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Fuzzy approach to incorporate hemodynamic variability and contextual information for detection of brain activation

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ABSTRACT

We propose to use fuzzy c-means clustering with contextual modeling on features extracted from fMRI data for detection of brain activation. Five discriminating features are extracted from fMRI data by using a sequence of temporal-sliding-windows. Fuzzy membership maps of individual subjects obtained through clustering with spatial regularization is capable of taking into account both hemodynamic variability and contextual information of brain activation. The present method outperforms statistical parametric mapping (SPM) approach on experiments with synthetic fMRI data contaminated by both independent and correlated noise. Performance on real fMRI data are comparable to those obtained with SPM.

1. Introduction

Functional magnetic resonance imaging (fMRI) is a non-invasive imaging modality measuring functional activity of the brain *in vivo* both spatially and temporally. fMRI signal results due to the changes of blood-oxygenation-level-dependent (BOLD) contrast, caused by the increase in blood oxygenation following neuronal activity. Detection of the changes of fMRI signal is non-trivial as BOLD signal change due to an input stimuli is very subtle, ranging from 1–5% on a 1.5 T scanner [20]. Furthermore, various noise and artifacts such as motion, electronic, physical, and physiological processes, significantly confound fMRI signal. Therefore, techniques analyzing fMRI signals should be insensitive to uncertainties and randomness of interference signals.

Methods to detect activated voxels from fMRI data fall into two categories: hypothesis-driven and data-driven methods. Statistical parametric mapping (SPM) [11] is a widely used hypothesis-driven method assuming a general linear model for fMR signal with a specific noise structure. It is voxel-based and tests the hypothesis about fMR time-series response on the stimuli by construction and assessment of spatially extended statistical processes based on Gaussian random fields (GRF). However, the actual relationship between the change of fMR signal and the stimuli presentation is nonlinear [29]; and the hemodynamic response function (HRF) varies spatially and among subjects [24,33]. Moreover, the structure of noise in fMRI is not well understood and remains a contentious subject [7].

Data-driven methods do not make any assumptions on hemodynamic response and are considered more appropriate and powerful for fMRI analysis, especially when unknown or complex differential responses are expected [18]. Data-driven approaches can be broadly classified into transformation-based or clustering-based methods. Principle component analysis (PCA) [3] and independent component analysis (ICA) [2] transform original high-dimensional fMRI data into a low-dimensional space to separate brain activation and various noise sources. The ICA enables recovery of underlying task-related signals from other components such as artifacts and noise by decomposing fMRI data spatially [16] and temporally [6] in an exploratory manner or with stimulus as constraints [14,15]. Clustering techniques, such as self-organizing maps [13,19] and fuzzy clustering [5,9], attempt to classify fMR time-series of the brain into several patterns according to temporal similarity. Data-driven methods usually interpret the contents of one class or component as activations but how signals are divided into classes is difficult to ascertain or comprehend; a few classes related to activation could have physiological interpretation but interpretations of others are unknown. Other data-driven techniques for fMRI analysis include multi-resolution methods such as wavelet analysis [12].

Besides the activation measured at each brain voxel, fMRI carries contextual information as neighboring voxels often have similar characteristics and belong to the same class. Gaussian smoothing is often applied to enhance signal to noise ratio (SNR) before statistical analysis, accounting for spatial dependency

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implicitly. This leads to overly smoothed images and a loss of high frequency information. Markov random fields (MRF) [27,25,10] and conditional random fields (CRF) [30] have been attempted to incorporate spatial and temporal correlations explicitly for the detection of brain activation. MRF based on mixture models with spatial regularization has been proposed for fMRI segmentation [32]. Autoregressive spatiotemporal models has also been proposed to incorporate tissue-type related noise priors as spatial constraints in fMRI analysis [33]. The above approaches still suffer from the assumptions made on structures of HRF and noise, the validity of such models depends on the extent to which data satisfy underlying assumptions.

Fuzzy c-means clustering (FCM) has been widely used in image segmentation, which incorporates fuzziness for the belongingness of each voxel to particular class or object. Contextual modeling is handled by a contextual regularized term into the cost function of FCM: for example, smooth constraints on the bias field of intensity inhomogeneity correction [21] and a term for immediate neighborhood information for tissue segmentation of anatomical MR images [1]. Kernelized version of FCM with spatial constraints has been recently proposed to further enhance the segmentation [8].

The present work is motivated by the need for a technique that handles the individual variability of hemodynamic responses and is less vulnerable to noise. In order to achieve this, we extract fuzzy features from fMR time-series and use unsupervised FCM with contextual modeling to identify activated voxels. To adapt to HRF variability across subjects, FCM is applied to each subject separately assuming no fixed structure for signals and noise. The cost function of FCM, regularized by spatial context, is adopted to capture local and neighboring information. Extracting fuzzy features from time-series reduces computational complexity and renders the ability to handle noise. FCM with contextual modeling on novel fuzzy feature space is similar to kernelized FCM on original fMR time-series but the advantage of our approach is that the kernel is well defined by the new feature space compared to normal Gaussian or polynomial function. The details of our approach are described in the next section. In the experiment and result section, the performance of the present approach is illustrated with functional activation detected on individual and group study on synthetic as well as on real fMRI data.

