BRAIN ACTIVITY DETECTION
Statistical Analysis of fMRI Data

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Abstract: We are concerned with modelling and analysing fMRI data. An fMRI experiment is a series of images obtained over time under two different conditions, in which regions of activity are detected by observing differences in blood magnetism due to hemodynamic response. In this paper we propose a spatiotemporal model for detecting brain activity in fMRI. The model makes no assumptions about the shape or form of activated areas, except that they emit higher signals in response to a stimulus than non-activated areas do, and that they form connected regions. The Bayesian spatial prior distributions provide a framework for detecting active regions much as a neurologist might; based on posterior evidence over a wide range of spatial scales, simultaneously considering the level of the voxel magnitudes together with the size of the activated area. A single spatiotemporal Bayesian model allows more information to be obtained about the corresponding magnetic resonance study. Despite higher computational cost, a spatiotemporal model improves the inference ability since it takes into account the uncertainty in both the spatial and the temporal dimension. A simulated study is used to test the model applicability and sensitivity.

1 INTRODUCTION

Magnetic Resonance Imaging is a method used to visualise the inside of living organisms as well as to detect the amount of bound water in geological structures. It does not require painful interventions and it is a widely used tool in medical diagnosis support. The fundamental research to develop magnetic resonance imaging techniques started at the beginning of XIX century although the image obtaining technology could not be developed until the appearance of high speed computers. The sensitivity of Magnetic Resonance to changes in blood oxygen level was discovered at the beginning of the 80's and this was the great advance that caused the advent of functional Magnetic Resonance Imaging. As it was already known that changes in blood flow and blood oxygenation (collectively known as hemodynamics) in the brain are closely linked to neural activity, fMRI could be used from then on to track physiological activity. Image acquisition with BOLD (Blood Oxygen Level Dependency) contrast is based on that principle (Ogawa et al., 1990). Since 1990, fMRI has greatly increased knowledge of the brain functions in neuroscience and, in other fields, has contributed to a better understanding of the physiology of different organs. Scientists use fMRI to identify changes in the brain activity of patients with certain pathologies in order to develop new and more effective treatments and therapies. It also serves as a guide to surgeons during operations for the pain to be minimised.

To understand the fMRI acquisition process it is necessary to understand the underlying physics (Huang, 1999; Jezzard et al., 2001). Essentially, magnetic resonance machines build the image analysing structural changes in an electromagnetic wave sent to hydrogen atom protons in the different tissues of the human body. The grey level of each voxel in the image corresponds to the behaviour of a large number of protons and it permits the identification of different tissues through the definition of the image contrast.

Once generated, magnetic resonance images are digitally treated to improve quality and to minimise error sources that could bias future statistical analy-

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sis. Image pre-processing steps are usually: realignment, unwrapping, coregistering, slice timing correction, low-pass filtering, linear trend removal, smoothing and normalisation. Statistical analysis is posterior to pre-processing and its goal is to localise activity regions in presence of noise. In a block-design fMRI study, a large number of scans are obtained under different conditions (usually, rest and activity states) in order to infer significative differences between them.

2 APPROACHES TO ANALYSIS OF fMRI DATA

Inference regarding brain activity in fMRI data is commonly addressed through the GLM analysis, (Friston et al., 1995), in which a linear dependency of the BOLD signal and the hemodynamic response function (HRF) is assumed.

Generally, the stimulus pattern is fitted simply as a box-shaped wave, slightly delayed, in order to account for the lapse of time between the stimulus onset and the arrival of the blood to the activated area. This box-shaped wave is convolved with a HRF template, for which several kernels have been considered, including Poisson (Friston et al., 1994), Gaussian (Friston et al., 1995) and gamma (Lange and Zeger, 1997). The result of this analysis is a t, F or Z estimate for each pixel. The next step is to threshold it (leading to a multiple comparisons problem), in order to decide, at a given level of significance, which parts of the brain are activated. The convolution approach is attractive for its simplicity. However, it imposes severe restrictions on the model.

The most popular and complete statistical package is SPM (Friston et al., 2006), created by (Frackowiak et al., 2004). SPM is based on GLM. Some other authors fit the HRF making use of GLM. As univariate methods do not take into account the spatial structure on data, they proposed a higher level spatial structure modelisation (Bowman et al., 2008; Harrison et al., 2007; Hartvig and Jensen, 2000; Gossl et al., 1999).

Multivariate methods provide an alternative to individual analysis of voxels, reducing the whole spatiotemporal data set into certain multivariate components with similar temporal characteristics. Multivariate techniques applied to the analysis of fMRI data include principal component analysis (Friston, 1994; Sjöstrand et al., 2006), independent component analysis (Beckmann and Smith, 2004; Esposito et al., 2003; McKeown et al., 2003; Calhoun et al., 2001; Porill et al., 1999) and cluster analysis (Goutte et al., 1999). Interpretation of results must be treated with care when using these techniques, as there is a high risk of data overfitting.

