A GLM-Based Approach to Estimate Stimulus-Evoked Hemodynamic Response from fNIRS Measurements

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Abstract— **Functional near-infrared spectroscopy (fNIRS) uses near-infrared light to measure changes in the concentration of oxygenated (HbO) and deoxygenated hemoglobin (HbR). Physiological processes, such as heart beat, respiration, vasomotor waves, induce concentration changes of HbO and HbR well detectable in the fNIRS signal. Some of these physiological components, as well as random disturbances, can interfere with the estimation of the stimulus-evoked hemodynamic response (HR), a key function for the quantitative understanding of the functional activity of the cerebral cortex evoked by cognitive tasks. In fact, the HR spectrum overlaps with that of the above mentioned physiological components, complicating the use of filtering techniques to extract HR from fNIRS measurements. Furthermore, the HR is characterized by a marked variability in shape, according to the type of experiment, or across conditions, brain regions and subjects. Given these observations, the development of a method to estimate stimulus-evoked HR from fNIRS measurements is challenging. In this work we present a new methodology for HR estimation from fNIRS data, based on the so-called general linear model (GLM). First a parametric model of the HR is identified for each subject, HbO and HbR separately. Then, this model of HR, together with its temporal derivative, is used as basis function of the GLM, which is applied to each channel and condition to estimate the corresponding HR. The automatic identification of the basis functions and the robustness of GLM with respect to measurement noise make the proposed method suitable for most fNIRS experimental paradigms. In the present work, results on simulated data show that the methodology is superior to other widely used methods for HR estimation, i.e. conventional averaging and band-pass filtering. Encouraging preliminary results are also obtained from real data collected during a simple finger tapping task.**

Keywords-fNIRS; near-infrared spectroscopy; hemodynamic response; general linear model; GLM; basis function.

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]. Although fNIRS provides measurements limited to the cerebral cortex, it provides several advantages with respect to other neuroimaging technologies: it is safe, portable and relatively robust to movement artifacts. 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 the modified Beer Lambert Law (MBLL) [2]. Notably, fNIRS is used to investigate functional activity of the cerebral cortex in a wide variety of cognitive tasks. The signal acquired with fNIRS is naturally affected by disturbances engendering from ongoing physiological activity (e.g., cardiac, respiratory, vasomotor wave) and random measurement noise. Several methods have been proposed in the literature to estimate the stimulus-evoked hemodynamic response (HR) from fNIRS signal, but the so-called conventional averaging (CA) technique is still probably the most used method [3], [4]. 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 for HR estimation are based on band-pass filtering [5], principal component analysis (PCA) [6] and adaptive filtering [7]. Although each of these methods is generally associated with increases in signal-to-noise ratio, they often require specific expedients (e.g., the acquisition of resting state data before each stimulus, or the registration of hemodynamic activity of the whole head) and each of them presents some drawbacks. Indeed, band-pass filtering might equally reduce both noise and HR, because of their overlapping in terms of frequency spectra. 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. Adaptive filtering approaches require the use of reference

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channels, which involve additional sources and detectors that are not always available. Promising methods to estimate HR from fNIRS measurements are based on the so-called general linear model (GLM) [8], and a free GLM-based software for analyzing fNIRS signal is available [9]. The GLM, which has become a standard method for analyzing fMRI data, explains data as a linear combination of an explanatory variable (composed by basis functions) plus an error term. GLM is robust in sub-optimal registrations, where there has been a severe optical signal attenuation due to scattering or poor contact. In event-related paradigms and, in particular, in rapid event-related paradigms (with an inter-stimulus interval, ISI, of few seconds), GLM-based approaches provides better results compared to the conventional approaches [10]. Nevertheless, several fundamental issues remain to be addressed. A matter of concern regarding GLM approaches regards the choice of the functions used to model the hemodynamic response (basis functions). Moreover, the same basis functions are often used for both HbO and HbR without accounting for their differences and the dependency on individual subjects, as well as the kind of experiment (note that the shape of the HR is strongly influenced by several characteristics, such as the stimulus type, the analyzed brain areas, the ISI).

