Spatio-temporal Covariance Model for Medical Images Sequences: Application to Functional MRI Data

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Abstract. Spatial and temporal correlations which affect the signal measured in functional MRI (fMRI) are usually not considered simultaneously (i.e., as non-independent random processes) in statistical methods dedicated to detecting cerebral activation. We propose a new method for modeling the covariance of a stationary spatio-temporal random process and apply this approach to fMRI data analysis. For doing so, we introduce a multivariate regression model which takes simultaneously the spatial and temporal correlations into account. We show that an experimental variogram of the regression error process can be fitted to a valid nonseparable spatio-temporal covariance model. This yields a more robust estimation of the intrinsic spatio-temporal covariance of the error process and allows a better modeling of the properties of the random fluctuations affecting the hemodynamic signal. The practical relevance of our model is illustrated using real event-related fMRI experiments.

1 Introduction

When analyzing data from functional Magnetic Resonance Imaging (fMRI), accurate detection of human cerebral activation raises many issues concerning not only the spatial localization of activated regions [1,2,3,4], but in addition the spatio-temporal properties of these regions [5]. An adequate modeling of the spatial and temporal correlations which affect the measured signal is mandatory [1,2,3,4,5,6] and models of spatio-temporal random processes are increasingly accounted for in statistical analyses. The hypotheses underlying these models must reflect as accurately as possible the properties of the measured data (e.g., spatio-temporal stationarity) to ensure a robust detection of the activation signal.

In this work, we focus on the analysis of fMRI time-series based on multivariate regression, as an original extension of the univariate regression widely used

M.F. Insana, R.M. Leahy (Eds.): IPMI 2001, LNCS 2082, pp. 197–203, 2001.

in the functional brain mapping literature. This multivariate approach allows to consider spatial and temporal correlations simultaneously. We introduce a new method for modeling the covariance of a stationary spatio-temporal random process. The proposed covariance model is *nonseparable* in time and space, which allows a better modeling of the intrinsic properties of the hemodynamic signal.

In Sect. 2, we introduce the multivariate regression model and show that the spatio-temporal covariance of the error process is required when making statistical inference from fMRI data. Theoretical results that allow defining classes of nonseparable spatio-temporal covariance models are given in Sect. 3. The proposed model is then applied to real data (Sect. 4) and discussed (Sect. 5).

2 Multivariate Regression Model

2.1 Definition

Let $\boldsymbol{y}_i$ be the T-vector corresponding to the fMRI time-series measured in voxel i (usually, preprocessed data). Denote by $\boldsymbol{X}$ a (T, P) matrix where each of the P columns of $\boldsymbol{X}$ is called a "regressor", which is either determined by the experimental design ("regressors of interest") or represents confounds ("dummy regressors"). Let $\boldsymbol{\epsilon}_i$ be the T-vector of error (or residual) terms. The multivariate regression model can be written as follows:

$$\begin{bmatrix} \boldsymbol{y}_1 \\ \vdots \\ \boldsymbol{y}_i \\ \vdots \\ \boldsymbol{y}_N \end{bmatrix} = \begin{bmatrix} \boldsymbol{X} & 0 & \dots & 0 \\ 0 & \boldsymbol{X} & \dots & 0 \\ \vdots & & \ddots & 0 \\ 0 & 0 & \dots & \boldsymbol{X} \end{bmatrix} \begin{bmatrix} \boldsymbol{\beta}_1 \\ \vdots \\ \boldsymbol{\beta}_i \\ \vdots \\ \boldsymbol{\beta}_N \end{bmatrix} + \begin{bmatrix} \boldsymbol{\epsilon}_1 \\ \vdots \\ \boldsymbol{\epsilon}_i \\ \vdots \\ \boldsymbol{\epsilon}_N \end{bmatrix} \quad \text{or} \quad \boldsymbol{Y} = (\boldsymbol{I}_N \otimes \boldsymbol{X})\boldsymbol{\beta} + \boldsymbol{\epsilon} \ , \qquad (1)$$

where N is the number of voxels included in the analysis, $\boldsymbol{I}$ is the identity matrix, $\boldsymbol{Y}$ and $\boldsymbol{\epsilon}$ are NT-vectors, $(\boldsymbol{I}_N \otimes \boldsymbol{X})$ is a (NT, NP) matrix and $\boldsymbol{\beta}$ is a NP-vector of regression coefficients. $\otimes$ denotes the Kronecker product. We further assume that $\boldsymbol{\epsilon}$ is a multidimensional stationary random process with:

- $\mathrm{E}[\boldsymbol{\epsilon}] = 0$, where $\mathrm{E}[.]$ denotes the expectation,
- $\mathrm{var}[\boldsymbol{\epsilon}] = \sigma^2 \boldsymbol{\Omega}$, where $\boldsymbol{\Omega}$ is the (NT, NT) covariance matrix of the errors and σ^2 is the variance at the origin.

