Proceedings of the 29th Annual International
Conference of the IEEE EMBS
Cité Internationale, Lyon, France
August 23-26, 2007.

Neural physiological modeling towards a hemodynamic response function for fMRI

David M. Afonso dafonso@isr.ist.utl.pt
João M. Sanches jmrs@isr.ist.utl.pt
Martin H. Lauterbach (MD) mlauterbach@fm.ul.pt
Instituto de Sistemas e Robótica - Instituto Superior Técnico

Abstract— **The BOLD signal provided by the functional MRI medical modality measures the ratio of oxy- to deoxy-haemoglobin at each location inside the brain. The detection of activated regions upon the application of an external stimulus, e.g., visual or auditive, is based on the comparison of the mentioned ratios of a rest condition (pre-stimulus) and of a stimulated condition (post-stimulus). Therefore, an accurate knowledge of the impulse response of the BOLD signal to neural stimulus in a given region is needed to design robust detectors that discriminate, with a high level of confidence activated from non activated regions. Usually, in the literature, the hemodynamic response has been modeled by known functions, e.g., gamma functions, fitting them, or not, to the experimental data. In this paper we present a different approach based on the physiologic behavior of the vascular and neural tissues.**

Here, a linear model based on reasonable physiological assumptions about oxygen consumption and vasodilatation processes are used to design a linear model from which a transfer function is derived. The estimation of the model parameters is performed by using the minimum square error (MSE) by forcing the adjustment of the stimulus response to the observations.

Experimental results using real data have shown that the proposed model successfully explains the observations allowing to achieve small values for the fitting error.

I. Introduction

During functional magnetic resonance imaging (fMRI), a brief focal neural activation evokes what is called a hemodynamic time-course response function (HRF) that mainly depends on tissue physiology [1]. Although variability exist on who, where, when and how the data was acquired and processed [2,3], standard HRF estimates are often an essential basis of fMRI analysis. Several assumptions are usually made, namely that all neural impulse events produce the same HRF (assuming minimal variability across subject, brain region and acquisition system) and that a time series data is modeled as an impulse train of neural events convolved with this invariant HRF [4]. Even though some evidences have shown these assumptions to be erroneous, its impact on many fMRI statistical analysis studies has not been considered relevant enough to generally abandon the simplification advantages. In fact the most commonly used HRF are parametric analytical functions, namely gamma functions [5]–[7], and to a less extent Poisson or Gaussian distributions [8], that satisfactorily modulate the rather invariant form of the blood-oxygen-level dependent (BOLD) time-signal to short stimuli. Still, the accuracy and relative superiority of these HRF models cannot be entirely questioned because of their analytical nature, without incorporation of the slightest knowledge of the physiological processes behind the BOLD signal itself. And though the exact coupling between brain activity, vascular response and cerebral metabolic oxygen rate that leads to the BOLD response are not well understood, there are several experimental evidences that lead to conclusions and assumptions that give us a sketchily, but important, view of the BOLD physiological features.

It has been shown that an increase in cerebral neuronal activity generally leads to co-localized increases in cerebral metabolic rate of oxygen ($CMRO_2$), followed by a much larger co-localized increase in local cerebral blood flow (CBF) and volume (CBV). These effects are consequence of energy consumption by neural and glial brain cells, leading to an increased ratio of oxy- to de-oxyhaemoglobin (for which blood-oxygenation-level is the obvious complement under normal conditions) in the vessels, capillaries and surrounding tissues. Particularly, this energy consumption is putatively accounted for neuron synapse activity, hence the assumed relation between the BOLD signal and neural activity. However, the BOLD time course signal has several transient features at the onset and end of the stimulus: an initial dip and a post-stimulus undershoot; that are not explained by the coupling of flow and metabolism referred above. The initial dip, corresponding to an increase in local deoxyhaemoglobin, has been interpreted as evidence for an initial increase in oxygen extraction before flow increase; and the post-stimulus undershoot as an elevated oxygen extraction after the flow has returned to baseline. These models for the transient features based on uncoupling, coupling and reuncoupling of vascular response and $CMRO_2$ provide a, possibly rough but valuable, key element in generating a physiological model that evokes an output similar to the HRF. In fact these interpretations have been recently reinforced by multimodal fMRI studies [9]. Buxton et.al. [10] have done such a task, resulting in one of the most interesting physiological models in the area, although there is some strong skepticism on some of its base assumptions [9]. Still, this model is currently being extended and perfected, but has not had much practical application contrary to the proposed gamma function HRF's. This is most probably due to two important features of the latter: simplicity and computational efficiency.