In the present work, a method able to automatically identify the most suitable basis functions is presented with the aim of obtaining an approach that might be adopted in the large majority of fNIRS experiments.

II. Materials and Methods

The proposed algorithm consists of *(A)* a pre-processing stage of the raw data, *(B)* the identification of the basis functions that will be used, and *(C)* the implementation of the general linear model. The methodology is assessed against a test set composed by *(D)* synthetic data generated according to *(E)* real data.

A. Pre-processing

In order to reduce the effect of physiological and noisy components which might compromise HR estimation, raw optical data were filtered with a Butterworth band-pass filter (4^{th} order), with low and high cutoff frequencies of 0.01 and 3 Hz, respectively. The filter removed slow drifts and other noise with frequencies distant from the signal band.

B. Identification of the Basis Functions

The stimulus-evoked hemodynamic response was modeled with a gamma-function-based model (1), time dependent (t):

$$h(t;p)=\left(\frac{t}{d}\right)^{a}\cdot e^{-\left(\frac{t-d}{b}\right)} \quad (1)$$

where $p=[a,b,d]^T$ was the unknown parameter vector.

The model was identified, on a subject-by-subject basis, on the signal obtained by averaging all trials belonging to the same condition: trials from all channels were block-averaged considering a period of 12 seconds after the stimulus onset. In particular, parameter vector p was obtained, for each condition, using Weighted Non-Linear Least Squares according to the equation (2):

$$p=\min_{p}\left\|z-h(t;p)\right\|^{2}_{\Sigma_V^{-1}} \quad (2)$$

where z was the signal obtained after the block-average and matrix Σ_V was a diagonal matrix whose entries were used to weight the corresponding time-points of the signal. As the most meaningful part of the HR profile is the one related to the peak (4-5 seconds after the onset), a small weight has been given to the first and last 2 seconds of the signal. HbO and HbR data were modeled separately, for both conditions. The models obtained for each of the two conditions and their temporal derivatives formed the basis functions. An example of the identified HR model for HbO and its temporal derivative is reported in Fig.1.

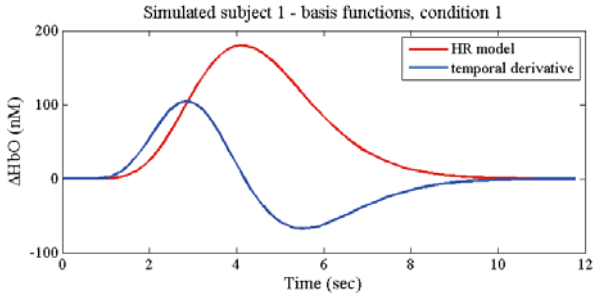

Fig.1: Identified HR model for HbO (red) and its temporal derivative used as basis funtions (blue).

C. Genear Linear Model (GLM)

For each subject, the general linear model was applied to the pre-processed data *(A)*, using the basis functions identified in *(B)*. GLM is a statistical model that describes data as a linear combination of functions plus an error term. Functions were obtained by multiplying the design matrix X with the parameter matrix β. Columns of X contained a "convolution" between the "experimental design referred to each condition" (i.e. a vector having "1" in the time-points corresponding to the times of presentation of the stimuli and "0" elsewhere) and each basis function. β contained the unknown parameters that multiply each column of X: each parameter correspond to the amplitude of each basis function in each channel. Thus, the corresponding model was (3):

$$Y=X\cdot\beta+\varepsilon \quad (3)$$

where Y was the pre-processed data, X was the design matrix, β was the unknown parameter matrix and ε was the error term. The matrix β was obtained with the linear least squares estimation (4):

$$\beta=\left(X^{T}\cdot X\right)^{-1}\cdot X^{T}\cdot Y \quad (4)$$

Once obtained the matrix β , the final estimation of HR was obtained for each condition and channel, by multiplying the basis functions with the relative amplitude (element of β).

