MODELLING THE NEUROVASCULAR HABITUATION EFFECT ON fMRI TIME SERIES

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ABSTRACT

In this paper, a novel non-stationary model of functional Magnetic Resonance Imaging (fMRI) time series is proposed. It allows us to account for some putative habituation effect arising in event-related fMRI paradigms that involves the so-called repetition-suppression phenomenon [1] and induces decreasing magnitude responses over successive trials. Akin to [2], this model is defined over functionally homogeneous regions-of-interest (ROIs) and embedded in a joint detection-estimation approach of brain activity. Importantly, its non-stationarity character is embodied in the trial-varying nature of the BOLD response magnitude. Habitation and activation maps are then estimated within the Bayesian framework in a fully unsupervised MCMC procedure. On artificial fMRI datasets, we show that habituation effects can be accurately recovered in activating voxels.

Index Terms—Bayes procedures, Biomedical signal detection, functional MRI, non-stationary model, repetition suppression effect.

1. INTRODUCTION

Since the first report of the Blood Oxygenated Level Dependent (BOLD) effect in human [3], fMRI has represented a powerful tool to non-invasively study the relation between cognitive task and the hemodynamic (BOLD) response. Within-subject analysis in fMRI consists first in localizing brain activation in response to a given stimulus type or experimental tasks and second in estimating the underlying brain dynamics. In [2,4], a Joint Detection-Estimation (JDE) approach has been proposed to address both issues simultaneously in a region-based analysis, i.e. on a set of prespecified regions of interest (ROI). In a few words, the most salient features of the JDE framework is that this methodology allows us to loosen the classical assumptions usually employed in fMRI data analysis based on Generalized Linear Models (GLM) [5]: (i) the HRF shape is not assumed to be fixed but estimated instead [2]; (ii) the model of the BOLD signal varies in space [2]; (iii): spatial Gaussian filtering of the fMRI dataset is no longer necessary [4].

A first characterization of brain dynamics is usually given by an estimate of the Hemodynamic Response Function (HRF), which corresponds to the impulse response of the neurovascular coupling. This characterization assumes that the BOLD signal modelling is linear and time-invariant. Recent works [6, 7] have also demonstrated that transient neurodynamics can be recovered from fMRI time series at the expense of a more complex modelling of the BOLD signal. In the same vein, we extend here the most recent JDE contribution [4] in order to account for the trial-by-trial variability. The proposed region-based BOLD signal model is no longer stationary in time. It can actually account for neurovascular habituation effects either due to the paradigm (repetition suppression effect in case of short inter-stimulus intervals (ISIs)) or to the subject (strategy, tiredness, attentional effects). Our model generalizes the classical convolution BOLD model since it provides the neuroscientist with a trial-varying magnitude of the BOLD response (see Section 2). Nonetheless, instead of considering independent BOLD response magnitudes across trials, our modelling of non-stationarity is parsimonious in order to avoid overfitting: all these parameters are linked to a mean habituation speed through a parametric model. Combined to this model, a Bernoulli-uniform prior is introduced in the Bayesian framework within the JDE methodology and associated to mean habituation speeds (MHS) for activating voxels. We then derive the posterior distribution of interest, from which realizations are drawn using a Gibbs sampler. The posterior mean (PM) estimates of the HRF, the MHS, the BOLD magnitudes, and the corresponding voxel states are computed from the generated samples. In Section 3, our algorithm is validated on realistic artificial fMRI time series.

