MULTI-SUBJECT JOINT PARCELLATION DETECTION ESTIMATION IN FUNCTIONAL MRI

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ABSTRACT

fMRI experiments are usually conducted over a population of interest for investigating brain activity across different regions stimuli and objects. Multi-subject analysis proceeds in two steps, intra-subject analysis is performed sequentially on each individual and then group-level analysis is addressed to report significant results at the population level. This paper considers an existing Joint Parcellation Detection Estimation (JPDE) model which performs joint hemodynamic parcellation, brain dynamics estimation and evoked activity detection. The hierarchy of the JPDE model is extended for multi-subject analysis in order to perform group-level parcellation. Then, the corresponding underlying dynamics is estimated in each parcel while the detection and estimation steps are iterated over each individual. Validation on synthetic and real fMRI data shows its robustness in inferring the group-level parcellation and the corresponding hemodynamic profiles.

Index Terms— multi-subject fMRI analysis, JPDE, Parcellation, Hemodynamic Response Function, VEM

I. INTRODUCTION

Functional Magnetic Resonance Imaging (fMRI) is a very powerful imaging technique that indirectly measures neural activity using the blood oxygen-level dependent (BOLD) contrast. Except in patients for lesion mapping, most of task-related fMRI studies aim to uncover evoked brain activity elicited by task performance in a specific population of interest. A more challenging topic consists of inferring both which brain regions are involved in a cognitive process and according to which dynamics, also termed the Hemodynamic Response Function (HRF). This has been typically addressed in a number of recent studies considering a joint detection estimation framework [1]–[3]. Such framework is powerful only if it provides a reliable spatial support for characterizing the HRF shape in a region-dependent and subject-specific manner. A relevant formalism that fulfills these constraints in the joint detection estimation (JDE) model developed in [7], [9]. However, the latter approach suffers from a severe pitfall; it requires the knowledge of a pre-existing brain parcellation in homogeneous hemodynamic territories (parcels) to achieve reliable detection of evoked activity and accurate HRF estimation. To overcome such limitation, the JPDE model has been proposed at the subject-level [4] where the ”P” means that an additional layer complements the model to infer the brain parcellation. However, so far, the JPDE model has not been used for multi-subject fMRI analysis. Besides, the JDE model has been used in a multi-subject context [6] but the parcellation remained fixed a priori and identical across subjects. Another approach was proposed in [2] based on a semi-parametric framework with the general linear model. This approach assumes that for a fixed voxel under a given stimulus, the HRFs share the same unknown functional form across subjects but with different characteristics such as the time to peak, height and width. This common functional form was estimated using a nonparametric spline-smoothing method. In this paper, we introduce a joint intra and inter-subject fMRI data analysis model in the JPDE framework.The latter allows us to estimate a group-level parcellation as well as the group-level underlying HRF in contrast with the JPDE model. This group-level JPDE also recovers evoked activity in each individual. Moreover, the analysis is carried out for all the parcels of a region of interest (ROI) contrary to [6] where the analysis is done for a specific parcel at a time.
The rest of the paper is organized as follows; Section II recalls the JPDE model introduced in [4]. Section III describes our Multi-Subject Joint Parcellation Detection Estimation (MS-JPDE) extension. Experiments on multi-subject synthetic and real data are shown in Section IV. Conclusions are drawn in Section V.

