Abstract—The functional MRI (Magnetic Resonance Imaging, fMRI), is a new imaging tool to study and evaluate the brain from a functional point of view. The blood-oxygenation-level-dependent (BOLD) signal is currently used to detect the activation of brain regions with a stimulus application, e.g., visual or auditory. In a block design approach the stimuli (called paradigm in the fMRI scope) are designed to detect activated and non activated brain regions with maximized certainty. However, corrupting noise in MRI volumes acquisition, patient motion and the normal brain activity interference makes this detection a difficult task. The most used activation detection fMRI algorithm, here called SPM-GLM [1] uses a conventional statistical inference methodology based on the t-statistics, where it assumes a rather rigid shape on the BOLD Hemodynamic Response Function (HRF), constant for the whole region of interest (ROI).

A different perspective is presented in this paper; a new Bayesian method, here called SPM-MAP, for the joint detection of brain activated regions and estimation of the underlying HRF. This approach presents two main advantages: 1) the activity detection benefits from the method’s high flexibility toward the HRF shape; 2) it provides local HRF estimations.

Monte Carlo tests were performed with synthetic data, first comparing the activity detection section of SPM-MAP with the standard SPM-GLM method and second analysing the whole SPM-MAP performance. Finally, detection analysis results on real fMRI block-designed data are presented.

Index Terms—functional Magnetic Resonance, Nervous system, MAP estimation, Biomedical signal detection, Adaptive signal processing.

I. INTRODUCTION

Functional Magnetic Resonance Imaging (fMRI) is a new and exciting method that, among other purposes, allows the determination of which parts of the brain are involved in a particular task. Offering considerably high resolution (e.g. comparing with electroencephalography (EEG)) and non-invasiveness, this recent and growing modality has already been able to established itself as the most prominent method used for functional brain imaging, and will certainly have a large impact in Neurology’s future.

This modality relies on changes in blood oxygenation and volume, consequence of the hemodynamic response events related to local neural activity. This signal, called blood-oxygenation-level-dependent (BOLD), results from the endogenous magnetic contrast between oxyhaemoglobin (diamagnetic) and deoxyhaemoglobin (paramagnetic). Hence, increased blood volume reduces the local concentration of deoxygenated hemoglobin causing an increase in the magnetic resonance (MR) signal on a T2 or T2*-weighted image [2].

The computational analysis of the data provided by this method is not trivial and is a subject open to much development. Usually, it aims at obtaining a visual statistical map representation of which areas were activated by the stimulation paradigm applied during the scan, and where in the brain these areas are located. To obtain the desirable results several processing steps are usually involved, e.g. image preprocessing (motion and noise correction), spacial normalization transformation, statistical tests and the final inferences procedures [3]. Considering the last two steps, which are the focus of this paper, most of the methods described in the literature are variants of the general linear model (GLM). Although some exploratory methods like clustering, PCA [4] and ICA [5], have been used, the general approach is to express the observed response variable in terms of a linear combination of explanatory variables (EVs) [1], and make use of classical statistics (T or F tests) to infer activity, using e.g. a p-value threshold.

The main EVs used in the GLM allocate temporal variance in the (preprocessed) data with strong cor-
relation with the paradigm stimulus. To achieve this, the stimulus paradigm timing is convolved with one or more fixed shape hemodynamic impulse response function (HRF).

In the literature there are two different approaches for the HRF modeling. The most common approach is purely heuristic, using known functions (e.g. gamma functions [6,7], or Gaussian functions [8]) to fit the experimental data. Some variability of the HRF has been accounted for with the use of functional basis [9], but the constrain imposed on the HRF shape is hard. The second approach is physiological, modeling the underlying physiological process involved in the BOLD signal generation, e.g. the Balloon Model [10] which is often used and augmented [11]. But, unfortunately, due to much higher conceptual and computational complexity and higher number of state variables and parameters to be estimated, these models have been remitted to studies in which the knowledge of the physiological events are important or essential.

In this paper we make use of the linear, infinite impulse response (IIR) physiologically based hemodynamic (PBH) model [12], which combines the best of both typical approaches presented. i) Simplicity and lightness of the heuristic approach; not compromising its use on simple, straight-ahead detection studies; ii) Physiologically based; possibly providing some information on significant underlying physiological events of the vascular and neural tissues.

The present paper focuses on a new analysis perspective that combines the activity estimation problem (which leads to a functional brain map) and the local HRF estimation problem, in order to minimize the detection error probability. The combination of these problems into one, provides an activity detection method that is more sensible to underlying HRF shapes that deviate from the "standard shape" generally assumed, eventually reducing its error probability. Furthermore, this method is presented parameter-free which could be valuable for comparison against results from parameter-dependent methods such as the SPM-GLM. In addition, the HRF it provides might be useful for studying the neurovascular events and physiological events behind local brain activity.

In order to estimate the binary (activated or not) information on each voxel (volume element), we present a Bayesian method that forces this binary activation solution while jointly estimating the HRF. This is done by first estimating a model-free finite impulse response (FIR) and then projecting it into the PBH model IIR space. Monte Carlo tests are presented for synthetic data and the errors probability obtained with the proposed method are compared with the standard classical procedures used in several software, e.g. the Statistical Parametric Mapping (SPM) [13], FMRIB Software Library [14] and BrainVoyager [15]. Furthermore HRF estimation is graphically presented and compared with the real HRF behind the synthetic data. Results of the proposed method on real data are also displayed.

The rest of the paper is organized as follows. Section II starts with the introduction and mathematical construction of the assumed model behind the BOLD data generation, and its intervening elements such as the stimulus paradigms, the HRF model and the noise model used. In Section III the Bayesian method is presented and its computational estimation described. Section IV presents the obtained results and is divided in three section: III-A compares the activity detection error probability with SPM-GLM on Monte Carlo testing; III-B displays the SPM-MAP joint estimation results on Monte Carlo testing; III-C displays the behavior of the proposed method on real datasets. Finally, section IV concludes this paper and discusses possible future extensions of this work.