In this paper we propose a simple linear model of the hemodynamic response function based on a modulation of basic physiological processes behind the BOLD signal, with the main objective of being used as basis for fRMI activation mapping statistical analysis. This has been done considering uncoupling, coupling and reuncoupling processes of the vascular response and $CMRO_2$ variables and accounting for neural demand and systemic feedback control of vascular response. The final results were tested on real data fMRI BOLD signal time-courses. A final Z-transform function is presented, which has obvious frequency analysis advantages providing computational processing efficiency.

II. Model Presentation

Brain activation is accompanied by a series of physiologic alterations, including focal changes in the vascular response (cerebral brain flow and blood volume), blood oxygenation and cerebral

This work was supported by Fundação para a Ciência e a Tecnologia (ISR/IST plurianual funding) through the POS Conhecimento Program which includes FEDER funds. This work was done in partial collaboration with the Hospital da Cruz Vermelha de Lisboa and the fMRI group of the Hospital de Santa Maria.

oxygen consumption. We have tried to encapsulate all of these physiological variables in a simple based linear discrete model that would translate their effects on a HRF estimation (see Fig.1). The physiologically based hemodynamic (PBH) model input is the neural activation, *r(n)* and the output is the BOLD contrast signal, *y(n)*. The reference value *Ref* is the baseline of the vascular properties. Since this work is focused on incremental variations of all its variables, this parameter is constantly null. All model blocks are zero and first order linear functions, which provide empirically reasonable approximations. Three main groups can be distinguished in the PBH model: a *brain group* which modulates the neural and glial cells oxygen consumption ($CMRO_2$) and vascular response demands; a *vessel group* which modulates the summed effect of CBV and CBF vascular changes on the rate of deoxyhaemoglobin concentration in and around blood vessels; a *control group* for the systemic negative feedback control over vasodilatation.

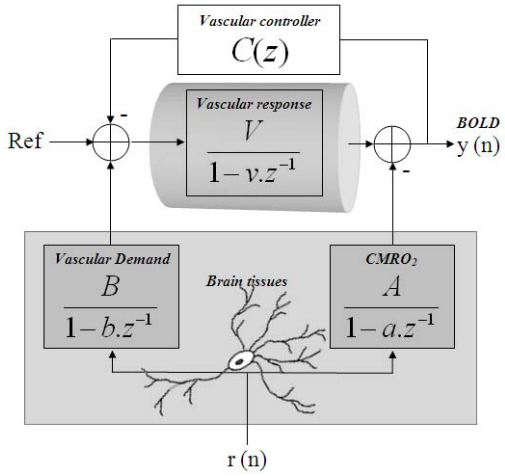

Fig. 1. Block diagram of the proposed physiologically based hemodynamic (PBH) model behind the HRF on BOLD fMRI data. It incorporates vascular response demand and oxygen metabolism consumption by brain tissue, vascular response producing changes in both CBV and CBF and systemic negative feedback control system of the vascular response. Baseline vascular properties and neural activation stimulus are considered in the *Ref* and *r(n)* inputs respectively.

The PBH model was developed upon the fundamental consideration of separate dynamics between $CMRO_2$ and vascular response features (CBV and CBF). This means that the transient initial dip and poststimulus undershoot of the HRF are then modeled as an uncoupling of these features, where the negative influence of $CMRO_2$ to the BOLD signal is not counterbalanced by the briefer vascular response. This has been an old assumption [1] that has recently gained strength through multimodal fMRI studies [9]. The uncoupling considered indicates that the vascular response demand is probably not due to the oxygen metabolism pathway, hence the separation of both blocks of the PBH models *brain group*. Still, they are both a consequence of the brain activity.