2. THE JOINT DETECTION-ESTIMATION FRAMEWORK

2.1. Classical BOLD signal modelling

First, the regional forward bilinear model of the BOLD signal introduced in [2] is summarized. It allows us to specify voxel-dependent and stimulus-specific magnitudes of the BOLD response, also called Neural Response Levels (NRLs). This time-invariant model characterizes each and every functionally homogeneous brain region \( R = (V_j)_{j=1...J} \) by a single HRF shape \( h \) and a NRL \( a_j^n \) for each voxel \( V_j \) and stimulus type \( m \). This means that \( h \) is assumed constant within \( R \), while its magnitude \( a_j^n \) can vary in space and across experimental conditions as suggested by:

\[
y_j = \sum_{m=1}^{M} a_j^m X_j^m h + P \epsilon_j + b_j,
\]

where \( y_j = (y_{jn})_{n=1...N} \) denotes the BOLD fMRI time course measured in voxel \( V_j \) at times \( n = 1:N \) (\( N \) is the number of scans), \( M \) is the total number of experimental conditions in the experiment. Vector \( h = (h_{d\Delta t})_{d=0..D} \) represents the unknown HRF shape in \( R \) (\( D + 1 \) is the number of HRF coefficients). \( \Delta t \) is the sampling period of the HRF. Matrix \( X_j^m = (X_j^m)_{n=1..N} \) is a binary matrix coding for the occurrences of the \( m \)th stimulus type. Hence, the activation time course associated to the \( m \)th stimulus type in voxel \( V_j \) is given by \( s_j^m \). Columns of the \( N \times Q \) matrix \( P \) are orthogonal vectors that span a subspace of low

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frequency signals. To each voxel is attached an unknown weighting vector \( \mathbf{b}_j \) to estimate the trend in \( V_j \). \( b_j \in \mathbb{R}^n \) is the noise component in voxel \( V_j \) and is assumed first-order autoregressive: 
\[
b_j \sim \mathcal{N}(0, \sigma_j^2 \mathbf{A}_j^{-1})
\]
where \( \mathbf{A}_j \) is tridiagonal (see [2] for details). A key feature is to progressively forget the past events. Hence, our parametric habituation model depends on the paradigm as follows:

\[
\forall k \geq 2, \quad \mathbf{a}_{jk} = \mathbf{r}_{jk}^{m} \mathbf{a}_{j1}^{m} \quad \text{with} \quad \mathbf{r}_{jk}^{m} = \left( 1 + \sum_{l=1}^{k-1} \mathbf{a}_{jl}^{m} \mathbf{r}_{jm}^{m} \right)^{-1}\quad (2)
\]

where \( \mathbf{r}_{jk}^{m} = \mathbf{r}_{j1}^{m} - \mathbf{r}_{k1}^{m} \) and \( (\mathbf{r}_{k1}^{m})_k \) define the successive ISIs and onsets of the \( m \)-th stimulus. The activation signal \( s_j^{m} \) in Eq. (1) becomes:

\[
s_j^{m} = \sum_{k=1}^{K} \mathbf{a}_{jk}^{m} \mathbf{X}_k^{m} \mathbf{h} = \mathbf{a}_{j1}^{m} \mathbf{X}_{j1}^{m} \mathbf{h} \quad \text{with} \quad \mathbf{X}_{j1}^{m} = \sum_{k=1}^{K} \mathbf{r}_{jk}^{m} \mathbf{X}_k^{m} \quad (3)
\]

where \( \gamma_{j1}^{m} = 1 \) and \( \mathbf{X}_{j1}^{m} \) is the \( k \)-th trial-specific submatrix of \( \mathbf{X}^{m} \). The ensuing region-based model of fMRI time series is depicted in Fig. 2. It clearly indicates that the habituation speed may vary in space and across stimulus types. As expected, when \( r_{jm} \rightarrow 0 \), the proposed extension becomes stationary since \( \mathbf{a}_{jk}^{m} \rightarrow \mathbf{a}_{j1}^{m} \), \( \forall k \geq 2 \) (cf red line in Fig. 1(a)). When \( r_{jm} \in (0, 1) \), the sequence \( \mathbf{a}_{jk}^{m} \) is non-monotonous and the between-trial variability is strongly influenced by the ISI values (see blue line in Fig. 1(a) and Fig. 1(b)). Finally, when \( r_{jm} \rightarrow 1 \), the sequence \( \mathbf{a}_{jk}^{m} \rightarrow 0 \) whatever the ISIs, as shown by the green curve in Fig. 1.