II. PROBLEM AND METHOD FORMULATION

Let us consider the voxels (volume elements) displayed in Fig. 1. Each voxel, after the application of a given paradigm, may be activated by one or more applied stimulus ($\exists_k : \beta_k = 1$) or may not be activated at all ($\forall_k : \beta_k = 0$).

Fig. 1. Example of activated and non activated regions in an fMRI image, overlaid on a higher resolution structural MRI image.

Fig. 2. BOLD signal generation model.
In this paper we consider the BOLD signal associated to a single voxel at a time - time course - with the following data observation model, displayed in Fig. 2,

\[ y(n) = h(n) * \sum_{k=1}^{N} \beta_k p_k(n) + \eta(n) \]  

(1)

where \( \eta(n) \) is modeled as Additive White Gaussian Noise (AWGN), \( h(n) \) is the HRF of the brain tissues, \( p_k(n) \) are the stimulus signals along time (see Fig. 3) and \( \beta_k \) are unknown binary variables to model the activation of the voxel by the \( k \)-th stimulus. For instance, Fig. 1 shows the result of application of a two stimulus paradigm where three voxels are referenced: i) a voxel was activated by the first stimulus, \( \beta_1 = 1 \) and \( \beta_2 = 0 \), ii) a voxel was not activated, \( \beta_1 = 0 \) and \( \beta_2 = 0 \), and iii) a voxel was only activated by the second stimulus, \( \beta_1 = 0 \) and \( \beta_2 = 1 \).

![Paradigm example with three block-designed stimulus.](image)

In this paper we describe a Bayesian Statistical Parametric Mapping algorithm (SPM) based on the Maximum A Posteriori (MAP) [16] criterion called SPM-MAP\(^1\). The proposed algorithm jointly estimates the vector \( \mathbf{b} = \{\beta_1, \beta_2, ... , \beta_N\}^T \), associated with each voxel and the corresponding hemodynamic response, \( h(n) \), which can be denoted in vectorial form, \( \mathbf{h} = \{h(1), h(2), ..., h(N)\}^T \).

The hemodynamic signal is assumed to be the response of an IIR linear time invariant system (LTI). This model [12] is graphically displayed in Fig. 4 and has the following third order transfer function

\[ H(z) = \frac{b_0 + b_1 z^{-1} + b_2 z^{-2}}{1 + a_1 z^{-1} + a_2 z^{-2} + a_3 z^{-3}} \]  

(2)

where the coefficients \( b_k \) and \( a_k \) must be estimated.

The estimation process is performed by minimizing an energy function depending on the binary unknowns \( \beta_k \), on the hemodynamic response \( h(n) \), and on the observations \( y(n) \) (see Fig. 2). The direct estimation of the \( H(z) \) coefficients is a difficult task because it is not easy to define simple priors for these coefficients based on the desired time response \( h(n) \) function. Therefore, to overcome this difficulty, instead of estimating the \( a_k \) and \( b_k \) IIR coefficients, a FIR is estimated, \( \mathbf{g} = \{g(1), g(2), ..., g(F)\}^T \), with length \( F \) minor or equal to the observations length, \( F \leq L \). In each iteration this estimated response is projected into the \( H(z) \) space, i.e., a set of coefficients \( a_k \) and \( b_k \) are estimated in order to minimize \( \|g(n) - h(n)\| \) by estimating the coefficients \( a_k \) and \( b_k \). The PBH \( a_k \) and \( b_k \) estimated coefficients are then used to re-project \( H(z) \) into the FIR space by computing a new finite response \( h \), which is used to obtain a new estimate of the binary unknowns \( \beta_k \). This process is schematically represented in Fig. 5, where each circle represents the set of admissible responses for each one of the IIR and FIR systems.

![Physiologically Based Hemodynamic model.](image)

Let \( \mathbf{x} = \{x(1), x(2), x(3), ..., x(L)\}^T \) (see Fig. 2), which may be expressed as follows

\[ \mathbf{x} = \mathbf{\theta} \mathbf{b} \]  

(3)

where

\[ \mathbf{\theta} = \begin{pmatrix} p_1(1) & p_2(1) & p_3(1) & \ldots & p_N(1) \\ p_1(2) & p_2(2) & p_3(2) & \ldots & p_N(2) \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ p_1(L) & p_2(L) & \ldots & \ldots & p_N(L) \end{pmatrix} \]  

(4)

The output vector of \( h(n) \) displayed in Fig. 2, \( \mathbf{z} = \{z(1), z(2), z(3), ..., z(L)\}^T \), is obtained by \( \mathbf{z}(n) = h(n) * \mathbf{x}(n) \), where \( h(n) \) is a \( F \) length FIR and \( * \) denotes

\(^1\)Statistical parametric mapping is generally used to identify functionally specialized brain responses[1]
the convolution operation. The output signal may be expressed in the two following ways

\[ z = Hx \quad (5) \]

\[ z = \Phi h \quad (6) \]

where \( H \) and \( \Phi \) are the following \( L \times L \) and \( L \times p \) Toeplitz matrices respectively.

\[
H = \begin{pmatrix}
h(1) & 0 & 0 & 0 & 0 \\
h(2) & h(1) & 0 & 0 & 0 \\
h(3) & h(2) & h(1) & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots \\
0 & \ldots & h(p) & h(p-1) & \ldots & h(1)
\end{pmatrix}
\]

\[
\Phi = \begin{pmatrix}
x(1) & 0 & 0 & 0 & 0 \\
x(2) & x(1) & 0 & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots \\
x(L) & x(L-1) & \ldots & \ldots & x(L-P+1)
\end{pmatrix}
\]

The observed BOLD signal \( y(n) \), \( y = \{y(1), y(2), \ldots, y(L)\}^T \), can therefore be obtained with the following two ways

\[ y = \Psi b + n \quad (9) \]

\[ y = \Phi h + n \quad (10) \]

where \( \Psi = H\theta \) and \( n = \{\eta(1), \eta(2), \ldots, \eta(L)\}^T \) is a vector of Independent and Identically Distributed (i.i.d) zero mean random variables normally distributed, that is, \( p(\eta(k)) = N(0, \sigma^2) \). This AWGN is usually used to model the corruption process in functional MRI [17], although other models may also be used, e.g., Rice [18] and Rayleigh [19]. In this work we suppose that the motion correction preprocessing step was efficient enough to remove most of the temporal correlation between voxels, and so its influence is included and corrected along with the corruption noise.