Solving (1) consists in deciding whether $\boldsymbol{Y}$ represents an activation signal, by estimating the coefficients $\boldsymbol{\beta}$ (Sect. 2.2) and determining using a statistical test whether they contribute significantly to predicting the signal $\boldsymbol{Y}$ (Sect. 2.3).

2.2 Estimating the Regression Coefficients

$\boldsymbol{\beta}$ is most frequently estimated using ordinary least-squares (OLS) as follows:

$$\widehat{\boldsymbol{\beta}} = \left[(\boldsymbol{I}_N \otimes \boldsymbol{X})^{\mathrm{t}}(\boldsymbol{I}_N \otimes \boldsymbol{X})\right]^{-1} (\boldsymbol{I}_N \otimes \boldsymbol{X})^{\mathrm{t}}\boldsymbol{Y} = \boldsymbol{P}\boldsymbol{Y} \ , \qquad (2)$$

where ^{t} denotes the transpose. However, OLS estimation relies on the assumption that $\mathrm{var}[\boldsymbol{\epsilon}] = \sigma^2 \boldsymbol{I}_{NT}$, whereas we have assumed that $\mathrm{var}[\boldsymbol{\epsilon}] = \sigma^2 \boldsymbol{\Omega}$ (Sect. 2.1). Nevertheless, $\widehat{\boldsymbol{\beta}}$ is an unbiased estimate of $\boldsymbol{\beta}$ provided $\mathrm{var}[\widehat{\boldsymbol{\beta}}]$ takes the covariance matrix $\boldsymbol{\Omega}$ into account as follows [7, p. 114]:

$$\mathrm{var}[\widehat{\boldsymbol{\beta}}] = \sigma^2 \boldsymbol{P} \boldsymbol{\Omega} \boldsymbol{P}^{\mathrm{t}} . \tag{3}$$

2.3 Statistical Tests

Statistical tests determine whether $q \leqslant P$ regression coefficients contribute significantly to predicting the signal $\boldsymbol{Y}$. They rely on a null hypothesis of the general form $\mathrm{H}_0 : \boldsymbol{A}\boldsymbol{\beta} = \boldsymbol{C}$, where $\boldsymbol{A}$ is a known (q, NT) matrix of rank q and $\boldsymbol{C}$ is a known q-vector. The following test value F is usually used to test H_0:

$$F = \frac{1}{q} \left(\boldsymbol{A}\widehat{\boldsymbol{\beta}} - \boldsymbol{C} \right)^{\mathrm{t}} \left[\boldsymbol{A} \, \mathrm{var}[\widehat{\boldsymbol{\beta}}] \, \boldsymbol{A}^{\mathrm{t}} \right]^{-1} \left(\boldsymbol{A}\widehat{\boldsymbol{\beta}} - \boldsymbol{C} \right) .$$

The null distribution of F is well approximated by an F-distribution with q and ν degrees of freedom, where ν is a number of degrees of freedom reflecting the amount of spatio-temporal correlations affecting the data. To calculate F, it is clear from (3) that the covariance matrix $\boldsymbol{\Omega}$ has to be known or estimated.

3 Estimating the Covariance Matrix of the Residuals

3.1 Modeling the Covariance of a Spatio-temporal Process

Denote by $\{\boldsymbol{E}(\boldsymbol{s}, t);\ \boldsymbol{s} \in \mathrm{D} \subset \mathbb{R}^d,\ t \in \mathbb{R}^+\}$ a spatio-temporal stationary random process measured on a regular lattice $(\boldsymbol{s}_1, t_1), \ldots, (\boldsymbol{s}_N, t_T)$ ($\boldsymbol{s}$: spatial coordinate; t: temporal coordinate). In practice, $\boldsymbol{E}$ corresponds to the residual process $\boldsymbol{\epsilon}$ of model (1) and the spatial dimension is $d = 3$. It is assumed that $\boldsymbol{E}$ satisfies the following regularity condition:

$$\mathrm{var}[\boldsymbol{E}(\boldsymbol{s}, t)] < \infty \text{ for all } \boldsymbol{s} \in \mathrm{D} \text{ and } t > 0 ,$$

and the covariance function of $\boldsymbol{E}$ is defined by:

$$\mathrm{cov}[\boldsymbol{E}(\boldsymbol{s}, t), \boldsymbol{E}(\boldsymbol{s}', t')] = \mathcal{C}(\boldsymbol{s} - \boldsymbol{s}', t - t') = \mathcal{C}(\boldsymbol{h}, u) ,$$

where $\mathcal{C}$ only depends on the spatial lag $\boldsymbol{h} = \boldsymbol{s} - \boldsymbol{s}'$ and the temporal lag $u = t - t'$.

Spatio-temporal Variogram To model the covariance $\mathcal{C}$, it is often convenient to estimate the function $\mathrm{var}[\boldsymbol{E}(\boldsymbol{s}, t) - \boldsymbol{E}(\boldsymbol{s}', t')]$ from the sampled process $\boldsymbol{E}$. This function is called the *variogram* [8] and is independent from the mean of $\boldsymbol{E}$. The variogram is related to the covariance function $\mathcal{C}$ by:

$$\mathrm{var}[\boldsymbol{E}(\boldsymbol{s}, t) - \boldsymbol{E}(\boldsymbol{s}', t')] = 2 \left(\mathcal{C}(\boldsymbol{0}, 0) - \mathcal{C}(\boldsymbol{h}, u) \right) . \tag{4}$$

Valid Models for the Theoretical Covariance $\boldsymbol{\Omega}$ It is usually not possible to estimate $\boldsymbol{\Omega}$ directly from a single fMRI time-series. Nevertheless, $\boldsymbol{\Omega}$ can be estimated if a parametric covariance model $\mathcal{C}_{\boldsymbol{\theta}}(\boldsymbol{h}, u)$ is available ($\boldsymbol{\theta}$: vector of unknown parameters). Such a parametric model must be *valid*, i.e., the resulting covariance function $\mathcal{C}$ must be positive-definite. Existing criteria for defining valid classes of parametric spatio-temporal models [8] are based upon Bochner's theorem [9], which expresses the spectral density $\mathcal{G}(\boldsymbol{\omega}, \tau)$ of the spectral distribution function of the covariance $\mathcal{C}(\boldsymbol{h}, u)$ as follows:

$$\mathcal{C}(\boldsymbol{h}, u) = \iint e^{i\boldsymbol{h}\boldsymbol{\omega}+iu\tau}\mathcal{G}(\boldsymbol{\omega}, \tau)\, d\boldsymbol{\omega}\, d\tau \ ,$$

where $\boldsymbol{\omega}$: spatial frequency and τ: temporal frequency. If the two conditions

$$\mathrm{C}_1 : \int \rho(\boldsymbol{\omega}, u)\, du < \infty \text{ and } \mathcal{K}(\boldsymbol{\omega}) > 0 \qquad \mathrm{C}_2 : \int \mathcal{K}(\boldsymbol{\omega})\, d\boldsymbol{\omega} < \infty \tag{5}$$

are satisfied, with

$$\mathcal{K}(\boldsymbol{\omega}) \equiv \int \mathcal{G}(\boldsymbol{\omega}, \tau) d\tau \quad \text{and} \quad \rho(\boldsymbol{\omega}, u) \equiv \frac{\int e^{iu\tau}\mathcal{G}(\boldsymbol{\omega}, \tau) d\tau}{\int \mathcal{G}(\boldsymbol{\omega}, \tau) d\tau} \ ,$$

then Cressie and Huang [8] showed that

$$\mathcal{C}(\boldsymbol{h}, u) \equiv \int e^{i\boldsymbol{h}\boldsymbol{\omega}}\rho(\boldsymbol{\omega}, u)\mathcal{K}(\boldsymbol{\omega})\, d\boldsymbol{\omega} \tag{6}$$

is a valid continuous stationary spatio-temporal covariance function.

Classes of parametric models can then be defined by designing functions ρ and $\mathcal{K}$ which satisfy C_1 and C_2. The covariance model $\mathcal{C}_{\boldsymbol{\theta}}$ is derived using (6) and $\boldsymbol{\Omega}$ is finally estimated from $\mathcal{C}_{\boldsymbol{\theta}}(\boldsymbol{h}, u)$ [8]. To estimate the parameters $\boldsymbol{\theta}$ in practice, a variogram model $\mathrm{var}_{\boldsymbol{\theta}}$ is obtained from $\mathcal{C}_{\boldsymbol{\theta}}$ using (4) and the experimental variogram computed from the sampled process $\boldsymbol{E}$ is fitted to this model using a generalized least-squares minimization method.