The dynamics of the actual vascular response are accounted in the *vessel group* block function. This deals with the reasonable assumption that, upon tissue demand for more blood delivery, the vascular response to this request is delayed and constrained. Besides these aspects, the gain in this block is also responsible for the relation between the vascular response features and the amplitude effect they cause on the BOLD signal. On the other hand, vascular response demand by brain tissues is most likely bigger than their needs, and alongside the vascular answering dynamic referred, there is a systemic vascular response control modeled in the *control group* that reduces the amplitude of the vascular response. Notice again that the gain of this block reflect the amplitude impact on the BOLD signal of the vasodilatation control.

III. Model Estimation

The transfer function of the discrete time PBH model displayed in Fig.1 is

$$H(z) = \frac{(AV - B) + (a + v - bAV)z^{-1} - (avB)z^{-2}}{(1 - az^{-1})(1 - bz^{-1})(1 + C(s)V - vz^{-1})} \quad (1)$$

which can re rewritten as follows

$$H(z) = \frac{Y(z)}{R(z)} = \frac{b_0 + b_1 z^{-1} + b_2 z^{-2}}{1 + a_1 z^{-1} + a_2 z^{-2} + a_3 z^{-3}} \quad (2)$$

where

$$b_0 = \frac{AV - B}{1 + VC(s)} \quad (3)$$

$$b_1 = \frac{a + v - bAV}{1 + VC(s)} \quad (4)$$

$$b_2 = -\frac{avB}{1 + VC(s)} \quad (5)$$

$$a_1 = -(a + b + \frac{v}{1 + VC(s)}) \quad (6)$$

$$a_2 = ab + (a + b)\frac{v}{1 + VC(s)} \quad (7)$$

$$a_3 = -ab\frac{v}{1 + VC(s)} \quad (8)$$

Assuming the simpler controller (more complex controllers will be considered in the future), $C(z) = K$, the correspondent difference equation is the following,

$$y(n) = \sum_{k=0}^{2} b_k r(n-k) - \sum_{l=1}^{3} a_l y(n-l) \quad (9)$$

The estimation of the parameters, b_k e a_k is performed with the minimum square error (MSE) method,

$$\hat{p} = \arg\min_{p} E(Y, R, p) \quad (10)$$

where $Y = y(0), y(1), ..., y(N-1)$ is the vector with the N experimental points, $R = r(0), r(1), ..., r(N-1)$ is the stimulus signal that is unknown and must also be estimated, $p = [b_0, b_1, b_2, a_1, a_2, a_3]$ is the vector of parameter to be estimated and $E(Y, R, p)$ is the function to be minimized,

$$E(Y, R, p) = \sum_{n=0}^{N} \left[y(n) - \sum_{k=0}^{2} b_k r(n-k) + \sum_{l=1}^{3} a_k r(n-k) \right]$$

which can be written as follows using matrix notation,

$$E(Y, R, p) = (Y - \Phi p)^T (Y - \Phi p) \quad (11)$$

where $\Phi = [\Phi_R \vdots - \Phi_Y]$ with

$$\Phi_R = \begin{pmatrix} r(0) & 0 & 0 \\ r(1) & r(0) & 0 \\ r(2) & r(1) & r(0) \\ r(3) & r(2) & r(1) \\ r(4) & r(3) & r(2) \\ ... & ... & ... \\ r(N-1) & r(N-2) & r(N-3) \\ r(N) & r(N-1) & r(N-2) \end{pmatrix}.$$

$$\Phi_Y = \begin{pmatrix} 0 & 0 & 0 \\ y(0) & 0 & 0 \\ y(1) & y(0) & 0 \\ y(2) & y(1) & y(0) \\ y(3) & y(2) & y(1) \\ ... & ... & ... \\ y(N-2) & y(N-3) & y(N-4) \\ y(N-1) & y(N-2) & y(N-3) \end{pmatrix}.$$

The minimization of $E(Y,R,p)$ is performed by finding its stationary point, $\nabla_p E(Y,R,p)=0$, with the following solution,

$$\hat{p}=\underbrace{\left[\Phi^T\Phi\right]^{-1}\Phi}_{\Psi}Y \tag{12}$$

where Ψ is called *pseudoinverse* of Φ. The stimulus $r(n)$ is not completely known and therefore must be estimated. It is assumed that

$$r(n)=\begin{cases}1 & 0\le n\le n_0\\ 0 & otherwise\end{cases} \tag{13}$$

where n_0 is unknown (notice that the data used in this paper [3] was previously aligned and shifted).