In order to make use of more complex models and to overcome the multiple comparisons problem, the best choice is to work in a Bayesian framework, which also allows including prior information on the expected location, shape and size of the activation areas. Most Bayesian approaches to the modelling of fMRI data use Markov random fields (MRF) as prior distributions, in order to account for the spatial structure present in the data (Holmes, 1995; Gossl et al., 2001; Woolrich et al., 2004b). An alternative to these priors are, for example, Laplacian priors on regression coefficients in GLM (Penny et al., 2005).

The fMRI data analysis is a problem that involves the spatiotemporal relationship between a stimulus or cognitive task and the cerebral response measured with fMRI. In spite of the obvious spatiotemporal nature of data, there are a few spatiotemporal models (Bowman, 2007; Katanoda et al., 2002; Woolrich et al., 2004a), all of them based on convolution.

3 THE MODEL

We propose a spatiotemporal model to analyse fMRI data in order to detect activity regions in the brain. We extend (Quirós et al., 2006), a fully Bayesian two-stage model to localise activity regions in fMRI. In the first stage, the observed HRF is fitted, pixelwise, by a scaled and shifted Poisson distribution curve. A map of values for the observed activity magnitude in each pixel is obtained during this stage. The second part consists of a spatial analysis of this map by the means of a statistical model in the form of a product of MRF. The goal of those fields is to set restrictions on the activity patterns smoothness as prior information. The formulation of the model is made in a simple and natural way thanks to a small number of parameters. Besides, the Bayesian approach provides the model of adaptability to fMRI data and makes it efficient.

The extension of this model by a single spatiotemporal Bayesian model allows us to obtain more information regarding the corresponding magnetic resonance study. In spite of the higher computational cost, a spatiotemporal model improves the inference ability since it takes into account the uncertainty in both the spatial and the temporal dimension.

3.1 The Hemodynamic Response Function

The archetypical HRF (see figure 1) describes the local response to the oxygen utilisation (by nerve cells)

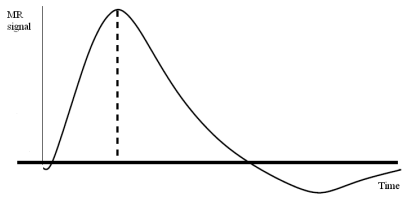

Figure 1: Archetypical hemodynamic response curve.

and it consists of an increase in blood flow to regions of increased neural activity, occurring after a delay of approximately 1-5 seconds. This hemodynamic response rises to a peak over 4-8 seconds, before falling back to the baseline (and typically undershooting slightly). This leads to local changes in the relative concentration of oxyhaemoglobin and deoxyhaemoglobin and changes in local cerebral blood volume in addition to this change in local cerebral blood flow. This delayed response is characterized by $h(\tau)$, where τ is the time since activity started.

Here we adopt the Poisson curve proposal (Friston et al., 1994) and we model the HRF, for each pixel s, by a scaled and shifted Poisson distribution density function with mean d_s, that is, a potential increase of signal and a subsequent exponential decay,

$$h_s(\tau) = \begin{cases} x_s \frac{d_s^{\tau-1} e^{-d_s}}{(\tau-1)!} & \tau = 1,2,\ldots,T-1 \\ 0 & \tau = 0 \end{cases}$$

where $x_s \in [0,\infty]$ and $d_s \in [0,T-1]$. Consequently, parameter d can be interpreted as the delay of the response with respect to the stimulus onset and x as a measure of the magnitude of response.

3.2 Model Description

We consider a 2-dimensional block-design fMRI study. Two consecutive blocks (a stimulation and a resting block) are called a cycle, i.e., each cycle is composed by T images, half of which are taken when the stimulus is on and half when the stimulus is off.

Let $y = \{y_{s,\tau} : s = 1,\ldots,N \times M; \tau = 0,\ldots,T-1\}$ be the mean of the observed hemodynamic response curves to the stimulus paradigm. The set y plays the role of data in our model (we take the mean to alleviate the computational burden).

As the spatiotemporal model, we propose the following expression:

$$y_{s,\tau} = z_s \left[x_s \frac{d_s^{\tau-1} e^{-d_s}}{(\tau-1)!} + \varepsilon_{s,\tau} \right] + k_s + \varepsilon'_{s,\tau}$$

where k is the set of basal values for each pixel that we estimate from the mean of the first images in the experiment (acquired when the stimulus is off).

We consider $z = \{z_s : s = 1,\ldots,N \times M\}$ to be a binary random field that indicates the activity presence or absence for each pixel of the image. To incorporate spatial connectedness (expected from activity), we define z from thresholding of a continuous field, w, i.e., $z_s = I_{\{w_s > 0\}}$ for $s = 1,\ldots,N \times M$.

