD responses, the observation model should be able to model the BOLD response in reasonable accuracy, but at the same time the model should not have too many parameters to be estimated. The restriction to the number of parameters is due to the relatively low interscan interval, i.e. a single BOLD response does not have very many data points. This problem can be avoided to some extent by interpolating the BOLD data in a denser time grid. It should however be realized that such an interpolation does not add information to the BOLD data, but merely improves the fitting statistics to some extent and makes the data look smoother. Here we used a band limited Fourier interpolation with 4 Hz sampling rate. As an observation model we used the model of Cohen *et. al* [13]

$$h(\theta; t) = At^{\delta} e^{-t/\tau} + C \tag{13}$$

with A, δ, τ and C as the unknown parameters.

Single-trial BOLD responses were calculated by using both the ordinary LS and the regularized LS formulation. Typical single-trial estimates for simulated and real data are presented in Fig. 1. The value of the regularization parameter was selected experimentally. As a result it was observed that the proposed subspace regularization method seems to enhance the estimates of the BOLD responses in cases with a lot of noise. Especially the estimate of the BOLD response amplitude seems to be enhanced.

The functional connectivity was then evaluated by simulating two different data sets, one with correlations between the BOLD responses from the two brain areas and one with independent BOLD responses. The BOLD responses in both cases were simulated by using the balloon model (1). The simulated BOLD responses were then added into the preprocessed real fMRI noise measurement. The simulated responses were then interpolated (4 Hz Fourier interpolation) mainly to improve the visualization of the responses and the eigenvectors to be extracted. Finally, the BOLD responses

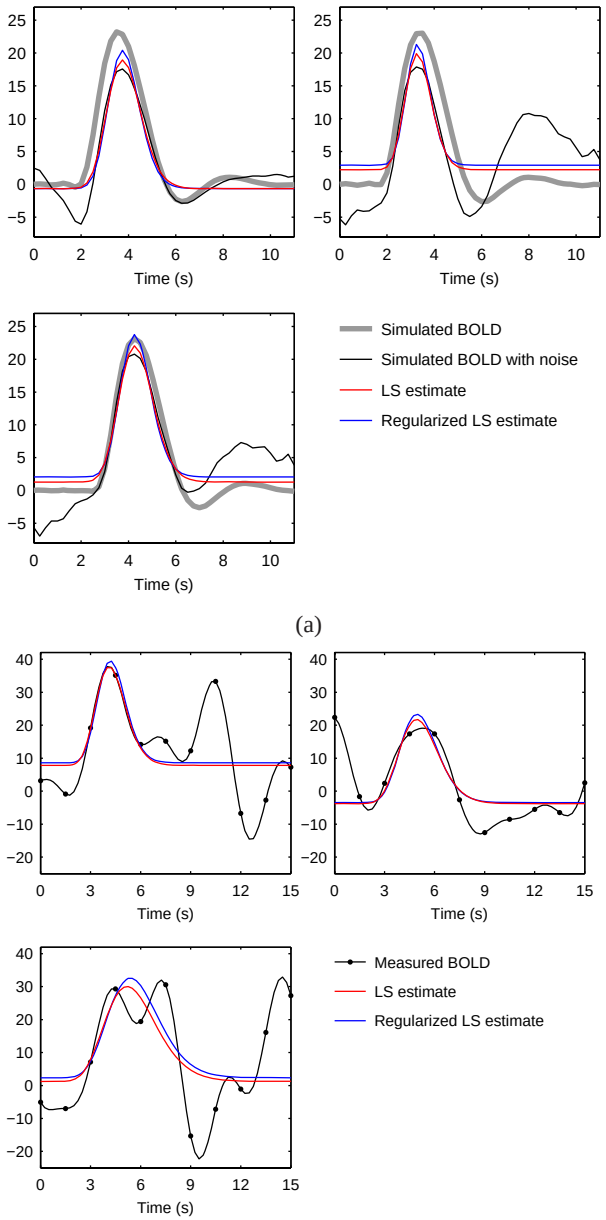

Fig. 1. Typical BOLD response estimates for (a) the simulated data and (b) the real data.

for areas 1 and 2 were concatenated according to (11) for independent and dependent cases, thus, creating two data sets. These concatenated data sets are presented on top of Fig. 2.