For each data set five values of n_0 were tested, $n_0=[M,...,M-4]$ in which M is the time instant where the maximum of the experimental data occurs, that is, the position of the larger maximum. The solution is obtained by choosing the set of parameters that lead to the minimum error,

$$[\hat{p},n_0]=\arg\min_{p,n_0}E(Y,R(n_0),p) \tag{14}$$

IV. Experimental Results

To test the PBH model we used the same normalized data, as used by the authors of [3]. As such it might also provide a means of comparison to their results and remarks. Note that the data was acquired in four different brain areas of twenty-seven male subjects with no history of neuronal or psychiatric diseases. T2*-weighted echo-planar images (EPI) were acquired at 4 Teslas, with variations in the TR and time resolution. For a more complete description on materials and methods used please see [3].

The experimental results are organized in three sets: i) data with poststimulus undershot (Fig.4), ii) data without poststimulus undershot (Fig.3) and iii) data that displays the initial dip (Fig.2).

For each experimental curve a set of modeled parameters was estimated as well as the optimal stimulus duration, which is unknown. Unfortunately, we did not had access to the paradigm information. But even if we did, we do not have direct access to the real duration time of the neural activation in each data sample.

From the displayed results it is concluded that the PBH model manages to explain well, in a MSE basis, the experimental curves. This provides a considerable confidence for the base assumptions upon which our PBH model is built. Note that many of these experimental data shapes rather deviate from the range of shapes that the HRF gamma functions are able to produce. Conversely our PBH model was successful in providing such form variability.

V. Conclusions

The characterization of brain regions from a functional point of view can be performed by using BOLD contrast fMRI. This technique uses the ratio of oxy- to deoxyhaemoglobin before and after the application of an external stimulus, e.g. visual or auditive, to identify the activated regions. The design of robust and reliable detectors that discriminate activated from non-activated regions, need accurate models for the HRF of the neural tissues. In the literature, usually, this hemodynamic response is obtained by fitting the experimental observations with known functions, e.g. gamma functions.

In this paper we propose a linear model, called PBH model, that describes the BOLD signal change after the application of an external stimulus, based on the *a priori* knowledge and reasonable assumptions of the physiologic behavior of the vascular and neural tissues. The neuron oxygen consumption, the vascular response demand induced by brain tissues and the vascular response process itself are modeled by first order linear systems. The systemic vasodilatation control of the vessels is modeled by a simple proportional controller.