D. Synthetic Data

Simulated data were generated to assess the performance of the developed algorithm as in [11], [12]. For each of the 30 simulated subjects, the time series relative to 10 channels for HbO and the corresponding 10 channels for HbR were generated. The HR was modeled by a linear combination of

two gamma-variant functions. Fluctuations due to physiological components were expressed as a linear combination of sinusoids, while the measurement noise was modeled as a gaussian white noise process. Numbers of trials, amplitude and latency of the HRs, frequency and amplitude of the sinusoids and standard deviation of the white normal process were chosen according to real data.

E. Real Data

Ten right-handed participants (5 females, mean age 28, from 24 to 37) performed the experiment after providing informed consent. Each participant was seated in a comfortable chair placed before a computer screen and a keyboard, and performed a simple finger-tapping protocol: when an arrow head pointing to the left or right appeared on the screen, the participant had to press twice the "A" key or the "L" key, with the forefinger of his left or right hand respectively. A fixation cross was presented at the center of the screen for 2 seconds, alerting participants about the incoming presentation of the stimulus. Participants performed a total of 80 trials within an event-related paradigm (with ISI ranging from 12 to 15 seconds): on 50% of them, the arrow was pointing to the right (condition 1) while on the other 50% it was pointing to the left (condition 2). Trials were organized in 2 consecutive blocks (with a short pause between successive blocks), and each block included 40 trials; trial order was randomized in both blocks. This simple protocol was chosen to validate the proposed method for two main reasons: first, it has been extensively investigated in fNIRS studies [6]; furthermore, the cortical areas which are involved in such task are well known. Subject had to move only twice the forefinger so as to elicit a limited hemodynamic response, which might be comparable to those obtained with other event-related paradigms [13], [14].

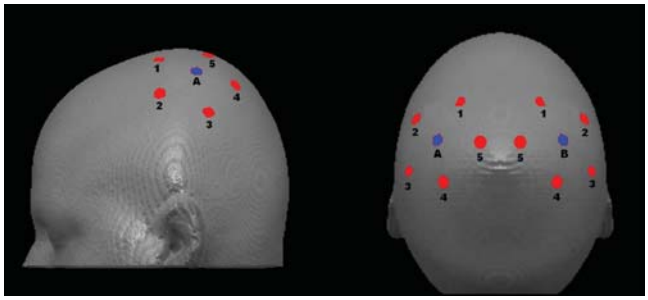

Fig.2: Probe placement: sources (red circles) and detectors (blue circles) overlaid on the head surface of the ICBM152 template.

The fNIRS signal was acquired with a multi-channel frequency-domain NIR spectrometer (ISS Imagent™, Champaign, Illinois), equipped with 20 laser diodes (10 emitting light at 690 nm, and 10 at 830 nm) and 2 photo-multiplier tubes. Sources and detectors were held in place on the scalp using a custom-made holder and velcro straps. Each source location comprised two source optical fibers, one for each wavelength. The distance between each source/detector pair was 3 cm, and they were placed in the motor area (parietal lobe): their position is reported in Fig.2 on a template [15]. Each channel contains about 12000 time-points, corresponding to 25 minutes (1500 seconds). The sampling frequency was 7.8125 Hz.

III. Results

A. Synthetic Data

The proposed methodology was applied to simulated data and compared with widely used methods: conventional averaging and band-pass filtering. 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. 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.3.

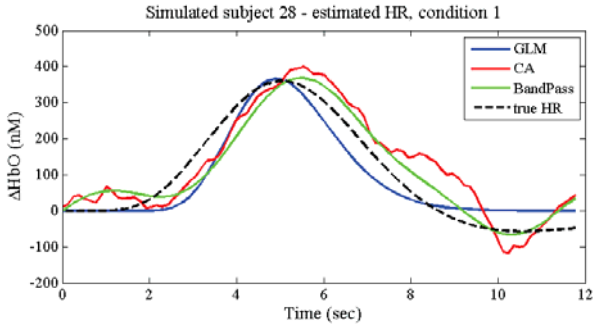

Fig.3: HR estimate (subject 28, channel 5, condition 1, HbO) obtained with CA (red), band-pass filtering (green) and the proposed method (GLM, blue). The true HR is reported in black.