3.2 A Nonseparable Spatio-temporal Model

In previous works, we studied the residuals obtained using univariate models. We showed that the covariance of temporal errors could be modeled by a "damped oscillator" process $\mathcal{C}(u) \equiv \exp(-a|u|)\cos(\alpha u)$ [10]. We also showed that the spatial error process could be modeled by a first-order autoregressive process [4,6]. However, all these models considered spatial and temporal correlations as independent phenomena, whereas experimental variograms suggest that spatio-temporal covariance processes are likely to be nonseparable. We therefore introduce a nonseparable spatio-temporal model defined by:

$$\rho(\boldsymbol{\omega}, u) = \frac{b^{d/2}}{(c|u| + b)^{d/2}} \exp\left[-\frac{||\boldsymbol{\omega}||^2}{4(c|u| + b)} + \frac{||\boldsymbol{\omega}||^2}{4b}\right] \exp\left[-\delta u^2\right] \cos(\alpha u) \tag{7}$$

$$\text{and} \qquad \mathcal{K}(\boldsymbol{\omega}) = \exp\left[-\frac{||\boldsymbol{\omega}||^2}{4b}\right] , \tag{8}$$

with $\delta > 0$, $b \geqslant 0$ and $c \geqslant 0$. We can prove that these functions satisfy conditions C_1 and C_2 given by (5). We can therefore conclude that the function $\mathcal{C}(\boldsymbol{h}, u)$ defined by (6), using (7) and (8), is a valid covariance model for the process $\boldsymbol{E}$. A parametric model for $\mathcal{C}(\boldsymbol{h}, u)$ is then derived following [8]:

$$\mathcal{C}_{\boldsymbol{\theta}}(\boldsymbol{h}, u) = \sigma^2 \exp\left[-a|u| - b||\boldsymbol{h}||^2 - c|u|.||\boldsymbol{h}||^2\right] \cos(\alpha u) , \tag{9}$$

$\boldsymbol{\theta} = \{a, b, c, \alpha, \sigma^2\}$, $a \geqslant 0$: scaling parameter of time, α: temporal frequency parameter, $b \geqslant 0$: scaling parameter of space, $c \geqslant 0$: spatio-temporal interaction parameter and $\sigma^2 = \mathcal{C}_{\boldsymbol{\theta}}(\mathbf{0}, 0)$. In the particular case $c = 0$, $\mathcal{C}_{\boldsymbol{\theta}}(\boldsymbol{h}, u)$ is a separable spatio-temporal model, the temporal component $\exp\left[-a|u|\right] \cos(\alpha u)$ corresponds to the damped oscillator model and the spatial component $\exp\left[-b||\boldsymbol{h}||^2\right]$ corresponds to a Gaussian model.

To estimate $\boldsymbol{\theta}$ in practice, we account for the so-called "nugget" effect (i.e., microscale variations of the error process that may cause a discontinuity at the origin [11]) by considering the spatio-temporal variogram model:

$$\mathrm{var}_{\boldsymbol{\theta}}[\boldsymbol{E}(\boldsymbol{s}, t) - \boldsymbol{E}(\boldsymbol{s} + \boldsymbol{h}, t + u)] =$$
$$\begin{cases} 0 & \text{if } \boldsymbol{h} = \mathbf{0} \text{ and } u = 0 \\ 2\sigma^2 \left(1 - \exp\left[-a|u| - b||\boldsymbol{h}||^2 - c|u|.||\boldsymbol{h}||^2\right] \cos(\alpha u)\right) + n^2 & \text{otherwise} \end{cases} .$$

n^2 corresponds to the variance of an additive white noise which accounts for small variations of $\boldsymbol{E}$ at the origin.

4 Application: Event-Related Working Memory Experiment

A real event-related experiment was selected to illustrate the usefulness of the proposed model. Subjects performed an item-recognition task [12]. Each trial consisted of a list of 3 to 6 uppercase target letters, presented simultaneously for 2 s, followed by a variable (from 2 s to 7 s) blank delay period, during which subjects had to remember the letters. After this delay a probe letter was displayed for 1 s. Subjects were asked to respond whether the probe letter belonged to the previously presented list. A variable inter-trial interval followed to complete constant duration (18 s) single trials. Eight functional axial slices were acquired parallel to the AC-PC plane (TE 30 ms, TR 1 s, thickness 5 mm, 3 mm gap) using a Bruker Medspec 30/100 3T MR system.