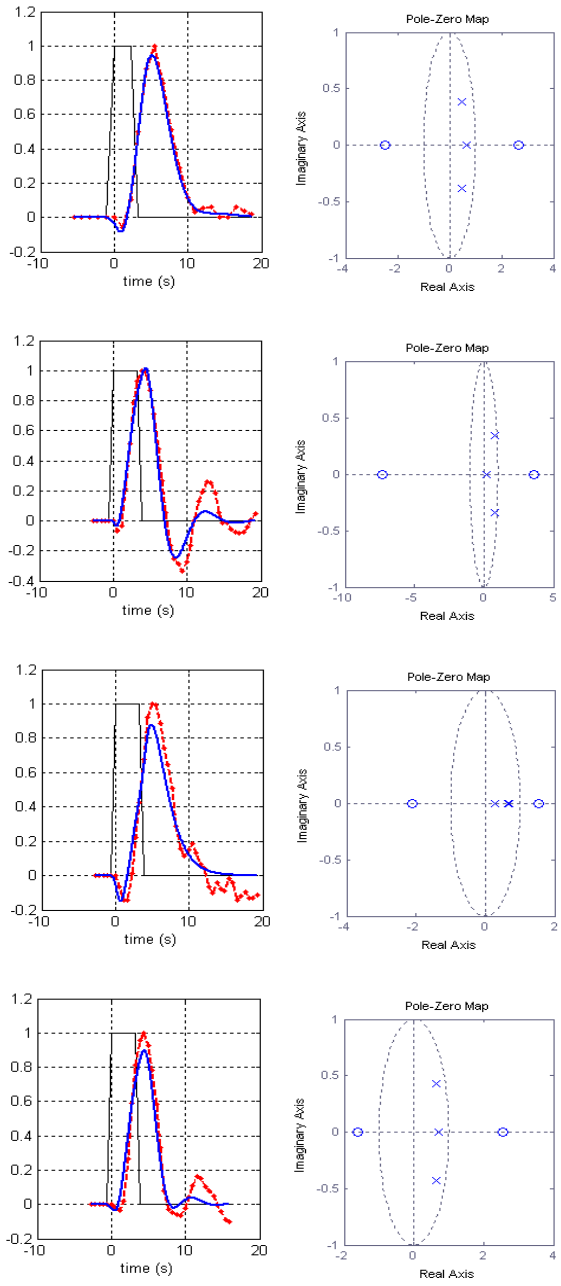

Fig. 2. Results from the PBH model estimation with 4 experimental data with initial dip. Red - real data; Blue - model; Black - stimulus.

Twelve experimental curves are presented and the corresponding model estimated. The model parameters are estimated using the minimum square error (MSE) method where the square error between the model response and the observations is minimized. Additionally, the true stimulus, which is also unknown, is also estimated and displayed.

The PBH model successfully explains the observations and will be incorporated in the activated region detector in the future.

VI. Acknowledgments

We are very grateful to D.A. Handwerker et. al. for providing the fMRI BOLD signal time course data they used on [3], which was essential to validate our model and enrich the quality of the paper.

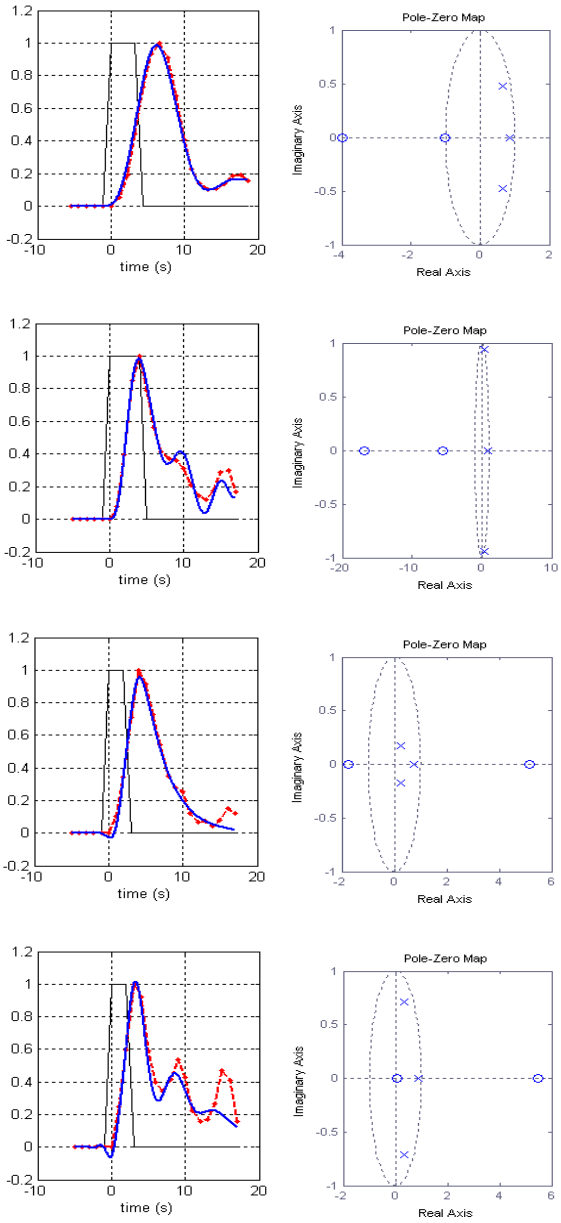

Fig. 3. Results from the PBH model estimation results with 4 experimental data without undershoot. Red - real data; Blue - model; Black - stimulus.