III. Estimation

The Maximum a Posteriori (MAP) estimation is obtained by minimizing the following energy function

\[ E(y, x(b), h) = E_y(y, x(b), h) + E_b(b) + E_h(x(b)) \quad (11) \]

where the data fidelity term is

\[ E_y(y, x(b), h) = -\log(p(y|x(b))) \quad (12) \]

and the prior terms associated to the unknowns to be estimated, \( b = \{\beta_1, \ldots, \beta_N\} \) and \( h = \{h(0), \ldots, h(p-1)\} \) are

\[ E_b(b) = -\log(p(b)) \quad (13) \]

\[ E_h(x(b)) = -\log(p(h)) \quad (14) \]

These priors incorporate the a priori knowledge about the unknowns to be estimated: i) \( \beta_k \) are binary and ii) \( h(n) \) is smooth.

Fig. 6. Fluxogram of the proposed SPM-MAP algorithm.

The estimation process is performed in the following three steps, as shown in Fig. 6.

\[ b^t = \arg \min_b E(y, x(b^{t-1}), h^{t-1}) \quad (15) \]

\[ g = \arg \min_g E(y, x(b^t), h^{t-1}) \quad (16) \]

\[ h^t = \text{Proj}_{IIR} \left[ \text{Proj}_{IIR}(g) \right] \quad (17) \]

where \((\cdot)^t\) means estimation at \( t^{th} \) iteration and \( \text{Proj} \) stands for the projection operation by using the minimum square error (MSE) criterion. The \( \text{Proj}_{IIR} \) problem is not trivial [20,21]. In this paper the approximation algorithm proposed by Shanks [22,23] is used. Other approximations proposed by Prony [23,24] and Padé [23] may also be used, but lead to worse results in the MSE criterion.

The independence assumption on the time-course observations may not be realistic. However, it is a reasonable assumption and a convenient mathematical simplification, because it separates the observations dependence and the estimated data dependence, simplifying
a considerable number of expressions. Furthermore, the inclusion of the observations statistical dependence in the mathematical formulation may not lead to relevant improvement on the final solution, as noted in [25].

The observations independence means that

\[ p(y|x(b), h) = \prod_{i=1}^{L} p(y(i)|(x * h)(i)) \]

The adoption of the AWGN model leads to,

\[ p(y(i)|(x * h)(i)) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(y(i) - (x(h)(i)))^2}{2\sigma^2}} \]

where \( \sigma^2 \) is the observations noise variance. The parameters \( \beta_k \) to be estimated are also assumed independent, that is,

\[ p(b) = \prod_{i=1}^{N} p(\beta_k) \tag{18} \]

where \( p(\beta_k) \) is a bi-modal distribution defined as a sum of two Gaussian distributions centered at zero and one, with \( \sigma^2_\beta \) variance,

\[ p(\beta_k) = \frac{1}{2} \left[ N(0, \sigma^2_\beta) + N(1, \sigma^2_\beta) \right] \tag{19} \]

because \( \beta_k \) are binary variables, \( \beta_k \in \{0, 1\} \). In order to better approximate the binary answer, the \( \sigma_\beta \) parameter should be as small as possible, but numerical stability reasons prevent the adoption of too small values. The prior term \( E_{b}(b) \) may therefore be written as

\[ E_{b}(b) = \sum_{k=1}^{N} \left[ \frac{2\beta_k^2 - 2\beta_k + 1}{4\sigma^2_\beta} - \log \left( \cosh \left( \frac{2\beta_k - 1}{4\sigma^2_\beta} \right) \right) \right] \tag{20} \]

To impose smoothness [26] on the estimated hemodynamic response, \( h(n) \) is assumed to be a Markov Random Field (MRF), which means, by the Hammersley-Clifford theorem [27], that \( p(h) \) is a Gibbs distribution:

\[ p(h) = \frac{1}{Z_h} e^{-\alpha \sum_{n=1}^{N} \gamma(h(n) - h(n-1))^2} \tag{21} \]

which leads to

\[ E_{h}(x(b)) = -\log(p(h)) = \alpha(\Delta h)^T(\Delta h) + C \tag{22} \]

where \( \alpha \) is a parameter that tunes the smoothing degree for \( h(n) \), \( C \) is a constant, \( Z_h \) is a partition function and \( \Delta \) is the following difference operator

\[ \Delta = \begin{pmatrix}
1 & 0 & 0 & \ldots & 0 & -1 \\
-1 & 1 & 0 & \ldots & 0 & 0 \\
0 & -1 & 1 & \ldots & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
0 & 0 & 0 & \ldots & -1 & 1
\end{pmatrix} \tag{23} \]

The energy function (11) to be minimized, \( E(y, x(b), h) \), has the following forms in step one (see section III-A) and step two (see section III-B) respectively

\[ E_{1}(y, x(b), h) = \frac{1}{2\sigma_y^2}(\Psi b - y)^T(\Psi b - y) + E_{b}(b) + C_1 \tag{24} \]

\[ E_{2}(y, x(b), h) = \frac{1}{2\sigma_y^2}(\Phi h - y)^T(\Phi h - y) + \alpha h^T(\Delta^T\Delta)h + C_2 \tag{25} \]

The MAP estimate is obtained by finding the \( E(y, x(b), h) \) stationary point,

\[ \nabla E(y, x(b), h) = 0. \tag{26} \]

where \( (\nabla) \) is the gradient operator.