II. SINGLE-SUBJECT JOINT PARCELLATION DETECTION ESTIMATION MODEL

The JPDE has been proposed in [4] for single subject fMRI data analysis. Let us assume that the measured BOLD signal for subject s is denoted by $\boldsymbol{Y}^s = \{\boldsymbol{y}_j^s, j \in \boldsymbol{\mathcal{P}}^s\}$ where $\boldsymbol{\mathcal{P}}^s$ is the set of voxels for subject $s = 1, \ldots, S$, S is the number of subjects, $\boldsymbol{y}_j^s$ denotes the fMRI time series at times $\{t_{n_s},\ n_s = 1, \ldots, N_s\}$ such that $t_{n_s} = n_s TR$ where N_s is the number of scans and TR is the repetition time. The model considers M different experimental conditions. The HRFs are assumed voxel-dependent and belong to a set denoted by $\boldsymbol{H}^s = \{\boldsymbol{h}_j^s, j \in \boldsymbol{\mathcal{P}}^s\}$ with $\boldsymbol{h}_j^s \in \mathbb{R}^D$, where (D) is the HRF size. For a voxel j, $\boldsymbol{h}_j^s$ is supposed to belong to one of the K^s HRF groups (also called parcels). A set of hidden labels $\boldsymbol{z}^s = \left\{z_j^s, j \in \boldsymbol{\mathcal{P}}^s\right\}$ is used to encode these groups where $z_j^s \in \{1, \ldots, K^s\}$. These labels are a priori distributed according to a K^s-class Potts model with interaction parameter β_z^s to account for spatial coherence (see [4] for motivations about this Potts model). We assume that in group $\#k$, the HRF $\boldsymbol{h}_j^s$ is a stochastic perturbation of an HRF pattern $\bar{\boldsymbol{h}}_k^s$. In other words, $\boldsymbol{h}_j^s$ is assigned a Gaussian prior distribution $\mathcal{N}(\bar{\boldsymbol{h}}_k^s, \nu_k^s I_D)$, where I_D is the $D \times D$ identity matrix and $\bar{\boldsymbol{h}}_k^s$ has a centered Gaussian prior distribution whose covariance matrix penalizes the second order derivatives to favor smooth HRF patterns: $\bar{\boldsymbol{h}}_k^s \sim (0, {\sigma^s}_h^2 \boldsymbol{R})$, $\boldsymbol{R} = (\Delta t)^4 (\boldsymbol{D}_2^t \boldsymbol{D}_2)^{-1}$, $\Delta t < TR$ is the sampling period of the unknown HRFs and $\boldsymbol{D}_2$ is the second order finite difference matrix (see [7] for more details). For a subject s and a voxel j, the adopted generative model is

$$\boldsymbol{y}_j^s = \sum_{m=1}^{M} a_j^{m,s} \boldsymbol{X}_m^s \boldsymbol{h}_j^s + \boldsymbol{P}\ell_j^s + \boldsymbol{\varepsilon}_j^s \tag{1}$$

where the low frequency drifts are denoted by $\boldsymbol{P}\ell_j^s$ (more details are given in [7]–[9]). For the m-th experimental condition, the information on the stimulus occurrences is provided in the $N_s \times D$ binary matrix $\boldsymbol{X}_m^s = \{x_m^{n_s - d\Delta t}, n_s = 1, \ldots, N_s, d = 0, \ldots, D-1\}$, $\boldsymbol{A}^s$ contains the neural response levels (NRL) of all the experimental conditions such that $\boldsymbol{A}^s = \{\boldsymbol{a}^{m,s}, m = 1, \ldots, M\}$ with $\boldsymbol{a}^{m,s} = \{a_j^{m,s}, j \in \boldsymbol{\mathcal{P}}^s\}$. Note that the regressors $\boldsymbol{a}^{m,s}$ are assumed to be a priori distributed according to spatial Gaussian mixtures defined by the parameters $\boldsymbol{\theta}_{\boldsymbol{a}}^s = \{\boldsymbol{\mu}_m^s, \boldsymbol{v}_m^s\}$ and regulated by binary Markov fields. To be more specific, each NRL is assigned to one of the activation classes encoded by the variables $\boldsymbol{Q}^s = \{\boldsymbol{q}^{m,s}, m = 1, \ldots, M\}$ where $\boldsymbol{q}^{m,s} = \{q_j^{m,s}, j \in \boldsymbol{\mathcal{P}}^s\}$ is a binary Markov field with interaction parameter β_m^s. In this model, two classes are considered, $q_j^{m,s} = 1$ and $q_j^{m,s} = 0$ if voxel j is activated or not for the mth condition. Finally, $\boldsymbol{\varepsilon}_j^s$ is an additive zero mean Gaussian noise with covariance matrix $\boldsymbol{\Gamma}_j^{s-1}$ as in [4], [7]–[9]. The set of hyperparameters of the JPDE model is denoted by $\boldsymbol{\Theta}^s = \{\boldsymbol{\Gamma}^s, \boldsymbol{L}^s, \boldsymbol{\mu}^s, \boldsymbol{v}^s, \boldsymbol{\beta}^s, \beta_z^s, {\sigma^s}_h^2, (\bar{\boldsymbol{h}}_k^s, \nu_k^s)_{1 \leqslant k \leqslant K}\}$, where $\boldsymbol{L}^s = \{\ell_j^s, j \in \boldsymbol{\mathcal{P}}^s\}$, $\boldsymbol{\Gamma}^s = \{\boldsymbol{\Gamma}_j^s, j \in \boldsymbol{\mathcal{P}}^s\}$, and $\boldsymbol{\beta}^s = \{\beta_m^s, m = 1, \ldots, M\}$. More details about the meaning of these hyperparameters are available in [4].