### 2.3. Likelihood definition

Although the noise structure is correlated in space [10], we neglect such spatial dependency and consider the fMRI time series \( \gamma_j = (y_{j1}, \ldots, y_{jJ}) \) independent in space but not identically distributed (iid):

\[
p(\gamma_j | h, a_1, r, 1, \theta_0) \propto \prod_{j=1}^{J} \det \mathbf{A}_j^{1/2} \sigma_j^{-N} \exp \left( - \frac{\mathbf{y}_j^T \mathbf{A}_j^{-1} \mathbf{y}_j}{2\sigma_j^2} \right) \quad (4)
\]

where \( 1 = (\mathbf{y}_j)^T = (\mathbf{r}_j, \sigma_j^2)_{j=1}^{J} \) and \( q_j = y_j - \sum_{m} s_j^{m} - P\mathbf{e}_j \). Here, \( a_1 \) and \( r \) make reference to the NRLs associated to the first trial and to the MHS, respectively.

### 2.4. Priors

The Bayesian approaches developed in [2, 4] introduce proper priors on the unknown parameters \((h, a_1, r, \theta_0)\) in order to recover a robust estimate of brain activity (localization and activation profile). Akin to [2], the prior density for the hemodynamic filter \( h \) remains Gaussian, \( h \sim \mathcal{N}(0, \sigma_h^2 \mathbf{R}) \) with \( \mathbf{R} = (D_x^T D_x)^{-1} \) and \( D_x \) the second-order finite difference matrix penalizing therefore abrupt changes. Moreover, the extreme time points of the HRF can be constrained to zero if necessary [2].

Here, the main originality lies in the definition of the joint prior involving the initial NRLs \( a_1 \) and the habituation parameters \( r \). First, we still assume that different stimulus type induce statistically independent NRLs and NKS: \( p(a_1, r | \theta_0) = \prod_{m} p(a_1^m | r^m | \theta_0^m) \) with \( (a_1, r) = (\mathbf{a}_1^m, \mathbf{r}_m)_{m=1}^{M} \), \((\mathbf{a}_1^m, \mathbf{r}_m)_{j=1}^{J} \) and \( \theta_0 = (\theta_0^m)_{m=1}^{M} \). Vector \( \theta_0^m \) denotes the set of unknown hyperparameters related to the \( m \)-th stimulus type. Then, following [4], the present paper is based upon spatial mixture models (SMM). This means that if \( \mathbf{q}_j^m \) is the allocation variable that states whether voxel \( V_j \) is activated \( (\mathbf{q}_j^m = 1) \) or not \( (\mathbf{q}_j^m = 0) \) in response to stimulus \( m \), the probability of activation \( \text{Pr}(\mathbf{q}_j^m = 1) \) depends on the states of \( \mathbf{q}_j^m \). with \( p \sim j \) (the set of neighbors of \( V_j \)). Here, spatial correlation is incorporated in the probabilities of activation through a hidden Ising random field on \( \mathbf{q}^m \):

\[
\text{Pr}(\mathbf{q}^m | \beta^m) = \frac{\exp(\beta^m U(\mathbf{q}^m))}{Z(\beta^m)}, \quad U(\mathbf{q}^m) = \sum_{j \sim p} \omega_{jp} I(\mathbf{q}_j^m = q_p^m)
\]

with \( I(A) = 1 \) if \( A \) is true and \( I(A) = 0 \) otherwise. The constants \( \omega_{jp} \) weight the interaction between voxels \((V_j, V_p)\) according to the neighborhood system, which is typically defined in 3D from the region under study \( R \). Here, we only consider the 6-connectivity. The
partition function \( Z(\cdot) \) is not estimated here since parameter \( \beta^m \), which controls the amount of spatial regularization, is set by hand: large values of \( \beta^m \) associate higher probabilities to configurations containing clusters of like-valued neighboring binary variables \( q^m \). An unsupervised extension is however available [11].

