Semiparametric Paradigm Free Mapping: Automatic detection and characterization of fMRI BOLD responses and physiological fluctuations without prior information

C. Caballero-Gaudes[1], N. Petridou[1,2], S. Francis[1], and P. Gowland[1]
[1]Sir Peter Mansfield Magnetic Resonance Centre, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom, [2]University Medical Centre Utrecht, Utrecht, Netherlands

Introduction: In recent work we showed that by means of sparse estimation techniques the spatial and temporal evolution of single-trial BOLD responses can be automatically detected without any prior knowledge of the stimulus timing and without thresholding: paradigm free mapping (PFM) [1]. However, fMRI time series also contain physiological and instrumental fluctuations which can hinder the detection of BOLD responses associated to neuronal activity [2]. Physiological fluctuations can be removed prior to PFM via high-pass filtering, or by RETROICOR, RVT or RVHRCOR [3,4,5], but these techniques must be employed in a pre-processing stage and require the additional recording of physiological respiratory and cardiac waveforms. Here, extending on our previous work, we present a novel technique which by decomposing the fMRI signal enables automatic detection of fMRI BOLD responses without prior stimulus information and automatic fitting of significant frequency fluctuations present in the signal, such as non-neuronal cardiac and respiratory fluctuations (semiparametric PFM, sPFM). This technique is based on a semiparametric linear representation of the fMRI signal [6,7] which is recursively fitted using a morphological component analysis algorithm [8]. The feasibility of this technique was evaluated in simulations and real fMRI data acquired at 7T, and its performance validated to RETROICOR.

Semiparametric Parametric Free Mapping: Let us assume the fMRI signal at time point n can be written as $y_n = b(t_n)+g(t_n)+e(t_n)$, where $b(t_n)$ represents the BOLD responses, $g(t_n)$ an arbitrary and unknown function and $e(t_n)$ a noise term. Assuming a linear model for the BOLD response, $b(t_n)$ can be described as the convolution of a stimulus-related signal $s(t)$ with the BOLD response $h(t)$. For N fMRI volumes, this component can be written in vectorial form as $\mathbf{b}=\mathbf{Hs}$, where $\mathbf{H}$ is a convolution matrix defined according to the BOLD response, and $\mathbf{b}$ and $\mathbf{s}$ are vectors of size N. Similarly, let us expand $\mathbf{g}$ as a linear combination of terms of the discrete cosine and sine (DCST) transforms, $\mathbf{g} = \mathbf{\Phi\alpha}$, where $\mathbf{\Phi}$ is a orthonomal matrix with the DCST terms and $\mathbf{\alpha}$ is a vector with the amplitude of the components. Hence, the model signal can be written as $\mathbf{y} = \mathbf{Hs} + \mathbf{\Phi\alpha} + \mathbf{e}$. Under this model, the vectors $\mathbf{s}$ and $\mathbf{\alpha}$ can be estimated by minimizing a L1-regularization problem which minimizes the squared sum of the residuals and the L1-norms of both estimates. This optimization problem can be solved by morphological component analysis which alternates the estimation of one of the vectors ($\mathbf{s}$ and $\mathbf{\alpha}$) with the Basis Pursuit Denoising (BPDN) estimator whereas keeping constant the other estimate [8].

Methods: Simulations: fMRI time series were simulated by generating random stimulus waveforms (single-trial stimuli with random onset, ISI, and duration ranging from 2 to 6 s) which were convolved with an HRF with random parameters (mean=SPM Canonical HRF, std=0.2*mean). Subsequently, random Gaussian noise (CNR=2..4) and sinusoidal signals at 1Hz and 0.3 Hz (and harmonics) to simulate cardiac and respiratory fluctuations were added to the ideal waveforms. Different TR values were also simulated to study the effect of the Nyquist sampling criteria of physiological fluctuations. **Real Data**: Two fMRI datasets acquired on a 7T Philips scanner during a visual-motor paradigm were used (single-shot GE EPI, TR=2s, TE=30ms, 2mm isotropic resolution, 1 slice, 342 scans). Datasets were only corrected for motion, a linear trend and normalized to percentage signal change. The hemodynamic matrix $\mathbf{H}$ was based on the SPM Canonical HRF and the DCST was used to define the semiparametric matrix $\mathbf{\Phi}$. Here, the regularization parameter was selected to the universal threshold given by $\lambda = \hat{\sigma}\sqrt{2\log N}$, where $\hat{\sigma}$ is the MAD estimate of the noise standard deviation [9]. Finally, spatial clustering was applied to reduce false positives. The frequency spectral of the raw data, the signal removed by RETROICOR and the semiparametric component estimated with sPFM were visually compared. Note that no stimulus timing information was employed for the analysis, and that no amplitude thresholding was applied after estimation. For comparison with sPFM, the datasets were also corrected for physiological noise with RETROICOR.

Results: Simulated results demonstrated the ability of the proposed algorithm to accurately estimate both the BOLD responses without prior timing information of onsets or physiological fluctuations, even with mismatches in modelled BOLD shape. The performance of the algorithm improved at shorter TR, where spectral overlap of physiological signals and hemodynamic responses is minimized. The results in real data demonstrate that sPFM can decouple the physiological fluctuations and the hemodynamic responses without prior physiological information or timing of the stimulus responses. The spatial distribution of the signal removed by RETROICOR and SPFM physiological components are similar (Figure 1a shows maps at frequencies corresponding to respiratory (0.23Hz) and cardiac (0.014Hz) components, respectively). In addition, the activations associated to the visuo-motor task were also detected (Figure 1b)

Discussion: A novel technique was presented which can automatically detect BOLD fMRI responses without prior information about the paradigm and also denoise the signal from physiological fluctuations. The technique achieves similar performance to RETROICOR without the need for physiological information, even at relatively high temporal resolution (TR=2s). Our initial restuls suggest that sPFM can be used to identify other sinusoidal fluctuations of physiological origin extracted with RVT or RVHRCOR [4,5]. As this technique is completely free of a-priori information it is ideally suited to the analysis of spontaneous brain activations at resting state and experimental conditions where the timing of the BOLD cannot be predicted or measured.

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