The eigenvectors and the corresponding eigenvalues were calculated for both data sets. The first three eigenvectors for both the independent and dependent data sets are presented on bottom of Fig. 2. The first eigenvectors were found to be quite similar for both data sets. The interesting difference between the data sets was found in the second and third eigenvectors. In the independent case the second eigenvector covered the latency variation of the BOLD responses in area 2 (i.e. primary motor cortex) and the third eigenvector

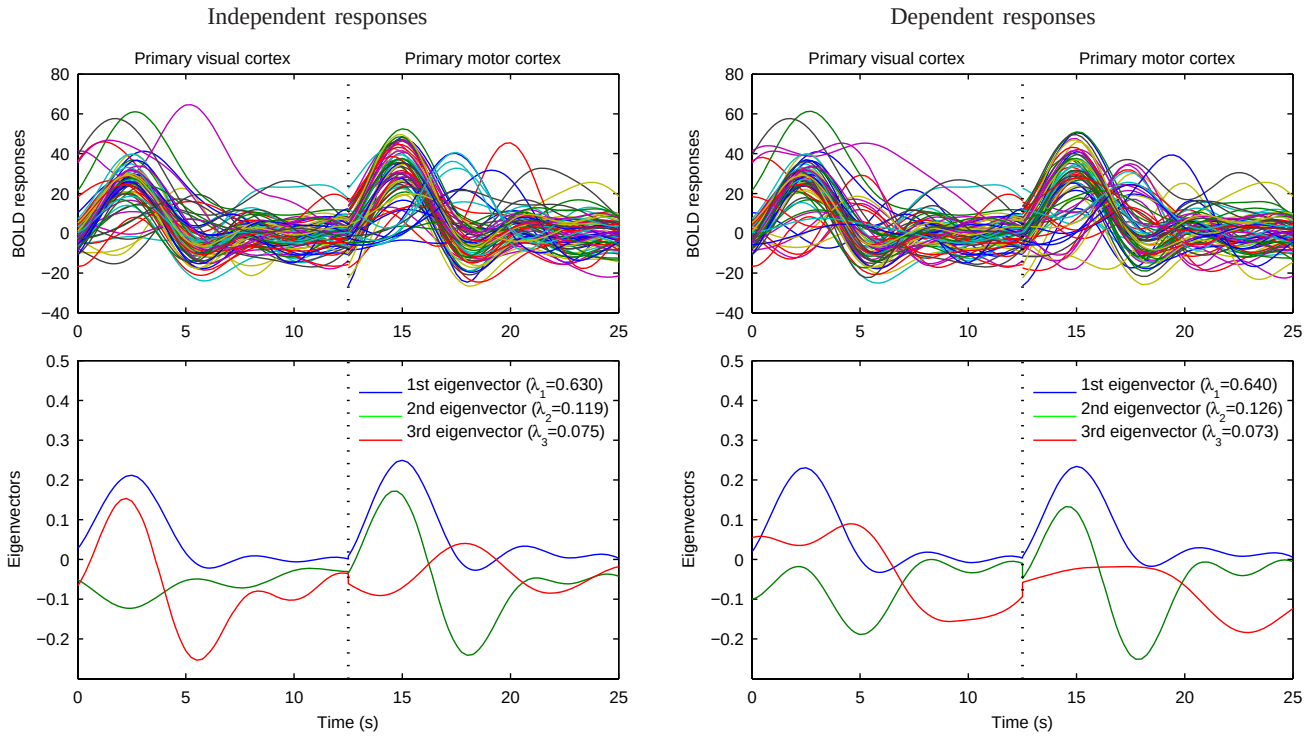

Fig. 2. Functional connectivity estimation. (a) The 70 simulated BOLD responses with no dependencies and the corresponding three largest eigenvectors. (b) The 70 simulated BOLD responses with dependencies and the corresponding three largest eigenvectors.

the latency variation of the BOLD responses in area 1 (i.e. primary visual cortex). In the dependent case, on the other hand, the second eigenvector covered most of the latency variation of BOLD responses in both areas.

IV. Conclusions

We have proposed a subspace based approach for fMRI time series analysis. We have shown how the same subspace ideology can be used both in the single-trial estimation of BOLD responses and also for studying the functional connectivity of distinct cortical areas. In the single-trial estimation of BOLD responses, the subspace regularization seems to improve the BOLD response estimates when compared to ordinary LS solution. In addition, it was shown how the eigenvector subspace of augmented BOLD response data can be used for evaluating functional connectivity.

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