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A Methodology to Improve Estimation of Stimulus-Evoked Hemodynamic Response from fNIRS Measurements

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Abstract— **Functional near-infrared spectroscopy (fNIRS) is a non-invasive optical neuroimaging method used to investigate functional activity of the cerebral cortex evoked by cognitive, visual, auditory and motor tasks, detecting regional changes of oxy- and deoxy-hemoglobin concentration. Accurate estimation of the stimulus-evoked hemodynamic response (HR) from fNIRS signals in order to quantitatively investigate cognitive functions requires to cope with several noise components. Some of them appear as random disturbances (typically tackled through averaging techniques), while others are due to physiological sources, such as heart beat, respiration, vasomotor waves, and are particularly challenging to be dealt with because they lie in the same frequency band of HR. In this work we present a new two-steps methodology for the HR estimation from fNIRS data. The first step is a pre-processing stage where physiological trends in fNIRS data are reduced by exploiting a mathematical model identified from the signal of a reference channel. In the second step, the pre-processed data of the other channels are filtered with a recently presented non-parametric Bayesian approach (Scarpa et al., Optics Express, 2010). The presented method for HR estimation is compared with widely used methods: conventional averaging, band-pass filtering and principal component analysis (PCA). Results on simulated data reveal the ability of the proposed method to improve the accuracy of the estimates of the functional hemodynamic response, as well as the estimate of peak amplitude and latency. Encouraging preliminary results in a representative real data set showing an improvement of contrast to noise ratio are also reported.**

I. Introduction

FUNCTIONAL near-infrared spectroscopy (fNIRS) is a neuroimaging technique that provides the opportunity to monitor hemodynamic activity within the human head in a low cost and noninvasive manner [1], [2]. Infrared light is sent into the head at the surface of the scalp (source) and then detected at another location on the scalp (detector). The distance between each source/detector pair (hereafter, channel) is typically 3 cm to ensure penetration through scalp and skull into the underlying cerebral cortex. Fluctuations in the detected signal are related to temporal changes in concentration of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) via a modified Beer Lambert Law (MBLL) [3]. fNIRS is used to investigate functional activity of the cerebral cortex evoked by motor, visual, auditory and, as in the present work, cognitive tasks.

The signal acquired with fNIRS is a mixture of stimulus-evoked hemodynamic response (HR) (≈0.1 Hz), global physiological noise, which is mainly constituted by heart beat (≈1 Hz), respiration (≈0.2 Hz), vasomotor waves (or Mayer's waves, ≈0.1 Hz), as well as low and very low frequency oscillations (≤0.01 Hz) and measurement noise. Several methods have been proposed in the literature to estimate HR from fNIRS signal, but the so-called conventional averaging (CA) technique is still probably the most used method [4], [5]. Succinctly, the HR is determined by averaging the fNIRS recordings (trials) collected after N identical stimuli, with N being often in the order of several tenth. Estimation of the HR is achieved by assuming both the independence of the background noise from the activity elicited by the to-be-processed stimulus, and the difference in phase of the physiological components from stimulus to stimulus. Other broadly used methods are based on band-pass filtering [6] and principal component analysis (PCA) [7]. The first method is based on the different frequencies of HR and physiological components. PCA is used to eliminate low frequency oscillations, removing the first one or two eigenvectors, which account for about 80% of the variance in the optical data.

Recently, methods based on the use of "reference channels" have been proposed [8], [9], [10]. The "reference signal" is acquired by a detector placed on the scalp at a distance of 1 cm from the source, rather than the 3 cm of standard channels. Since the depth-penetration of the reference channel is limited, the acquired signal includes global physiological trends but no stimulus-evoked hemodynamic response. Consequently, the reference channels can be used to model physiological noise containing hemodynamic trends from superficial tissue, and it is a key element of the proposed method.

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II. Materials And Methods

The proposed methodology consists of two steps: (*A*) a model of the physiological noise is derived by the reference signal and subtracted from the raw data of the other channels; (*B*) resulting data are then filtered with a non-parametric Bayesian approach to reduce the measurement noise [11], [12]. The methodology is assessed against a test set composed by synthetic data where the true HR is known (*C*). In addition, a limited set of real data is considered (*D*).