The experiment was described in $\boldsymbol{X}$ (see (1)) using separate regressors related to the cue, delay and probe phase, convolved with a Gaussian function (lag 5.5 s, dispersion 1.8 s) to model the smoothness of the hemodynamic response. Three regression models were compared: (**M1**) the SPM99 univariate model, (**M2**) the univariate regression model correcting for *temporal* correlations using a damped oscillator model [10] and (**M3**) the proposed multivariate model. Assignment of significance was achieved by testing $H_0 : \boldsymbol{\beta} = \mathbf{0}$ on a voxel-wise basis.

Table 1 shows estimated covariance parameters obtained using M3. Note that the model was not separable in time and space ($c > 0$). Figure 1 shows sample activation maps. Comparing the activation amount, M3 ranged between M1 and M2, with much more focused activation. Note that the strip-like activation, which was presumably motion-related, was not rendered as significant by the nonseparable spatio-temporal model.

Table 1. Covariance function parameters for slices 5 to 7.

Slice	Covariance Function Parameters					
	σ^2	a	b	c	α	n^2
5	18104	0.410	1.055	0.230	0.458	0.000
6	14015	0.313	0.962	0.145	0.388	0.007
7	12462	0.329	0.935	0.172	0.474	0.000

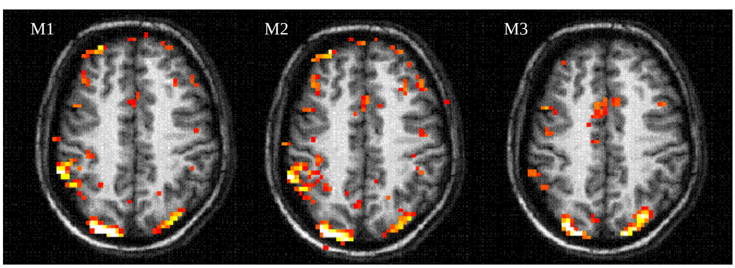

Fig. 1. For slice 6, activation maps (z-scale: 4-12) obtained for the probe phase and overlaid onto T_1-weighted anatomical scans.

5 Discussion

In this work, we introduced a new method for modeling the covariance of a stationary spatio-temporal random process and applied this approach to fMRI data analysis. To know whether a parametric covariance model is valid *a priori*, conditions C_1 and C_2 can be used in practice and the difficulty lies in deriving the covariance $\mathcal{C}$ following (6). The proposed nonseparable model was based upon both [8] (i.e., Gaussian model in space) and our previous work [10] (i.e., damped oscillator model in time). This approach is powerful in that it accounts for spatio-temporal interaction, which makes the model more flexible than previous models which considered spatial and temporal correlations separately. This is likely to yield a better modeling of the variance of a random process.

The proposed model was used in the framework of multivariate regression analysis and validated on real fMRI data. For doing so, we introduced a *multivariate* regression model taking simultaneously the spatial and temporal correlations into account. Estimating the regression coefficients $\widehat{\boldsymbol{\beta}}$ requires no extra computational cost compared to univariate analysis. Indeed, (2) reduces to $[\boldsymbol{I} \otimes (\boldsymbol{X}^{\mathrm{t}}\boldsymbol{X})^{-1}\boldsymbol{X}^{\mathrm{t}}]\boldsymbol{Y} = \boldsymbol{I} \otimes [(\boldsymbol{X}^{\mathrm{t}}\boldsymbol{X})^{-1}\boldsymbol{X}^{\mathrm{t}}\boldsymbol{y}_i]$, which is equivalent to OLS estimation in univariate regression. Note that the null hypothesis given in Sect. 2.3 can be tested using either a *global* test on all estimated $\widehat{\boldsymbol{\beta}}$ or a *local* test (e.g., on each voxel separately) [13]. In the latter case $\boldsymbol{A}$ selects the coefficients of interest for the voxel under study.

The activated regions obtained using the spatio-temporal model had a lesser extent than those obtained using only univariate models, for a given statistical threshold. The reasons for these differences will have to be investigated further, to better characterize the sensitivity and the specificity of the proposed multivariate approach.

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