A variational approach was proposed in [4], [7] to approximate the posterior of the JPDE model as the product of simple distributions, i.e.,

$$\tilde{p}(\boldsymbol{A}^s, \boldsymbol{H}^s, \boldsymbol{Q}^s, \boldsymbol{z}^s \mid \boldsymbol{Y}^s) = \tilde{p}_{A^s}(\boldsymbol{A}^s) \tilde{p}_{H^s}(\boldsymbol{H}^s) \tilde{p}_{Q^s}(\boldsymbol{Q}^s) \tilde{p}_{z^s}(\boldsymbol{z}^s). \tag{2}$$

The inference was carried out in two parts: the expectation part which was divided into four main steps to compute approximate posteriors of the missing variables $\{\boldsymbol{A}^s, \boldsymbol{H}^s, \boldsymbol{Q}^s, \boldsymbol{z}^s\}$, and the maximization part to estimate the unknown parameters. The interested reader can refer to [4], [7] for further details.

III. MULTI-SUBJECT JOINT PARCELLATION DETECTION ESTIMATION MODEL

This section is devoted to the extension of the JPDE model to multiple subjects. The proposed extension jointly handles fMRI data related to S subjects involved in the same experiment where the set of voxels, i.e., the mask, is the same for all the individuals. More specifically, the extension performs joint parcellation-detection-estimation at the group level. It relies on the generative model (1) while introducing some departure to the standard JPDE approach especially in the parcellation step. Subject-level inference of parcellation is actually replaced by a group-level one considering data collected from all individuals. We will therefore estimate a group-level parcellation of K^G parcels. We assume that the voxel-wise HRF of the individuals is expressed conditionally to its group-level HRF group k^G, where $k^G = 1, \ldots, K^G$, as

$$p(\boldsymbol{h}_j^s \mid z_j^G = k^G) \sim \mathcal{N}(\bar{\boldsymbol{h}}_k^G, \nu_k^G I_{D+1}) \tag{3}$$

where $z_j^G \in \{1, \ldots, K^G\}$ is the group parcellation label, $\bar{\boldsymbol{h}}_k^G$ and $\nu_k^G I_{D+1}$ are the HRF pattern and covariance matrix for class k^G, respectively. Note that all the voxels of group k^G in different subjects are stochastic perturbations of the same HRF pattern $\bar{\boldsymbol{h}}_k^G$. Regarding the prior for the group parcellation, we keep using a K^G-class Potts model with spatial interaction parameter β_z^G. Using this modified model, we distinguish the parameters of each individual contained in $\boldsymbol{\Theta}^s$ (denoted as $\boldsymbol{\omega}^s = \{\boldsymbol{\Gamma}^s, \boldsymbol{L}^s, \boldsymbol{\mu}^s, \boldsymbol{v}^s, \boldsymbol{\beta}^s\}$) from the parameters of the group-level HRF classes (that are denoted as $\boldsymbol{\alpha}^G = \{\beta_z^G, {\sigma_h^G}^2, (\bar{\boldsymbol{h}}_k^G, \nu_k^G)_{k^G=1,\ldots,K^G}\}$). We also denote $\mathbb{Y} = \{\boldsymbol{Y}^s\}^{s=1:S}$, $\mathbb{H} = \{\boldsymbol{H}^s\}^{s=1:S}$, $\mathbb{A} = \{\boldsymbol{A}^s\}^{s=1:S}$, $\mathbb{Q} = \{\boldsymbol{Q}^s\}^{s=1:S}$ and $\Omega = \{\boldsymbol{\omega}^s\}^{s=1:S}$. Following an expectation-maximization (EM) procedure, the target posterior distribution after the variational approximation is