In order to give a quantitative measure of the goodness of the obtained estimates, the estimation error was defined (5):

$$E_{HR} = 100 \cdot \left\| u_{true} - \bar{u} \right\|^2 / \left\| u_{true} \right\|^2 \qquad (5)$$

where $\bar{u}$ was the estimate of the HR and u_{true} was the HR used 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 and the proposed method. They are reported in table I.

The best estimation error (E_{HR}) is obtained with the proposed method (14 ± 8, for HbO), which reduces E_{HR} of 42% and 33% with respect to CA and Band-pass filtering, respectively. The improvement in E_{HR} is significant ($p<0.01$) if compared both with CA and Band-Pass. The proposed method achieved good estimates of peak's amplitude and excellent estimate of peak's latency for HbO. For HbO, E_A and E_L obtained with the three methods are not significantly different from each other. The higher values of E_{HR} in estimates relative to HbR are due to the presence of higher noise with respect to HR amplitude, and underline the complexity in analyzing HbR data [16]. The reduced amplitude of HR with respect to physiological components and measurement noise leads the GLM to fail in HbR peak's latency estimation: this could be solved with a more sophisticated pre-processing strategy aimed at attenuating global trend [17].

TABLE I

	%	CA	Band-Pass	Proposed Method
HbO	E_{HR}	24 ± 21	21 ± 18	14 ± 8
	E_A	22 ± 17	20 ± 15	25 ± 16
	E_L	7 ± 5	6 ± 5	5 ± 4
HbR	E_{HR}	42 ± 44	35 ± 37	30 ± 12
	E_A	28 ± 21	26 ± 19	28 ± 14
	E_L	5 ± 5	4 ± 4	14 ± 3

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 and the proposed method.

B. Real Data

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. As expected, all channels resulted active. For each condition, the obtained peak amplitude were compared in all symmetric channels: A1-B1, A2-B2, A3-B3, A4-B4, A5-B5 (see Fig.2). For condition 1, corresponding to the movement of the forefinger of the right hand, no significant difference was found. The right hand was the dominant hand of our subjects, its movement induced a lower activation, similar in both hemisphere [13]. For condition 2, movement of the forefinger of the left hand, a significant larger amplitude was found in channel B4, confirming a greater activation in the right hemisphere, contralateral to the moved hand [14]. The mean difference between peak amplitude of the HR corresponding to condition 2 in channel A4 and B4 obtained with the proposed method (61 nM) was greater than that obtained with CA and Bandpass (32 and 33 nM, respectively), suggesting that the proposed method achieves a more proper HR estimation.

IV. Conclusions

The completely automatic identification of the basis functions makes the proposed method usable with both event-related design or block design and it does not require, unlike the public available software GLM-based (NIRS-SPM) [9], a priori knowledge about the evoked HR profile. The block-average of trials from all channels is useful to obtain a good preliminary description of the HR, whose amplitude and latency are then better estimated, for each channel and condition, with the GLM approach. The use of the temporal derivative as basis function of GLM allows to correctly estimate peak latency and the undershoot, which is not considered in the initial model (only one gamma-function) of the HR. An improvement of the proposed method can be done by adding to the basis functions the second temporal derivative of HR model or the derivative computed with respect to one of the parameters of the model, as in NIRS-SPM. In conclusion, even if an exhaustive evaluation of the proposed method has still to be conducted on real data, the preliminary results are encouraging, given that the method is able to provide a good estimate of the functional hemodynamic response in comparison to other widely used methods. Results on simulated and real date underline that the proposed GLM-based methodology is a general and flexible way to properly estimate evoked hemodynamic response, and it can be employed for a wide variety of fNIRS experiments.

References

[1] D. A. Boas, M. A. Franceschini, A. K. Dunn, and G. Strangman, "Noninvasive Imaging of Cerebral Activation with Diffuse Optical Tomography", in *In Vivo Optical Imaging of Brain Function*. E. D. (CRC Press), Chap 8, pp. 193–221, 2002.