A. Step One: b estimation

In the first step the following equation must be solved

\[ \nabla_{b}E_{1} = \Psi^T(\Psi b - y) + \frac{\sigma^2_y}{\sigma^2_\beta} \left[ b - \frac{1}{2} R(b) \right] = 0 \tag{27} \]

where \( \nabla_{b} \) is the gradient operator with respect to \( b \) and \( R(b) \) is a column vector with \( N \) elements \( r_k \),

\[ r_k = 1 + tanh \left[ \frac{2\beta_k - 1}{4\sigma^2_\beta} \right]. \tag{28} \]

The solution of (26) may be obtained by using the fixed point method which leads to the following recursion

\[ b^t = (\Psi^T\Psi + \lambda I)^{-1}(\Psi^Ty + \frac{\lambda}{2} R(b^{t-1})) \tag{29} \]

where \( \lambda = \sigma^2_y/2\sigma^2_\beta \) is a parameter, \( I \) is a \( N \) dimensiona identity matrix and \( b^t \) is the \( b \) estimate at \( t^{th} \) iteration.

B. Step Two: h estimation

In the second step, where a new estimate of \( h(n) \) is obtained, the following equation is solved

\[ \nabla_{h}E_{2} = \Phi^T(\Phi h - y) + 2\lambda \sigma^2_y L h = 0 \tag{30} \]

where \( \nabla_{h} \) is the gradient operator with respect to \( h \) and \( L = \Delta^T\Delta \) (see (22)).

The solution of (29) is

\[ g = [\Phi^T \Phi + 2\lambda \sigma^2_y L]^{-1} \Phi^T y \tag{31} \]

where \( \Phi(x(b)) \) is computed (8) with the \( b \) estimate, \( b^t \), obtained in step one (28).
C. Step Three: \( \text{Proj}_{FIR}[\text{Proj}_{IIR}(g)] \)

A HRF smoothness constrain is much more easy to define on a FIR hemodynamic response, than on the IIR space. However, this FIR response does not necessarily belong to the responses space of the adopted IIR PBH model, presented in section II, which imposes harder restrictions on \( h(n) \). To cope with this, restriction to its shape is adopted, in each iteration, by projecting the finite length hemodynamic response, \( g \), estimated in step two (30) into the IIR space of \( H(z) \) and then re-projecting it into the FIR space to obtain a new estimate of \( h, h' \), as schematized in Fig. 5.

For the \( g \rightarrow IIR \) projection, we use the Shanks’s method [22,23] which provides the least, although far from ideal, MSE when compared with Padé’s [23] and Prony’s [23,24] method.

The \( IIR \rightarrow FIR \) projection is achieved by simply sampling the estimated continuous IIR function into a discrete signal of length \( F \), which is the best possible estimate in a MSE sense.

These three steps (III-A, III-B and III-C) are repeated until convergence, when very low variability of \( \hat{b} \), from the previous iterations to the current one, is achieved (stop criteria refered in Fig. 6). Hence, the estimated elements of \( \hat{b}, \hat{b}_k \), are not binary but, close to 0 or 1, real numbers. To accomplish the desired binary nature of \( \hat{b} \) the following threshold is applied to \( \hat{b}_k \)

\[
\hat{b}_k = \begin{cases} 
0 & \hat{b}_k < 0.5 \\
1 & \text{otherwise.} 
\end{cases} 
\tag{31}
\]

and this is the final activation estimation that provides information on whether the brain area represented in the corresponding voxel was activated by each of the paradigm stimulus or not. If the answer is positive, then the estimated HRF provides a possibly valuable insight into the BOLD local dynamics.

IV. EXPERIMENTAL RESULTS

In the pursuit of validating the proposed algorithm, several tests where performed on synthetic and real data and when possible compared against the standard detection technique SPM-GLM. First the SPM-MAP is compared to SPM-GLM in terms of their activity detection error probability. Secondly, the joint activity detection and HRF estimation of SPM-MAP is presented and analyzed.

A. Detection comparison to SPM-GLM on Synthetic Data

The proposed SPM-MAP method formalizes the neural activation detection problem in step one (section III-A), and the HRF estimation problem in the following steps (section III-B, III-C). The results of each step has a strong influence on the others. So, in order to compare our method to the standard SPM-GLM [1,3], only the activation detection procedure is considered. Two main differences must be stressed between both methods:

1) In the SPM-GLM method the whole \( N \) period signal is sometimes broken into \( N \) pieces corresponding to each paradigm period and the resulting observation pieces are averaged to reduce the noise corrupting the observations \( Y \). The matrix \( \theta \), defined in (4), is built by using only a single paradigm period. In the proposed method, instead of braking the signal, it is dealt with as a whole signal. And the same goes for the paradigm signal. The noise reduction is performed in a Bayesian framework where a realistic observation model is used to cope with it. In the case of AWGN both methods are very similar, but if other noise models (e.g. multiplicative) are used this would no longer be true. This is because the averaging procedure is only adequate for certain noise models.