A. Step 1: Reduction of Physiological Trends

The signal acquired by the reference channels contains only physiological and measurement noise, and does not hold information about HR. The cardiac trend is reduced with a notch filter, with a centre frequency set to the frequency corresponding to the maximum value of the spectrum in the range 0.7-1.5 Hz, and it is computed for each trial in order to take into account possible variations of heart rate. Due to their quasi-periodic nature, the other physiological trends are modeled, on a trial by trial basis, as a sum of *M* sine waves (1), where *M* is chosen according to the number of dominant low frequencies (<0.18 Hz) detectable in the spectrum:

$$y^{*}_{PH}(t) = \sum_{i=1}^{M} \left[a_i \sin(\omega_i t) + b_i \cos(\omega_i t) \right] + c \qquad (1)$$

In practice, the maximum value allowed for *M* is 3, since this is the maximum number of physiological components that could be detected in our real data [12]. Indeed, due to the presence of a great amount of measurement noise and to individual variability, Mayer wave, low respiratory frequency and very low frequency oscillations may not be all visible in the spectrum. From the reference signal, amplitudes (a_i, b_i, c) and frequencies (ω_i) in (1) are identified using a least squares minimization algorithm and a grid search method [13], respectively. Then, the model-predicted reconstruction of the physiological trends (y^{*}_{PH}) is subtracted from the raw channels data, which are then filtered with the Bayesian approach of *Step 2*.

B. Step 2: Bayesian filtering

The used Bayesian filtering approach (previously developed and assessed in [12] against fNIRS signals which had not undergo *Step 1*), exploits models of the 2nd order a priori statistical information on the background fNIRS noise and on the unknown HR. While such a statistical description of the ongoing fNIRS noise is obtained, trial by trial, by fitting an auto-regressive model against pre-stimulus data, the a priori known smoothness of the unknown HR is formalized by describing it as the multiple integration of a white noise process. The model has only one unknown parameter which, for each trial, is estimated by the discrepancy criterion. The estimated HR is then obtained from the average of the filtered trials.

C. Simulated data

Simulated data were generated to assess the performance of the developed algorithm. 30 simulated subjects were produced according to real data acquired in [12] and [14]. For each subject, the time series relative to 18 channels for HbO and the corresponding 18 channels for HbR were generated. A reference channel for each hemisphere was simulated, for both HbO and HbR. The position of the channels is reported in Fig. 1 on a template [15]. Each channel contains about 15600 time-points, corresponding to 2000 s with a sampling frequency equal to 7.8125 Hz.

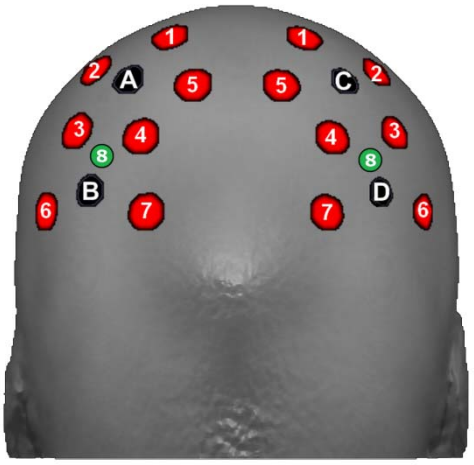

Fig. 1. Probe placement on the ICBM152 template (occipital view). Sources (red circles) and detectors (black circles) overlaid on the head surface of the ICBM152-PM template. The green circles represent the reference channels.

It is well known that in fNIRS measurements background signals from systemic physiology are additional signals to the functional hemodynamic response [12]. These fluctuations were thus expressed as a linear combination, as in (1), of five sinusoids. Frequency and amplitude of each sinusoid were not constant in the time series, and were different between subjects. They are reported in Table I.

TABLE I
Physiological Components

	Frequency (Hz)	Amplitude (nM)
cardiac	1.1 ± 0.1	350 ± 10
respiratory	0.2 ± 0.03	150 ± 10
vasomotor	0.07 ± 0.04	400 ± 10
low freq.	0.01 ± 0.001	700 ± 100
very low freq.	0.001±0.0001	700 ± 100

Mean and standard deviation of frequency and amplitude of each physiological component.

The measurement noise η was modeled as a white normal process with standard deviation tuned to bear the standard deviation of real data. The measurement noise was different between subjects and between channels. In order to simulate artifacts (e.g., due to movements of the subject or shifts of a source or a detector) short non-cyclic abrupt drifts were added in 6 subjects, at a random temporal position and with random amplitude.