The error in the activity estimation and in the basal values are, respectively, $\varepsilon_{s,\tau}$ and $\varepsilon'_{s,\tau}$, for which we assume the distributions

$$\varepsilon'_{s,\tau} \sim \mathcal{N}(0, \eta^2_{s,\tau}),$$

$$\varepsilon_{s,\tau} \sim \mathcal{N}(0, \sigma^2_{s,\tau}).$$

Assuming independence between variables and that $\sigma^2_{s,\tau} = \sigma^2$ and $\eta^2_{s,\tau} = \eta^2$, we obtain

$$y_{s,\tau} \sim \mathcal{N}\left(z_s x_s \frac{d_s^{\tau-1} e^{-d_s}}{(\tau-1)!} + k_s, z_s\sigma^2 + \eta^2 \right).$$

3.3 Prior Distributions

When image analysis problems are treated under a Bayesian perspective, it is necessary to formulate a prior distribution for the image of interest, in this case, the x field and the generator field of z, w. MRF are an adequate tool for this purpose as they define expected characteristics of the image as, for example, smoothness and connection between regions (Winkler, 2003).

Making use of MRF as prior distributions for the image of interest, activity location in a pixel is determined by its response magnitude and also by the activity evidence in its neighbouring pixels. That is, we establish, a priori, the expectation that activity takes the form of regions made up of several neighbouring pixels, penalising activity presence in isolated pixels. Additionally, MRF can be considered as smoothing kernels and therefore, its use as prior distributions let us dispense with data smoothing process during the pre-process.

The prior distribution for w is an intrinsic Gaussian Markov Random Field (Rue and Held, 2005) of first order:

$$\pi(w) \propto \exp\{-\frac{1}{2}\sum_{s\sim t}(w_s - w_t)^2\}. \qquad (1)$$

The prior distribution for w is improper as it corresponds to the bidimensional generalization of a random walk. Combining it with the likelihood, marginal distribution for each w_s becomes proper. The advantage of using an intrinsic form for w is that there is no need to specify a priori the proportion of activated pixels.

Following the proposal of (Kornak, 2000), we describe the x–field by the means of the natural logarithm of a proper Gaussian Markov Random Field

(Rue and Held, 2005), i.e.:

$$\log(x) \sim \mathcal{NMV}(\mu\mathbf{1}, \kappa^2(I-\beta N)^{-1}), \qquad (2)$$

where $N = (n_{ij})_{i,j=1,\ldots,N\times M}$ and $n_{ij} = 1$ if pixels i and j are neighbours and $n_{ij} = 0$, otherwise. The mean parameter μ controls the mean level of the response magnitude, κ^2 controls the spatial smoothness of the response level and β models the strength of influence that neighbouring pixel values have on each other relative to that of the field's global mean level μ.

For μ and κ^2 we take conjugate prior distributions:

$$\mu \sim \mathcal{N}(\mu_1, \sigma_1^2),$$

$$\kappa^2 \sim \mathcal{GI}(a_1, b_1),$$

but with large variances, to make them be almost non informative.

In the case of β parameter a conjugate prior distribution does not exist and therefore, given the flexibility of Beta distribution, we propose:

$$4\beta \sim \mathcal{B}e(p,q)$$

and hence, $\beta \in [0, 0.25]$.

Prior distributions for the rest of parameters and hyperparameters are:

$$\begin{aligned} \pi(d) &\sim \mathcal{N}(\mu_2, \sigma_2^2) \\ \pi(\sigma^2) &\sim \mathcal{GI}(a_2, b_2) \\ \pi(\eta^2) &\sim \mathcal{GI}(a_3, b_3) \end{aligned}$$

We obtain the posterior distribution combining prior information with the likelihood under a Bayesian approach. Given the model's complexity, to make inference over the parameters we use MCMC methods (Gilks et al., 1996).

4 RESULTS

To test the model applicability and sensitivity, we use a fMRI data simulation. We created this simulated study from a real fMRI rest study made in the Ruber Internacional hospital with a 3T machine. We selected a central slice and we convolved it with an activation pattern. This activation pattern takes the shape of a gamma distribution in the temporal dimension and of different geometric figures to model spatial activation regions. The result is a series of bidimensional slices $N \times M = 64 \times 64$ pixels. Figure 2 shows the phantom that we use to simulate the activity. Pixels of different regions have different signal intensity (1% and 2% of the signal). The simulated study resembles a block-design experiment with 70 scans: 3 cycles of $T = 20$ images each plus a rest period at the beginning of the experiment (to calculate k, the baseline value for each pixel map). In each cycle, the first ten images are taken while the stimulus is on and the last ten images when it ceases. Figure 3 shows several slices of the simulated study. Some of them are taken during the rest period and some during the activity period. We observe that, to the human eye, there are no notable differences between them, and consequently it is not possible to discriminate activity regions at sight.