2) In the SPM-GLM method the estimation of each \( \beta_k \) is based on the well known classical \( t \)-test [28] applied to the estimated coefficients \( \hat{\beta}_k \). This statistical inference technique is based on the null hypothesis test, \( H_0 \), where the activation probability of a given voxel is computed with a certain confidence degree. This test is performed over the estimated coefficients, \( \hat{\beta}_k \), obtained with the GLM. These coefficients used to linearly combine the EVs (usually a convolution between the paradigm stimulus and the HRF model (s)) are estimated by using the MSE criterion. These real coefficients reflect the estimated "presence" amplitude of each EV in the observed data. In the SPM-MAP method the coefficients set are assumed to be binary and are estimated in a Bayesian framework where a prior distribution forces its values to be close of \( \{0, 1\} \). Once again, our concern is to follow a realistic model where it is assumed that a given voxel was activated or not by a given stimulus. Partial voxel activation is not acceptable in this scope: it is totally activated or it is not activated at all, by a given stimulus, \( p_k(n) \).

To better understand the difference between both methods, a short description of the SPM-GLM method is
presented where the t-test is used to determine if a given voxel is or is not activated by a single EV, \( p(n) \ast h(n) \), which means that \( b \) is a scalar, \( b = [\beta] \).

The observed BOLD signal is assumed to be obtained from the following model

\[
y = \beta (\theta \ast h(n)) + \epsilon \tag{32}
\]

where \( \theta \) is defined in (4) but with only one stimulus, \( \theta = (p(1), p(2), \ldots, p(L))^T \), \( h(n) \) is the canonical gamma function [1,3,29] and \( \epsilon \) is the residual error vector explained by the model. The \( \beta \) estimation given by the GLM method, in this very simple case, is computed as follows

\[
\hat{\beta} = \chi^+ Y
\tag{33}
\]

where \( \chi = \theta \ast h(n) \) is the EV and \( \chi^+ = (\chi^T \chi)^{-1} \chi^T \) is the so called pseudoinverse of \( \chi \) [26].

The SPM-GLM method core, tags each voxel as activated, \( b = 1 \), or as inactivated, \( b = 0 \), by computing the probability of a random generation of the analysed \( y(n) \) time-course with a confidence level \( \alpha \), that is,

\[
b = \begin{cases} 
1 \text{ (Active)} & \text{if} \ p < \alpha; \text{(reject } H_0) \\
0 \text{ (No Active)} & \text{Otherwise; (accept } H_0) 
\end{cases} \tag{34}
\]

where \( H_0 \) is the null hypothesis which assumes no activation with a confidence level \( \alpha \).

The \( p \)-value is obtained as follows

\[
p = P(t \geq T) = 1 - I_{-\frac{t^2}{2}}(L/2, 0.5) \tag{35}
\]

where \( I_x(a,b) \) is the incomplete Beta-function [28] defined as

\[
I_x(a,b) = \frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)} \int_0^x \tau^{a-1}(1-\tau)^{b-1}d\tau \tag{36}
\]

and

\[
T = \frac{\hat{\beta}}{\sigma_\beta} \tag{37}
\]

is the \( T \) estimator associated \( t \)-statistics, where \( \hat{\beta} \) is the estimation value of \( \beta \), and \( \sigma_\beta \) the standard deviation. \( t \) is large if the estimated value is much larger than the estimator variance and \( t \) is small if the estimated value is comparable with the corresponding estimator variance.

The estimator variance, \( \sigma_\beta^2 \), may be numerically estimated using the following expression

\[
\sigma_\beta^2 = \frac{\sigma_y^2}{L-1} \sum_{n=1}^{L} p^2(n) \tag{38}
\]

where \( p(n) \) is the \( n \)th \( \theta \) element and \( \sigma_y^2 \) is the estimated noise energy

\[
\sigma_y^2 = \frac{1}{L-1} \sum_{n=1}^{L} [y(n) - \hat{\beta}p(n)]^2 \tag{39}
\]

To access the effectiveness of the proposed \( SPM\)-MAP method against the presented \( SPM\)-GLM, synthetic 1D-block-designed single stimulus data, with several AWGN noise levels (\( \sigma_y \)) and several stimulus epochs (periods in a block design paradigm approach), \( N \), are used in Monte Carlo simulations. In these, the error probability (\( P_e \)), was obtained for each method as follows

\[
P_e(\sigma, N) = \frac{1}{R} \sum_{i=1}^{R} |\hat{b}_i - b_i| \tag{40}
\]

where \( R = 250 \) is the number of data repetitions used in the Monte Carlo tests. The HRF function is assumed to be known and was selected from the PBH model estimation on real data [12].

The resulting \( P_e \) differences between \( SPM\)-MAP and \( SPM\)-GLM, i.e.: \( \Delta P_e = P_e(SPM\)-MAP) - \( P_e(SPM\)-GLM), was computed for each experiment, and the average results for the different noise levels and epochs are displayed in Fig.7 and in Table I. Notice that in Table I, \( \sigma_y \) values that resulted in all null \( P_e \) are not displayed.

Although the performance of both algorithms decreases, as expected, with the amount of noise and with the decrease in epochs number, the \( \Delta P_e \) obtained is negative for most of the \( (N, \sigma) \) data pairs tested, which means that the \( SPM\)-MAP outperforms the \( SPM\)-GLM method for almost every configuration tested. This is confirmed by Table I, where the summation of \( \Delta P_e \), \( \sum_{i,j} \Delta P_e(N_i, \sigma_j) = -0.46 \), is negative. The number of negative values of \( \Delta P_e \), \( \#(\Delta P_e < 0) = 23 \) and the number of positive values of \( \Delta P_e \), \( \#(\Delta P_e > 0) = 6 \), which confirms that the \( SPM\)-MAP surpasses the traditional \( SPM\)-GLM method. Still it is obvious that both methods present high accuracy in these tests due to the exact knowledge of both the HRF and noise distribution.

It is important to notice that in the \( SPM\)-GLM approach, the HRF is indirectly estimated and used for every time-course activation analysis. On the contrary, in the \( SPM\)-MAP method, this HRF is jointly estimated with the activation variables and is space variant. The \( SPM\)-MAP is therefore adaptive, which allows the proposition that in real conditions the performance gap should increase.