The HR, function of time *t* (*t=0* correspond to the presentation of the stimulus), was modeled by a linear

combination of two gamma-variant functions Γ [16], time dependent, with a total of 6 variable parameters (2):

$$u_{true}(t) = \alpha \times \left[\Gamma(t,\tau_1,\varphi_1) - \beta \times \Gamma(t,\tau_2,\varphi_2)\right] \quad (2)$$

where u_{true} is the known HR, α tuned the amplitude, τ_i and φ_i tuned the shape and scale, respectively, and β determined the ratio of the response to undershoot. In order to simulate the HR due to two different visual stimuli, two u_{true} were generated by properly tuning the parameters in (2) . This led to a first HR profile with a peak amplitude of 180 ± 10 nM and a peak latency equal to 5.0 ± 0.2 s, while the second HR profile had a peak amplitude of 210 ± 10 nM and a peak latency equal to 5.5 ± 0.2 s. Note that HR's amplitude is lower than that of physiological components. 70 stimuli for each condition were simulated, with an interval inter-stimuli varying between 15 and 20 s. The HRs were added in channels A1, A2, B4, C1, C2, D4. In channels A3, A4, B3, B7, C3, C4, D3, D7 the peak amplitudes were halved. In the other channels no HR was added.

Thus, samples $y(t)$ of each simulated channel of HbO were generated as in (3):

$$y(t) = u(t) + v(t) = u_{ture}(t) + y_{PH}(t) + \eta(t) \quad (3)$$

where u (if present) contains the samples of u_{true} in (2), and the noise term v contains the physiological components y_{PH} and the measurement noise η.

HbR's channels were generated in the same way. According to our real data, the sign of each component was changed, a delay of 1 s was added and all the amplitudes, except measurement noise, were reduced to 25%.

D. Real Data

Hemodynamic data of a subject were acquired. Cognitive task and sources-detectors locations are the same of [14]. In order to obtain reference signals, data were acquired adding two sources, placed as shown in Fig. 1 (green circles).

III. Results

A. Simulated Data

The proposed methodology was applied to simulated data and compared with widely used methods: conventional averaging, band-pass filtering and PCA. For each method, raw data were first band-pass filtered (Butterworth, pass band: from 0.01 Hz to 3 Hz) to further remove any slowly drifting signal components and other noise with frequencies far from the signal band. The band-pass filtering consisted in a classical Butterworth, band-pass, from 0.01 to 0.3 Hz. PCA was used to remove the global physiological activity by subtracting the component with the largest value of the coefficient of spatial uniformity (CSU) from the data [17]. The obtained HRs were then smoothed with a Savitzky and Golay's filter with polynomial order equal to 3 and framesize equal to 25 time-points. An example of the obtained HRs is shown in Fig. 2.

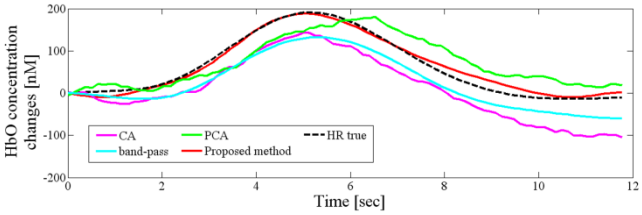

Fig. 2. HR estimate (subject 23, channel 1, condition 1, HbO) obtained with CA (magenta), band-pass filtering (cyan), PCA (green), and the proposed method (red). The true HR is reported in black.

In order to give a quantitative measure of the goodness of the obtained estimates, the estimation error was defined (4):

$$E_{HR} = \left\| u_{true} - \bar{u} \right\|^2 / \left\| u_{true} \right\|^2 \quad (4)$$

where $\bar{u}$ was the estimate of the HR and u_{true} was the HR used in (2) to generate the simulated data. The value of E_{HR} is a sort of percentage estimation error. The parameters used to measure brain activation are the peak amplitude and latency of the HRs. Thus, the absolute percentage error of the estimate of these two parameters, E_A and E_L respectively, has been evaluated. The indexes E_{HR}, E_A and E_L were obtained for CA, band-pass filtering, PCA and the proposed method. They are reported in Table II.