NRLs and NHSSs still remain independent conditionally upon \( q^m \). This means that \( \mathbb{P}(a^m_1, r^m \mid q^m, \theta^m) = \prod_{j} \mathbb{P}(a^m_{j}, r^m_{j} \mid q^m_{j}, \theta^m) \quad \forall m \). Moreover, these parameters are supposed independent of each other: \( \mathbb{P}(a^m_1, r^m_{j} \mid q^m_{j}, \theta^m) = \mathbb{P}(a^m_1 | q^m_{j}, \theta^m) \mathbb{P}(r^m_{j} | q^m_{j}, \theta^m) \). Akin to [4], the NRLs \( a^m_{j} \) follow a two-class Gaussian mixture: \( a^m_{j} | q^m_{j} = i \sim \mathcal{N}(\mu_{i,j,m}, \sigma^2_{i,j,m}) \), with \( i = 0, 1 \). The mean of the NRLs in non-activating voxels is fixed (\( \mu_{o,m} = 0 \)), while the other parameters \( \theta^m = [\mu_{o,m}, \mu_{1,m}, \sigma^2_{o,m}] \) remain free and need to be estimated. To get rid of identifiability problems, the NHSSs \( r^m \) are constrained to zero in non-activating voxels: \( \forall m, r^m_{j} = 0 \mid q^m_{j} = 0 \). It seems a priori meaningless to fit habituation effect on noise-only time series. In contrast, for activating voxels, the NHSSs \( r^m \) are assumed identically and uniformly distributed: \( (r^m_{j} | q^m_{j} = 1) \sim \mathcal{U}([0, 1]) \). The compound prior mixture therefore reads for every stimulus type:

\[
p(a^m_1, r^m | \theta^m) = \sum_{q^m} \left( \prod_{j = 1}^{J} \mathbb{P}(a^m_{j} \mid p_{r^m_{j}}) \mathbb{P}(q^m_{j} | \beta^m) \right).
\]

To complete the Bayesian model, priors are required for all the remaining parameters. Without any prior knowledge, the noise and drift parameters \( (\rho_{j}, \sigma^2_{r_{j}}, \ell_{j}) \) are assumed independent in space and: \( \ell_{j} \sim \mathcal{N}(0, \sigma^2_{\ell} I_{Q}) \), \( \rho_{j}, \sigma^2_{r_{j}} \sim \mathcal{S}_{\text{H}}^2 \), to ensure stability of the AR(1) noise process. Non-informative priors are retained for the drift and HRF shape variances: \( \mathbb{P}(a^m_{j}, \sigma^2_{r_{j}}) = (\sigma_{h}, \sigma_{\ell})^{-1} \). In contrast, conjugate priors are considered for \( \theta^m \).

### 2.5. Bayesian inference

Considering the constructed model and assuming no further prior dependence between parameters, Bayes’ rule gives us:

\[
p(h, a, l, \Theta | y) \propto p(y | h, a, \lambda, \ell, \theta_{0}) \mathbb{P}(a_1, r | \theta_{0}) \mathbb{P}(h | \sigma_{h}^{2}) \times \mathbb{P}(l | \sigma_{\ell}^{2}) \mathbb{P}(\Theta) \propto \sigma_{h}^{-D} \sigma_{\ell}^{-1} \prod_{j=1}^{J} \left( \frac{1 - \rho_{j}^{2}}{\sigma_{r_{j}}^{2}} \right)^{1/2} \mathcal{N}_{1}(\mu_{i,j,m}, \sigma^2_{i,j,m}) \exp \left( -\sum_{j=1}^{J} \frac{1}{2 \sigma_{r_{j}}^{2}} (y_{j} - A_{j} \nu_{j})^{2} + \frac{1}{2 \sigma_{\ell}^{2}} \| \ell_{j} \|^{2} \right) \exp \left( -\frac{h^{2} R^{-1} h}{2 \sigma_{h}^{2}} \right) \mathcal{N}_{M}(a^{m}_{1}, r^{m} | \theta^{m}) \mathcal{N}_{M}(a^{m}_{1}, r^{m} | \theta^{m})
\]