### B. Joint Activity Detection and HRF estimation Results On Synthetic Data

In this section Monte Carlo tests of the complete proposed method are presented in order to evaluate the performance of the algorithm. Two synthetic binary images of 128x128 pixels where generated, which represent a single BOLD slice signal, as can be seen overlapped
The BOLD signal, $y(n)$, is generated by using the model presented in Fig. 2. A reasonable two stimuli block-design paradigm, $p_1(n)$ and $p_2(n)$, of 10 seconds task duration followed by a 30 second rest period each in 5 epochs, were used in order to obtain a non superposition of $p_1(n)$ and $p_2(n)$ while allowing for the BOLD signal to decay to rest. The true impulse HRF signal, $h(n)$, was generated from a representative IIR, selected from the PBH estimation on real single-event data [12], and the following noise energies were used: $\sigma_y = \{0.2, 0.5, 0.7, 0.8, 1\}$. These noise energies are better evaluated when compared against the BOLD signal energy level, which is done with the signal-to-noise ratio ($SNR = 10 \log \sum_{k=1}^{N} \frac{(\beta k + p_1(n) + p_2(n) + h(n))^2}{\sigma_y^2}$) for the two data cases in which the BOLD signal is present: $\sum_{k=1}^{N} b(k) \geq 1$ (see Table II).

This generated synthetic data is equivalent to $2 \times 128 \times 128 = 32768$ independent $y(n)$ time-courses, containing all possible combinations for the $b$ vector. These are used on Monte Carlo tests to compute the $P_e$ (see eq. (40)). The results obtained are graphically presented in Fig. 9 and in Table II. These values were computed as the ratio of the total number of wrong estimations over the total number of Monte Carlo tests ($32768$).

Table II shows that even for the high noise levels of $\sigma_y = 0.8$ the proposed SMP-MAP method presents a $P_e < 0.3\%$. It is important to point-out that although the SNR in MRI depends on a large number of variables, it is usually more than 1 dB [3,30]. So the most realistic $\sigma_y$ values would be situated between $\{0.2, 0.5, 0.7, 0.8, 1\}$. Furthermore, for the very high noise amount $\sigma_y = 1$ ($SNR = [-6.7; -3.5]$) the $P_e$ stays below 5%, resulting in the bottom image in Fig. 9. Notice that

\[
\Delta P_e = P_{e(SPM-MAP)} - P_{e(SPM-GLM)} \text{ for } 2 \leq N \leq 20 \text{ and } \sigma_y = \{1, 2, 4\}. \text{ For all other tested values of } \sigma_y = \{0.01, 0.02, 0.05, 0.1, 0.2, 0.5\}, P_e = 0.
\]

TABLE I

<table>
<thead>
<tr>
<th>$N \setminus \sigma_y$</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-0.012</td>
<td>0</td>
<td>-0.168</td>
</tr>
<tr>
<td>3</td>
<td>-0.012</td>
<td>0.004</td>
<td>-0.108</td>
</tr>
<tr>
<td>4</td>
<td>-0.008</td>
<td>-0.012</td>
<td>-0.044</td>
</tr>
<tr>
<td>5</td>
<td>-0.004</td>
<td>-0.012</td>
<td>-0.032</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>-0.008</td>
<td>-0.016</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>-0.008</td>
<td>-0.008</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>-0.004</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
<td>-0.004</td>
</tr>
<tr>
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<td>0</td>
<td>0.004</td>
</tr>
<tr>
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<td>-0.004</td>
<td>0.012</td>
</tr>
<tr>
<td>12</td>
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<td>0</td>
<td>0.004</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
<td>-0.004</td>
<td>0</td>
</tr>
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<td>-0.004</td>
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<td>-0.004</td>
<td>0.004</td>
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<tr>
<td>16</td>
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<td>0</td>
<td>-0.004</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>0</td>
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<td>19</td>
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<td>0</td>
<td>-0.004</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>0</td>
<td>-0.008</td>
</tr>
</tbody>
</table>

The BOLD signal is usually more than 1 dB [3,30]. So the most realistic $\sigma_y$ values would be situated between 0.2 and 0.5, for the data used. In this range the method achieves values of $P_e < 0.1\%$. Furthermore, for the very high noise amount of $\sigma_y = 1$ ($SNR = [-6.7; -3.5]$) the $P_e$ stays below 5%, resulting in the bottom image in Fig. 9. Notice that

in Fig. 8. In it, colored voxels (red, yellow and white) where activated by, at least, a stimulus paradigm and the black pixels where not activated at all. So according to the mathematical notation presented above, red: $b = \{1, 0\}^T$; yellow: $b = \{0, 1\}^T$; white: $b = \{1, 1\}^T$ and black: $b = \{0, 0\}^T$, which is the activation ground truth to be estimated for each voxel.
TABLE II
MONTE CARLO $P_e$ (40) OF SPM-MAP FOR SEVERAL VALUES OF
AWGN $\sigma_y$ AND CORRESPONDENT SNR VALUES FOR THE
$\sum_{k=1}^2 b(k) = 1$ AND $\sum_{k=1}^2 b(k) = 2$ TWO DIFFERENT SIGNAL
ENERGY SITUATIONS. SPATIAL CORRELATION CORRECTION IS
EXEMPLIFIED IN $\hat{P}_e$ AND $\ddot{P}_e$ WHERE ONE AND TWO ISOLATED
PIXELS WERE DISMISSED, RESPECTIVELY.