$$\tilde{p}\left(\mathbb{A}, \mathbb{H}, \mathbb{Q}, \boldsymbol{z}^G \mid \mathbb{Y}\right) = \tilde{p}_A\left(\mathbb{A}\right) \tilde{p}_H\left(\mathbb{H}\right) \tilde{p}_Q\left(\mathbb{Q}\right) \tilde{p}_z\left(\boldsymbol{z}^G\right). \tag{4}$$

Regarding the variational EM inference, the E-$\mathbb{A}$ and E-$\mathbb{Q}$ steps consist of S E-A^s and E-Q^s steps that are the same as in the standard subject-level JPDE model [4]. Iterating over the S subjects is therefore essential to perform the whole expectation steps. The E-$\mathbb{H}$ step is performed by S E-H^s sub-steps. However, this estimation depends on the group-level HRF classes that are given by the parcellation labels in $\boldsymbol{z}^G$. For a subject s, the corresponding E-H^s and E-Z^G sub-steps consist of estimating

$$\tilde{p}_{H^s}^{(r)}(\boldsymbol{H}^s) \propto \exp\left(\mathrm{E}_{\tilde{p}_{A^s}^{(r-1)} \tilde{p}_{z^G}^{(r-1)}}\left[\log p(\boldsymbol{H}^s \mid \boldsymbol{Y}^s, \boldsymbol{A}^s, \boldsymbol{z}^G; \boldsymbol{\omega}^{s(r-1)}, \boldsymbol{\alpha}^{G(r-1)})\right]\right) \tag{5}$$

$$\tilde{p}_{z^G}^{(r)}(\boldsymbol{z}^G) \propto \exp\left(\mathrm{E}_{\tilde{p}_{\mathbb{H}}^{(r)}}\left[\log p(\boldsymbol{z}^G \mid \mathbb{Y}, \mathbb{H}; \boldsymbol{\Omega}^{(r-1)}, \boldsymbol{\alpha}^{G(r-1)})\right]\right). \tag{6}$$

This step can be split into J sub-steps assuming that $\tilde{p}_{z^G}(\boldsymbol{z}^G) = \prod_{j=1}^{J} \tilde{p}_{z_j^G}(z_j^G)$[1]. Each E-Z$_j$ will therefore consist of estimating

$$\tilde{p}_{z_j^G}^{(r)}(z_j^G) \propto \exp\left(\sum_{s=1}^{S} \mathrm{E}_{\tilde{p}_{h_j^s}}\left[\log p(\boldsymbol{h}_j^s \mid z_j^G)\right] + \mathrm{E}_{\tilde{p}_{z_{\backslash j}^G}}\left[p(\boldsymbol{z}^G \mid \beta_z^G)\right]\right) \tag{7}$$

where $z_{\backslash j}^G = \{z_{j'}^G, j' \neq j\}$.

Regarding the maximization step (M-step), estimating the

[1] The independence assumption between voxels has been used intensively in the literature [7], [10]. It simplifies the analysis and avoids the use of the mean-field approximation

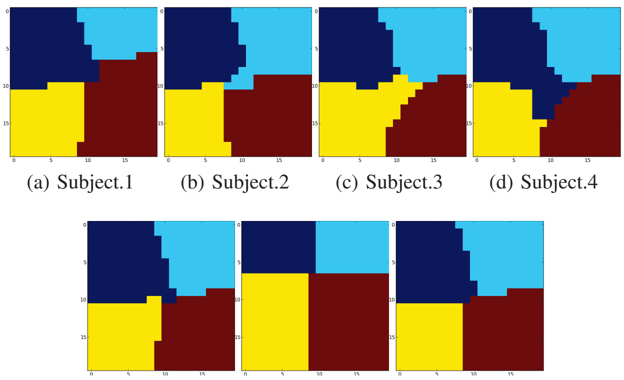
parameters involved in the MS-JPDE model is similar to the M-steps of the standard JPDE model except the $\bar{\boldsymbol{h}}_k^G$ estimation which can be computed by solving the following minimization problem