To get samples of the posterior pdf, we use a Gibbs sampler whose target distribution is (5). Since the full conditional posterior \( \pi_{1}^{*}(r^{m}_{j}) = p(r^{m}_{j} | y_{j}, q^{m}_{j}) = 1, \text{rest} \) reads:

\[
\pi_{1}^{*}(r^{m}_{j}) \propto \exp \left( -\frac{1}{2 \sigma_{r_{j}}^{2}} (y_{j} - C_{j,m} r^{m}_{j} - s^{m}_{j} \| \nu_{j} / 2 \sigma_{r_{j}}^{2} \|_{0,1}(r^{m}_{j}) \right),
\]

where \( s^{m}_{j} \) depends on \( r^{m}_{j} \) and \( C_{j,m} = P_{\ell_{j}} - \sum_{m \neq m} s^{m}_{j} \) is independent of \( r^{m}_{j} \); it cannot be sampled directly. Hence, we resort to a Metropolis-Hastings step with an uncentered Laplacian density, truncated over \([0,1]\), as proposal: \( f(r | r_{0}) = Z_{\beta_{0}}^{-1} e^{-\beta_{0} |r - r_{0}|^{2} \|_{0,1}(r_{0})} \), where \( r_{0} = r^{m}(t - 1) \). At iteration \( t \), the MH acceptance ratio is given by \( \alpha(r_{0} \rightarrow r) = \min \left[ \frac{\pi_{1}^{*}(r) \pi_{1}^{*}(r_{0})}{\pi_{1}^{*}(r_{0}) \pi_{1}^{*}(r)} \right] \) which requires to generate the trial-varying NRLs (2) at points \( r \) and \( r_{0} \). Finally, posterior mean (PM) estimates are computed from the samples as follows: \( x_{i}^{PM} = (T - 1)^{-1} \sum_{t=1}^{T} x_{i}^{(k)} \), \( \forall x \in \{ h, a, \alpha, \Theta \} \) where \( I \) stands for the length of the burn-in period. Note also that detection is performed according to the Maximum A Posteriori criterion: \( \hat{g}^{m}_{j} = e \hat{g}_{j}^{m} \), \( \hat{g}_{j}^{m} = \arg \max \mathcal{P}(q^{m}_{j} = 1 | y_{j}) \). The MHS estimate is derived as follows. In every non-activating voxel (\( \hat{g}_{j}^{m} \mid \text{MAP} = 0 \)), we impose \( r^{m}_{j} = 0 \). For activating voxels (\( \hat{g}_{j}^{m} \mid \text{MAP} = 1 \)), the MHS estimate is computed as the average of samples \( r^{m}_{j,k} \) over iterations \( k \) that satisfy \( q^{m}_{j,k} = 1 \). The goal is to avoid mixing effects with zero-valued MHS samples in case of label switching.