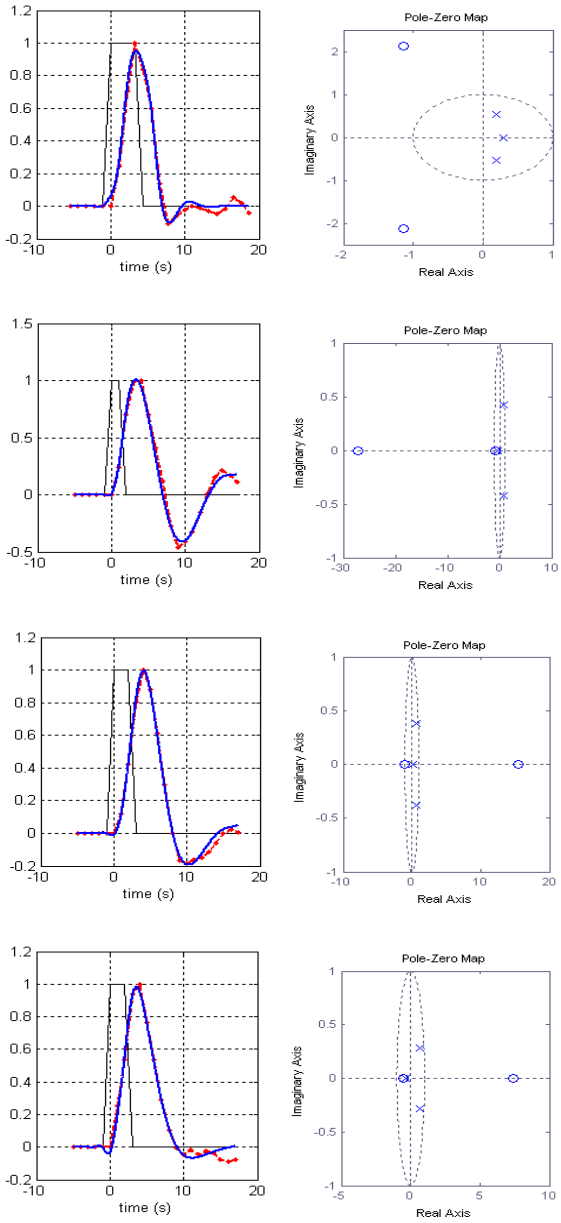

Fig. 4. Results from the PBH model estimation results with 4 experimental data with undershoot. Red - real data; Blue - model; Black - stimulus.

REFERENCES

[1] P. Jezzard, P. M. Matthews, and S. M. Smith, *Functional magnetic resonance imaging: An introduction to methods.* Oxford Medical Publications, 2006.

[2] G. K. Aguirre, E. Zarahn, and M. D'esposito, "The variability of human, BOLD hemodynamic responses," *Neuroimage*, vol. 8, no. 4, pp. 360–369, Nov 1998, clinical Trial.

[3] D. A. Handwerker, J. M. Ollinger, and M. D'Esposito, "Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses," *Neuroimage*, vol. 21, no. 4, pp. 1639–1651, Apr 2004.

[4] G. M. Boynton, S. A. Engel, G. H. Glover, and D. J. Heeger, "Linear systems analysis of functional magnetic resonance imaging in human V1," *J Neurosci*, vol. 16, no. 13, pp. 4207–4221, Jul 1996.

[5] S. L. Z. Nicholas Lange, "Non-linear fourier time series analysis for human brain mapping by functional magnetic resonance imaging." *Applied Statistics*, vol. 46, no. 1, pp. 1–29, 1997.

[6] K. J. Friston, P. Fletcher, O. Josephs, A. Holmes, M. D. Rugg, and R. Turner, "Event-related fMRI: characterizing differential responses," *Neuroimage*, vol. 7, no. 1, pp. 30–40, Jan 1998.

[7] M. A. Burock, R. L. Buckner, M. G. Woldorff, B. R. Rosen, and A. M. Dale, "Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI," *Neuroreport*, vol. 9, no. 16, pp. 3735–3739, Nov 1998.

[8] J. C. Rajapakse, F. Kruggel, J. M. Maisog, and D. Y. von Cramon, "Modeling hemodynamic response for analysis of functional MRI time-series," *Hum Brain Mapp*, vol. 6, no. 4, pp. 283–300, 1998.

[9] H. Lu, X. Golay, J. J. Pekar, and P. C. M. Van Zijl, "Sustained poststimulus elevation in cerebral oxygen utilization after vascular recovery," *J Cereb Blood Flow Metab*, vol. 24, no. 7, pp. 764–770, Jul 2004.

[10] R. B. Buxton, E. C. Wong, and L. R. Frank, "Dynamics of blood flow and oxygenation changes during brain activation: the balloon model," *Magn Reson Med*, vol. 39, no. 6, pp. 855–864, Jun 1998.