TABLE II
Estimation Error

		CA	Band-Pass	PCA	Proposed Method
HbO	E_{HR}	22 ± 2 90 ± 10	18 ± 2 74 ± 9	42 ± 4 107 ± 16	6 ± 1 22 ± 4
	E_A	7.2 ± 3.8% 18.7 ± 5.7%	4.5 ± 2.5% 10.2 ± 6.3%	25.4 ± 3.1% 31.0 ± 5.9%	9.5 ± 2.2% 7.3 ± 4.0%
	E_L	4.4 ± 1.5% 3.6 ± 3.0%	3.7 ± 0.9% 3.0 ± 2.7%	7.2 ± 6.2% 14.9 ± 9.4%	3.3 ± 0.9% 2.0 ± 1.7%
HbR	E_{HR}	30 ± 4 121 ± 22	24 ± 5 96 ± 18	47 ± 5% 122 ± 31%	12 ± 3 47 ± 8
	E_A	10.3 ± 3.2% 32.2 ± 5.8%	3.2 ± 2.4% 22.8 ± 4.8%	3.8 ± 2.8% 28.0 ± 8.7%	6.2 ± 3.7% 5.3 ± 4.0%
	E_L	3.9 ± 2.1% 4.4 ± 2.6%	3.4 ± 1.1% 4.2 ± 3.4%	6.6 ± 5.4% 7.9 ± 4.1%	2.3 ± 1.5% 3.6 ± 1.6%

Mean and standard deviation of estimation error E_{HR}, absolute percentage error on the estimation of peak amplitude E_A (%) and peak latency E_L (%) obtained with CA, band-pass filtering, PCA and the proposed method. The red values are obtained in the channels in which the HR were halved.

The best estimation error (E_{HR}) is obtained with the proposed method (6 ± 1, for HbO), which reduces E_{HR} of 73%, 67%, 86% with respect to CA, Band-pass filtering and PCA, respectively. The proposed method achieved excellent estimates of peak's amplitude and latency even if HR's amplitude is halved. Even if performance of the proposed method on E_A, although good, was not always the best, its results on E_{HR} and E_L suggest a more robust estimation of the peak amplitude with respect to the other methods. The higher values of E_{HR} with respect to E_A and E_L are due to the fact that E_{HR} is computed on the whole HR, whose entire

profile is difficult to estimate, especially in the first and in the last seconds. The higher values of E_{HR} in estimates relative to HbR are due to the presence of a greater measurement noise with respect to HR amplitude, and underline the complexity in analyzing HbR data [18].

For each method, the values of peak amplitude were considered (for both HbO and HbR), and a one tail t-test was performed to identify the channels showing a significant activation increase relative to the baseline. A second series of one-tail paired t-tests was conducted to compare the two conditions. All active channels (the channels in which HR was added) were correctly identified by all methods. With the proposed method, a significant difference ($p<0.05$) between the two conditions was found in all but one of the 14 active channels, the exception being the channel with the greatest measurement noise. With CA, Band-pass filtering and PCA a significant difference was found respectively on 4, 1, and 8 of the 14 active channels. Furthermore, a series of one-tail paired t-tests was conducted to compare the two conditions considering the values of peak latency, for both HbO and HbR. A significant difference ($p<0.05$) between the two conditions was found with CA, Band-pass filtering, PCA and the proposed method respectively in 13, 8, 7, 14 of the 14 active channels.

B. Real Data

Preliminary results on real data reveal an improvement in the contrast-to-noise ratio (CNR, [8]). The CNR obtained with the proposed method is 1.52, while the ones obtained with CA, band-pass filtering and PCA are 1.29, 1.38, 1.34 respectively. An exhaustive evaluation of the proposed method will be conducted on real data.

IV. Conclusion

The proposed two steps methodology provides a valuable reduction of physiological noise and leads to correct measures of brain activation. It achieves a good estimate of the functional hemodynamic response in comparison to widely used methods and it does not present some drawbacks of these methods which are likely to cause worse estimation errors. Conventional averaging is algorithmically blind to information about HR and fNIRS signals that can be independently extracted from the optical signal, and it requires many trials (≈100) to obtain a valuable estimate of HR. Unlike Band-pass filtering, the proposed method reduces noise while preserving the evoked hemodynamic response, even if they overlap in terms of frequency spectra. This drawback of the band-pass filtering is underlined by the non significant difference between the two conditions. Problems with PCA include its tendency to decrease the amplitude of the hemodynamic response in the activated regions and to propagate noise from noisy channels to all other channels. Indeed, due to the presence of the HR in 14 out of 20 channels, the HR itself was partially identified as a global oscillation and removed, leading to an underestimation of its amplitude. In addition, PCA works well if systemic physiological spatiotemporal covariance is well separated from the evoked hemodynamic response, but this is not true for all subjects. Furthermore, the physiological spatiotemporal covariance is not necessarily space-time separable, as assumed in PCA [7].

These results underline that the proposed two-steps methodology is a general and flexible way to correctly estimate evoked hemodynamic response, and it can be employed for a large class of fNIRS experiments.

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