$$\bar{\boldsymbol{h}}_k^{G(r)} = \arg\max_{\bar{\boldsymbol{h}}_k^G} \mathrm{E}_{\tilde{p}^{(r)}_{\boldsymbol{H}^s}\tilde{p}^{(r)}_{\boldsymbol{z}^G}}\left[\sum_{s=1}^{S} \log p(\boldsymbol{H}^s \mid \boldsymbol{z}^G; \bar{\boldsymbol{h}}_k^G, \boldsymbol{\nu}^G)\right] + \log p(\bar{\boldsymbol{h}}_k^G; \sigma_h^{G^2}). \tag{8}$$

IV. EXPERIMENTAL VALIDATION

IV-A. Synthetic data experiments

FMRI synthetic data for four subjects have been generated according to the generative model (1) to validate the MS-JPDE model. A group parcellation mask has been first considered as a mean parcellation mask over the four subject. This group-level mask, as well as its individual instances are depicted in Fig. 1[Bottom-left][Top], respectively. All masks involve four different parcels. The ground truth HRF patterns associated with these four parcels are shown in Fig. 2 (continuous lines). The same two experimental conditions ($M = 2$) were used for all the subjects each consisting of 30 trials. The reference activation labels are illustrated in Fig. 3[left]. The corresponding NRLs (Fig. 3[right]) were drawn according to their prior distribution so that $a_j^{m,s} \mid q_j^{m,s} = 0 \sim \mathcal{N}(0, 0.5)$ and $a_j^{m,s} \mid q_j^{m,s} = 1 \sim \mathcal{N}(3.2, 0.5)$.



(a) Subject.1 (b) Subject.2 (c) Subject.3 (d) Subject.4

(e) Reference GL parcellation (f) Initial parcellation (g) Estimated GL parcellation

Fig. 1: Top row: Individual subjects parcellation; Bottom row: reference group-level (GL), initial and estimated GL parcellations, respectively.

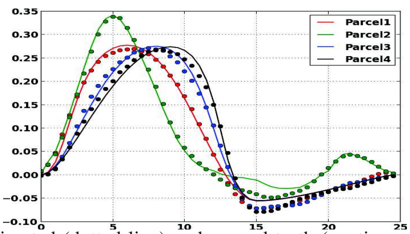


Fig. 2: Estimated (dotted line) and ground truth (continuous line) group-level HRF profiles (synthetic data).

The time of repetition used in this experiment was $TR = 1$s. The fMRI time series associated with the four subjects were processed simultaneously to get the group-level parcellation and HRF shapes. Fig. 2 shows estimates for the four group-level HRFs for the four parcels (dotted line), while group-level parcellation estimates are reported in Fig. 1[Bottom-right]. The HRF estimates are close to the ground truth illustrating the good performance of the algorithm. As regards the parcellation results, the group-level estimate which is shown in Fig. 1(g), fairly well matches the ground truth (Fig. 1(e)). Quantitative results yield a parcellation error of 4.25%. The confusion matrix between the estimated and the ground truth group-level parcellations is provided in Table I, which confirms the robust parcellation performance of the MS-JPDE model. Regarding the NRL and activation label estimations, a quantitative analysis leads to average mean square errors (MSE) of 0.05 and 0.01. These low values show that the good detection performance of the original JPDE model is preserved in the MS-JPDE model.

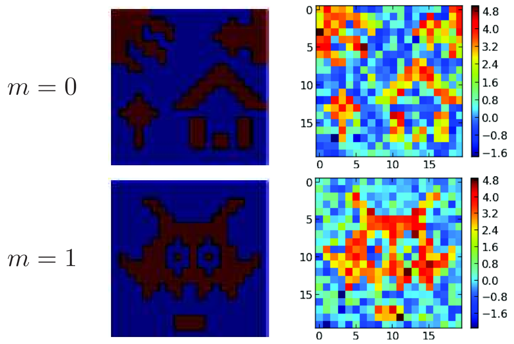


Fig. 3: Left column:Reference activation labels for the two experimental conditions; Right column: reference NRLs for the two experimental conditions.