<table>
<thead>
<tr>
<th>$\sigma_y$</th>
<th>$P_e(%)$</th>
<th>$\hat{P}_e(%)$</th>
<th>$\ddot{P}_e(%)$</th>
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<tr>
<td>0.2</td>
<td>0.0427</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>0.0916</td>
<td>0.0244</td>
<td>0.0073</td>
</tr>
<tr>
<td>0.7</td>
<td>0.168</td>
<td>0.0245</td>
<td>0.0061</td>
</tr>
<tr>
<td>0.8</td>
<td>0.260</td>
<td>1.51</td>
<td>0.513</td>
</tr>
<tr>
<td>1</td>
<td>4.27</td>
<td>0.513</td>
<td>0.513</td>
</tr>
</tbody>
</table>

Fig. 9. SPM-MAP activation detection results for $\sigma_y = 0.5$ (up)
and $\sigma_y = 1$ (down). Same color code as in Fig. 8

when looking at Fig. 9, the intuitive notion on the error
probability might seem higher than the referred 0.1% and
0.5% values, due to the fact that the images are actually an overlap of two images.

It is intuitive when looking at the results in figure 9, that the accuracy of the method can be improved if spacial correlation information is included, removing several of those isolated, spatially uncorrelated, voxels. For illustration purposes, the $P_e$ is recalculated after removing areas of one ($\hat{P}_e$) and two ($\ddot{P}_e$) isolated voxels in an 8 voxels neighborhood. The resultant error probabilities (see Table II) decreases for all the noise amounts, yielding null for the 0.2 and 0.5 $\sigma_y$ values. The gain in performance with this simple morphological correction applied, is unquestionable in this example because there are no small regions. If real regions of 1 or 2 voxels existed in the data, then their elimination would provide false-negative errors. Therefore, the inclusion of spatial correlation between voxels should follow a more robust methodology.

The $P_e$ results cannot be directly compared with the results in section IV-A, because there, the HRF is exactly known and uses only one stimulus in the paradigm. Here, the HRF is jointly estimated with the brain activation indicators, $\beta_k$, and the paradigm is comprised of two stimulus. These aspects greatly influence the $P_e$ due to an explosion in the possible number of solutions, particularly if we consider the great degree of freedom in the HRF estimation (as mentioned in section III-C). In both tests, the exact noise distribution (AWGN) knowledge is an advantage that does not exist in real data. Adding to this, the existence of other factors like field inhomogeneity and motion errors, the $P_e$ on real data (as shown on section IV-C) should be higher. Unfortunately, ground truth in real fMRI is difficult to obtain. Only rough expectations based on the prior knowledge of which brain areas should be activated by the applied stimulus, may be used to validate the results.

The HRF estimation results are harder to analyse. For each one of the 32768 voxels a $h(n)$ HRF is estimated, but only the ones corresponding to activated brain areas $\beta_k = 1$ are relevant. So, in the false-negative case, that information is discarded. On the other hand, the false-positive case is not discarded and the estimated $h(n)$ tends to follow the random AWGN form, around zero. These reduce the amplitude of the HRF estimated mean,
computed over all positive estimated voxels $\hat{h}_k$, including false-positives. This effect can be seen in Fig. 10, where the false-positives effect is removed. Considering that in real data we do not have information on false-positives, a correction could be done dismissing estimated $h(n)$ functions with AWGN distribution, but since the primary goal of this work is the activation detection, this is left for further works. Furthermore there is a global decrease in amplitude of every HRF estimation in the $FIR \rightarrow IIR$ (section III-C) projection operation, which can be seen on figure 10 right column. In fact, when there is not an IIR filter that perfectly describes the estimated $g(n)$ FIR, the IIR computed by the Shanks [22,23] algorithm is always of lower amplitude. In spite of all this, the HRF estimation provided reasonable results (Fig. 10) and proved robust even in high noise levels.

C. Joint Activity Detection Results On Real Data

Subjects and Data Collection

Three volunteers with no history of neurological or psychiatric diseases participated on stimulated verbal, motor and trajectory activity during fMRI data acquisition on a Philips Intera Achieva Quasar Dual 3T whole-body system with a 8 channel head-coil. T2*-weighted echo-planar images (EPI) 23cm square field of view with a $128 \times 128$ matrix size resulting in an in-plane resolution of $1.8 \times 1.8$mm for each $4$mm slice, echo time = $33$ms, flip angle = $20^\circ$ were acquired with a TR = $3000$ms.

Three motor paradigms, one verb generation paradigm and one trajectory generation paradigm, summing up to the total of five paradigms, described in the following table, were applied to the subjects.

| (a) Verbs   | Stimulus: Seeing nouns and thinking of related verbs.  
Baseline: Seeing the "####" string. |
|------------|--------------------------------------------------|
| (b) Trajectories | Stimulus: Reminding routes through familiar places.  
Baseline: Silently counting numbers. |
| (c) Right Foot | Stimulus: Moving right foot fingers.  
Baseline: Complete rest with closed eyes. |
| (d) Right Hand | Stimulus: Closing/opening right hand.  
Baseline: Complete rest with closed eyes. |
| (e) Hands | Stimulus: Closing/opening both hands.  
Baseline: Complete rest with closed eyes. |

TABLE III
DESCRIPTION OF THE PARADIGMS CONDITIONS APPLIED TO THE PARTICIPANT SUBJECTS.

These paradigms were all structured on the same block-design, with 20 samples per epoch (meaning 10 samples of stimulus following 10 samples of baseline, summing up to $60$s time per epoch) and 4 total epochs.

Subjects and Data Collection

The fMRI data was preprocessed with the standard procedures implemented in the BrainVoyager software [15], namely decrease of data distortions due to motion or other phase changes over time (registration) and spacial smoothing. This data was then statistically processed by the BrainVoyager SPM-GLM and SPM-MAP algorithms, and the resolving results are plotted in Fig. 11 for a selection of slices that have considerable activity areas in them. Since the obtainable brain maps by SPM-GLM highly depends on the selected p-values (see section IV-A), a neurologist provided the results, for each data set, which he considered more correct (reference result), based on its experience. Since this result is subjective, he also provided two other results which we considered loose and restricted.