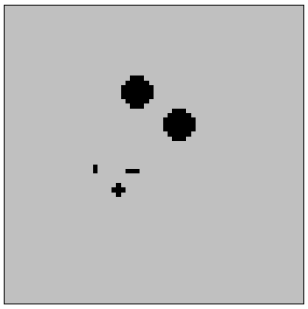

Figure 2: Activity phantom used to simulate the response paradigm to an stimulus in the simulated study.

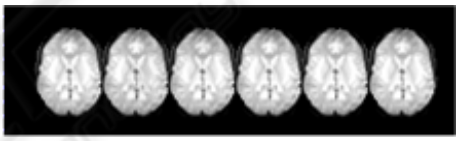

Figure 3: Several slices of the study.

Using MCMC methods, we obtained a total of 12000 samples, 4000 of which were discarded as burn-in. Subsequently, 8000 samples were used for posterior inference.

In the temporal dimension, we observe for each pixel how the hemodynamic response curve is fitted by a Poisson distribution of parameter d_s, multiplied by a scale factor (for the curve to reach the response magnitude), x_s. Figure 4 shows the fitting for one of the active pixels. It can be appreciated that the empirical curve (in black) is essentially noisy and that it adopt the archetypical shape of the hemodynamic response described above. In the same figure, the red curve corresponds to the Poisson curve that fits the empirical one.

In the spatial dimension, we obtained results in relation to the activation regions' shape together with its magnitude. The z–field posterior mean map provides us, for each pixel, of the posterior probability of activation.

Figure 5 shows how the model is sensitive to connected activation regions, rejecting posible activation in isolated pixels, as a neurologist might judge. This is achieved thanks to the z–field construction from a

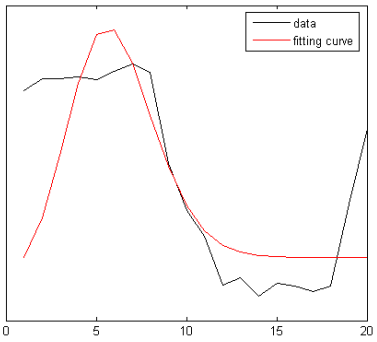

Figure 4: Hemodynamic response curve fit in an active pixel.

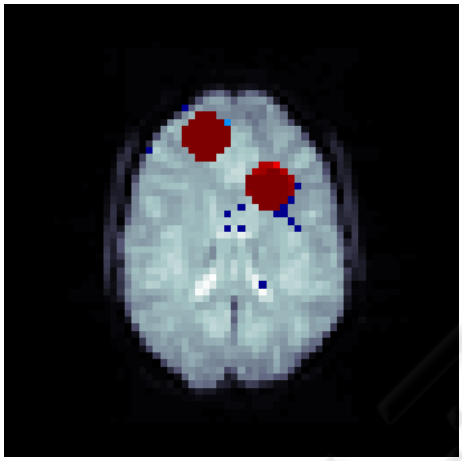

Figure 5: z–field posterior mean map.

continuous field w, whose prior distribution is a MRF, that favours this kind of regions.

Finally, figure 6 shows the result of multiplying pixel by pixel the z and the x fields, obtaining a magnitude of activation "image" in those activated areas.

5 DISCUSSION

The Bayesian model developed here incorporates spatial restrictions in order to estimate response patterns to stimulus in fMRI experiments using MRF as prior distributions. These MRF act as two-level spatial smoothing filters: parameter estimation in the x–field (the classical level) and pixel activity identifying in the z–field. This smoothing process is made taking into account the information provided by the neighbours of a pixel, apart from the pixel value itself.

In addition, including temporal information into the spatial model (forming a spatiotemporal model), a source of information that other models do not take into account is incorporated, without a significant increase of computational cost in our model. This would permit improvement of the model in the future, for example, extending the model to all data (and not only to the mean with respect to cycles), including the baseline field, k, as another parameter (instead of estimating it beforehand) and integrating the model into a graphical interface.

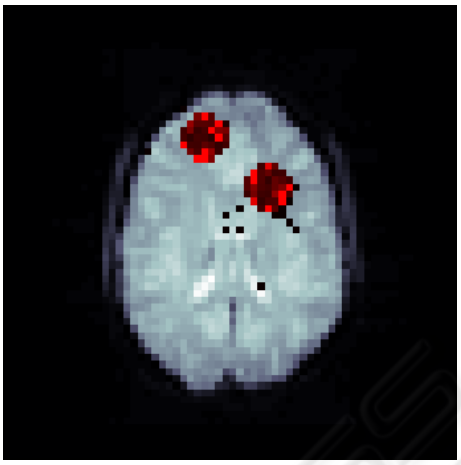

Figure 6: Active regions magnitude of activation map, $x \odot z$.

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