[2] A. Sassaroli, S. Fantini "Comment on the modified Beer–Lambert law for scattering media". Phys. Med. Biol, vol 49, pp N255–N257, 2004.

[3] J.J. Todd, R. Marois "Capacity limit of visual short-term memory in human posterior parietal cortex". Nature, vol. 428, pp. 751-754, 2004.

[4] S. Cutini, P. Scatturin, E. Menon, P.S. Bisiacchi, L. Gamberini, M. Zorzi, R. Dell'Acqua "Selective activation of the superior frontal gyrus in task-switching: An event-related fNIRS study". NeuroImage, vol. 42, pp. 945-955, 2008.

[5] G. Jasdzewski, G. Strangman, J. Wagner, K.K. Kwong, R.A., Poldrack, D.A. Boas "Differences in the hemodynamic response to event-related motor and visual paradigms as measured by near-infrared spectroscopy". NeuroImage, vol. 20, pp. 479-488, 2003.

[6] M.A. Franceschini, D.K. Joseph, T.J. Huppert, S.G. Diamond, D.A. Boas "Diffuse optical imaging of the whole head," J. Biomed. Opt. vol 11, 054007, 2006.

[7] Q. Zhang, G.E. Strangman, G. Ganis "Adaptive filtering to reduce global interference in non-invasive NIRS measures of brain activation: How well and when does it work?". NeuroImage, vol. 45, pp. 788-794, 2009.

[8] M.L. Schroeter, M.M. Bücheler, K. Müller, K. Uludağ, H. Obrig, G. Lohmann, M. Tittgemeyer, A. Villringer, D.Y. von Cramon. "Towards a standard analysis for functional near-infrared imaging". NeuroImage, vol. 21, pp. 283-290, 2004.

[9] J.C. Ye, S. Tak, K.E. Jang, J.W. Jung, J.D. Jang "NIRS-SPM: Statistical parametric mapping for near-infrared spectroscopy". NeuroImage, vol. 44, pp. 428-447, 2009.

[10] M.M. Plichta, S. Heinzel, A.-C. Ehlis, P. Pauli, and A.J. Fallgattera "Model-based analysis of rapid event-related functional near-infrared spectroscopy (NIRS) data: A parametric validation study". NeuroImage, vol. 35, pp 625–634, 2007.

[11] F. Scarpa, S. Brigadoi, S. Cutini, P. Scatturin, R. Dell'Acqua, G. Sparacino "A Methodology to Improve Estimation of Stimulus-Evoked Hemodynamic Response from fNIRS Measurements". Proc. 33th IEEE EMBC, Boston, MA, USA, Aug 30 – Sept 3, pp. 785-788, 2011.

[12] F. Scarpa, S. Cutini, P. Scatturin, R. Dell'Acqua, G. Sparacino "Bayesian filtering of human brain hemodynamic activity elicited by visual short-term maintenance recorded through functional near-infrared spectroscopy (fNIRS)" Optics Express, vol 18, pp. 26550-26568, 2010.

[13] K. Lutza, S. Koenekea, T. Wustenbergb, L. Jancke "Asymmetry of cortical activation during maximum and convenient tapping speed" Neuroscience Letters, 373, pp 61–66, 2005.

[14] L. Holper, M. Biallas, M. Wolf "Task complexity relates to activation of cortical motor areas during uni- and bimanual performance: A functional NIRS study" Neuroimage, vol 49,pp 1105-1113,2009.

[15] S. Cutini, P. Scatturin, M. Zorzi "A new method based on ICBM152 head surface for probe placement in multichannel fNIRS". Neuroimage, vol 54, pp. 919-927, 2011.

[16] H. Sato, M. Kiguchi, F. Kawaguchi, A. Maki, "Practicality of wavelength selection to improve signal-to-noise ratio in near-infrared spectroscopy". NeuroImage, vol 21, pp. 1554–1562, 2004.

[17] K.E. Jang, S. Tak, J. Jung, J. Jang, Y. Jeong, J.C. Ye "Wavelet minimum description length detrending for near-infrared spectroscopy". Journal of Biomedical Optics, vol. 14, 2009.