Visual inspection of the results in Fig. 11 show some expected resemblance between the reasonable SPM-GLM brain maps, selected by the neurologist, and the brain maps obtained by the proposed SPM-MAP algorithm. Still the compared algorithms are methodologically different. First, SPM-MAP does not rely on the null hypothesis for activity detection as SPM-GLM, but rather considers two hypothesis (the null and the alternative) and so is able to answer different classes of questions not handled by the standard fMRI analysis. Second, SPM-MAP jointly estimates the HRF shape and the associated activity brain map, and therefore, should theoretically be more precise in its activity results. These main differences should account for most of the dissimilarities observed in each image set (identified as $a$, $b$, $c$, $d$ and $e$ on Fig. 11) between the algorithms results.

In several of the brain map image sets (and in all of the selected image sets in Fig. 11), there are brain regions detected as activated by SPM-MAP that were not detected by SPM-GLM. These are unlikely false positives. Considering that the error probability has been shown considerably low (see section IV-B), the probability of several false positives occurring grouped in a small image area, instead of randomly dispersed in the image, is infinitesimally small. Therefore, new brain areas detected by the proposed method should be considered reliable in most cases, depending on its size (number of voxel in that group). The detection of these "new" areas happens when a voxel time-course does fluctuates in correlation with the stimulus paradigm, but with an HRF of deviant shape from the EVs considered in the GLM (see examples in Fig. 12). Still, there are possibly some false positive regions (e.g. activated groups of only
one or two voxels) in the SPM-MAP results that have been taken care of by means of clustering in the SPM-GLM results by the BrainVoyager software. Further developments of SPM-MAP are planned to include spatial correlation priors to correct this handicap and improve results.

Fig. 12. Example of two voxel time-courses, from two different brain areas, detected as activated by the SPM-MAP that were not detected by the SPM-GLM. Binary paradigm is in red and the voxel time-course in blue.

To enhance confidence in the the "new" activated brain regions detected by the proposed algorithm, a closer neurological functional analysis should be done. This would involve a neurologist careful evaluation, on each case, following a spatial transformation of the SPM-MAP brain maps into a standard mapped space like the Talairach stereotaxic coordinates [3]. Although this would involve another study, it is noticeable that many of these "new" areas are located in the frontal cortex, which is the focus of the conscious activity. We suspect that these may well be involved in performing the respective paradigm tasks, since all of the paradigm stimulus applied to the subjects have a strong conscious influence (see Tab. III).

V. CONCLUSIONS

The characterization of brain regions from a functional point of view can be performed by using BOLD contrast fMRI technology. In order to do so, statistical data analysis is needed to extract reliable information from the noisy and low amplitude BOLD signal. In this paper a new Bayesian method is presented, where the neural activity detection is jointly obtained along with the HRF estimation. This approach presents two main advantages: 1) the activity detection benefits from the adaptative nature of the HRF shape estimation; 2) it provides local, space variant, HRF estimation. This might provide a useful tool to evaluate and compare estimated brain activity between regions or subjects and for possible behavioral [31], neural and vascular local consideration.

In the joint Bayesian method presented, noisy observations are modeled by the additive white Gaussian noise (AWGN) model and the stimulus activation indicators are modeled by binary variables that are estimated. The prior associated with the binary indicators is a bimodal Gaussian distribution around the 0 and 1 values to cope with the uncertainty related to data noise. The HRF is adaptively estimated on the restricted space responses of the adopted IIR PBH model [12].

The neural activity detection section of the proposed method is compared with the standard method proposed in [1] that uses a classical statistical inference methodology based on the t-test method. Monte Carlo tests on synthetic-1D-block-designed data with both methods have shown that the proposed Bayesian method, called SPM-MAP, outperforms the classical one based on the general linear model (GLM), here called SPM-GLM. The performance evaluation was based on the computation of the error probability, \( P_e(N,\sigma) \), for each method which proved to be smaller for the proposed SPM-MAP method than the corresponding ones obtained with the SPM-GLM method, for almost every tested conditions: different noise levels, \( \sigma_j \) and number of paradigm epochs, \( N_i \), in a block design framework.

On Monte Carlo tests of the whole method with, again, synthetic data, the \( P_e \) obtained was lower than 0.1% for noise levels close to expected real ones. But even for extreme noise levels the method showed itself considerably reliable. This \( P_e \) should increase on real data, but considering its low values, a prominent increase is not expected. Preliminary results after a very simple spatial correlation on the activity detection results are presented and foretells some significant achievable accuracy improvement. This is planned to be incorporated in future developments of the SPM-MAP algorithm to make the voxel activation probability dependent on its neighbors. Regarding the HRF estimation, the average results showed a robust-to-noise close similarity between the real synthetic data HRF and the estimated HRF, although there is a justified small bias towards an amplitude reduction.

The real fMRI data tests showed that the SPM-MAP was able to detect most of the activity detected by SPM-GLM and also detect other activated brain regions. Further analysis of these new brain areas will be done in future works.

In the end we presented and a Bayesian method for statistical analysis and inference of fMRI data with a new
perspective and reliable results validated on synthetic and real data. This method is parameter-free presented (if the noise distribution is known) while many methods are parameter-dependent, like the $p$-value dependant SPM-GLM standard algorithm. This may be very useful for standalone analysis or for comparison against results from other methods.

REFERENCES


Fig. 11. *SPM-MAP* activity detection results on real data compared against data processed by a neurologist on *SPM-GLM*. On the top of each image-set ((a), (b), (c), (d) and (e)) is the *SPM-MAP* result and on the bottom the *SPM-GLM* results with left to right increase in restriction on the $p$-value, where the middle image was intuitively set as the reference result. The background fMRI image in the *SPM-MAP* results is the smoothed data used for the statistical analysis, and in *SPM-GLM* is the unsmoothed data.