### 3. SIMULATION RESULTS

#### 3.1. Synthetic fMRI time series

Artificial fMRI time series were generated according to the additive principle defined in model (1). A random mixed sequence coding two stimulus types (\( M = 2 \)) comprising 30 trials each (\( K_{m} = 30, m = 1 : 2 \)) was simulated to define the onsets and thus matrices \( X^{m} \). Then, the voxel-based BOLD signals \( s^{m} \) were computed from Eqs. (2)-(3) on a 2D 5x5 grid. The true parameters \( (a_{1}, r, \alpha) \) involved in the compound prior mixtures are shown in Fig. 3. The labels \( q \) were set manually and not simulated according to the Ising prior. Activating and non-activating voxels appear in red and black, respectively in Fig. 3. Also, the same statistical parameters \( \theta^{m} \) were used to generate the NRLs \( a^{m}_{1} (\mu_{1,m}, \mu_{1,m}, v_{1,m}) = (5.5, 0.3, 0.4) \). Hence, the same contrast-to-noise ratio (CNR) holds for both stimulus types. Following Fig. 2, the trial varying NRLs \( a^{m}_{1} \) were then convolved with a HRF \( h \), whose exact shape appears in Fig. 5(a). Space-varying AR(1) Gaussian noise \( \nu_{j} \) and low-frequency drift \( P \ell_{j} \) were then superimposed to \( \sum_{m} s^{m}_{j} \) in every voxel of the grid. The amount of noise was varied in space according to a signal-to-noise ratio ranging from -10 to 12 dB. This simulation is thus representative of real fMRI datasets.

#### 3.2. Results

MAP and PM estimates were computed from the outputs of the Gibbs sampler with \( I = 500 \) and \( T = 2000 \) iterations and obtained with \( \beta^{m} = \beta = 0.3, \forall m \) (reasonable trade-off between sensitivities).

![Fig. 3. True parameters (left: labels \( q \), middle: NRLs \( a_{1} \) and right: MHS \( r \)) for simulating fMRI time series according to Eqs. (2)-(3).](image)
sibility and specificity). As shown in Fig. 4, only two false negatives (FNs) appear in $\tilde{a}_1^{MAP}$ in positions $\{(4, 0); (0, 2)\}$ for $m = 1, 2$, respectively. No false positive has emerged for these simulation settings while this could occur for lower CNRs. The reason for which two FNs were estimated lies in the values of habituation parameter, where strong MHS values remarkably occur. Regarding the NRLs, the true parameters are accurately estimated by $\tilde{a}_1^{PM}$ except for the two abovementioned voxels. However, it is worth noting that there is a slight shift in magnitude between $a$ and its PM estimate $\tilde{a}_1^{PM}$ being larger), which is compensated by an inverse trend occurring on the HRF (the peak of $\tilde{h}^{PM}$ being smaller). This is a direct consequence of the scale ambiguity problem arising in model (1), which is bilinear with respect to $a_1$ and $h$. Hence, the pair of solutions $(h^*, a_1^*)$ is known up to a multiplicative constant. Finally, note that the habituation parameters $\tilde{\pi}^{PM}$ are well recovered in activating voxels which have been properly detected, while zero-valued habituation speeds are estimated in non-activating voxels. Fig. 6 illustrates on three different voxels the profiles of the trial-varying NRLs $\tilde{a}_j^m$ for different MHS values. Low habituation speed reported in Fig. 6(a) does not strongly affect the stationarity assumption. In contrast, medium and large MHs values emphasize the decrease of the trial-varying NRLs as pointed out in Fig. 6(b)-(c).

![Fig. 4. PM parameter estimates (left: labels $\tilde{a}_i^{MAP}$, middle: NRLs $\tilde{a}_i^{PM}$ and right: MHS $\tilde{\pi}^{PM}$).](image)

![Fig. 5. Left: True HRF shape. Right: HRF estimate $\tilde{h}^{PM}$.](image)

Fig. 6. Trial-varying NRLs reconstructed from $\tilde{a}_i^{PM}$ and $\tilde{\pi}^{PM}$. (a): $m = 1$, $V_j = (3, 0)$ and $\tilde{r}^{2(3, 0)} = 0.29$. (b): $m = 2$, $V_j = (3, 3)$ and $\tilde{r}^{2(3, 3)} = 0.52$. (c): $m = 2$, $V_j = (3, 4)$ and $\tilde{r}^{2(3, 4)} = 0.92$.

5. REFERENCES