Table I: Confusion matrix between estimated (ES) and ground truth (GT) parcellations.

ES \ GT	Parcel.1	Parcel.2	Parcel.3	Parcel.4
Parcel.1.	**0.92**	0.0	0.023	0.0
Parcel.2.	0.06	**0.99**	0.0	0.0
Parcel.3.	0.0	0.0	**0.92**	0.0
Parcel.4.	0.02	0.01	0.057	**1.0**

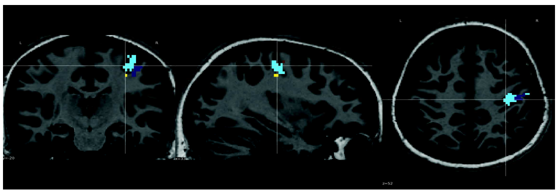
IV-B. Real data experiments

A gradient echo planar imaging sequence (echo time=30ms / repetition time=2.4s / slice thickness = 3mm / field of view = 192x192mm^2) was used to acquire the real fMRI data at 3T during a localizer experiment [11]. This paradigm involved sixty auditory, visual and motor stimuli, defined in ten experimental conditions ($M = 10$). During this paradigm, 128 scans were acquired at a $2 \times 2 \times 3$mm^3 3D spatial resolution. Ten subjects were involved in the experiment. The ROI in this paper is the right motor cortex. The mask for the parcellation was the right motor cortex given the presence of motor task with the right hand in the paradigm. The subjects were analysed simultaneously using the MS-JPDE model. The same initial parcellation was applied to all subjects with 4 parcels (see Fig. 4[top]). This initial number of parcels was chosen by calculating the free energy associated with different model orders [5]. The estimated group-level parcellation is shown in Fig. 4[bottom]. These results indicate that parcels 1, 2, 3 and 4 have 39, 114, 2 and 14 voxels respectively. The estimated group-level HRFs are shown in Fig. 5 for the 4 different estimated group-level parcels. Figs. 4[bottom] and 5 allow the results to be interpreted at the group-level. For this specific fMRI data, we can see that parcels 1 and 2 (resp. 3 and 4) have similar HRF profiles and thus could be merged into a single parcel. The times to peak (TTP) associated with these parcels are $\mathrm{TTP}_1 = 5.4$s, $\mathrm{TTP}_2 = 5.4$s, $\mathrm{TTP}_3 = 6.0$s, $\mathrm{TTP}_4 = 6.0$s, which is consistent with the previous conclusion. The MS-JPDE model performance was further investigated by comparing the estimated group-level parcellation with the single-level parcellation (estimated by the JPDE model). Using a subject selected randomly from the subjects of interest, the confusion matrix between the two parcellations is reported in Table II where a major intersection can be noticed across all the parcels.

V. CONCLUSION

This paper proposed a new approach for multi-subject fMRI analysis relying on the JPDE model. This approach performs joint group-level parcellation and HRF dynamics estimation with activation detection and voxel-dependent HRF estimation at the subject-level. In contrast with the original JPDE model, this approach provides estimated group-level parcellation and HRF profiles. Future work will investigate the application of this MS-JPDE model to large-scale fMRI data.

(a) Initial parcellation



(b) Group-level parcellation

Fig. 4: Top: initial parcellation for real data experiment; Bottom: group-level parcellation.

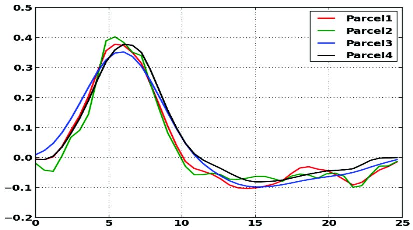


Fig. 5: Estimated HRFs for the 4 group-level parcels (real data).

Table II: Confusion matrix between estimated subject-level (SL) and group-level (GL) parcellations.

GL / SL	Parcel.1	Parcel.2	Parcel.3	Parcel.4
Parcel.1.	**0.92**	0.05	0.0	0.07
Parcel.2.	0.08	**0.7**	0.0	0.0
Parcel.3.	0.0	0.0	**1.0**	0.0
Parcel.4.	0.0	0.25	0.0	**0.93**

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