2. Method

Our method consists of two steps: (1) extracting fuzzy features from raw fMR time-series by temporal-sliding-windows (TSW); (2) FCM clustering with contextual constraints on the feature space.

2.1. Extracting features

Different brain voxels have different hemodynamic characteristics, for example, the time to reach the peak intensity of an activated voxels. We move a sequence of TSW over the time-series of a voxel to derive fuzzy features discriminating activated and non-activated voxels under each experimental condition. These features are derived independent of shape, magnitude, and delay of HRF. Let $\Psi : \Omega \times \Theta \to Y$ be a functional MR image where $\Omega \subset N^3$ denotes three-dimensional spatial domain of brain voxels, $\Theta = \{1, 2, \ldots, n\}$ indexes n number of 3D scans taken during the experiment. Let $Y = \{y_{i,t} : i \in \Omega, t \in \Theta, y_{i,t} \in Q\}$ be the 4D fMRI data where Q denotes the range of image intensities and $y_{i,t}$ denotes the intensity of voxel i at time t.

Consider an experiment with only one condition, denoted by X, for notational simplicity; the technique of feature extraction is easily extended for fMR experiments involving several conditions [37]. The condition X is presented with the reference (resting) state alternatively for P times in a single run while n 3D brain scans are taken. Each block of condition X is denoted by B_p, $p = 1, 2, \ldots, P$. The block B_p lasts for a duration of length l_p from the beginning time denoted as b_p. The above notation represents a general paradigm design which applies to both block and event-related designs. A sequence of TSW for the condition X is constructed from fMR time-series as follows:

(1) Create a sequence of P number of windows denoted by $W = \{W_p : p = 1, 2, \ldots, P\}$, one window W_p for each condition block B_p. The length of window W_p is denoted by w_p, and let $w_p = l_p$. The initial starting point of window W_p is thus given by b_p.
(2) Shift the sequence of windows W temporally forward by a sliding time interval s simultaneously, resulting in a new sequence of windows denoted by $W(s) = \{W_p(s) : s = 0, 1, \ldots, S, p = 1, 2, \ldots, P\}$. Depending on different inter-scan time, the maximum sliding time interval S varies: $S = 32/RT$ (seconds) based on the fact that the total length of HRF is approximately 32 s. Thus, the starting and ending time of window $W_p(s)$ is $b_p + s$ and $b_p + s + w_p - 1$; we denote them by $T_{p,1}(s)$ and $T_{p,2}(s)$, respectively, for notational simplicity.
(3) Calculate average intensity $A_p(i, s)$ of each voxel i for each window $W_p(s)$, $s = 0, 1, \ldots, S$ as

$$A_p(i,s) = \frac{\sum_{t=T_{p,1}(s)}^{\tilde{T}_{p,2}(s)} y_{i,t}}{\tilde{T}_{p,2}(s) - T_{p,1}(s)} \tag{1}$$

where $\tilde{T}_{p,2}(s) = \min\{n, T_{p,2}(s)\}$.

Thus, we observe a curve $A_p(i) = \{A_p(i, s) : s = 0, 1, \ldots, S\}$ for each voxel i of each block B_p, whose shape is highly discriminative between activated and non-activated voxels. We refer it as *quasi-hemodynamic curve* (QHC) because it represents the HRF derived from the time-series in a data-driven manner. Five fuzzy discriminating features $F_k^p(i)$, $k = 1, 2, \ldots, 5$, are extracted from QHC for each block B_p at each voxel i as follows:

(1) Area under curve ratio for QHC:

$$F_1^p(i) = \frac{\sum_{s=0}^{\tilde{w}_p} A_p(i,s)}{(\max_s A_p(i,s) - \min_s A_p(i,s)) \cdot \tilde{w}_p} \tag{2}$$

where $\tilde{w}_p = \min\{w_p, S\}$.
(2) Area difference ratio for QHC:

$$F_2^p(i) = \frac{\sum_{s=0}^{\tilde{w}_p} A_p(i,s)}{\sum_{s=\tilde{w}_p+1}^{S} A_p(i,s)} \tag{3}$$

(3) Correlation between QHC $A_p(i)$ and the standard QHC, SA_p:

$$F_3^p(i) = \frac{\sum_{s=0}^{\tilde{w}_p} (A_p(i,s) - \overline{A_p(i,s)})(SA_p - \overline{SA_p})}{\sqrt{\sum_{s=0}^{\tilde{w}_p} (A_p(i,s) - \overline{A_p(i,s)})^2 \sum_{s=0}^{\tilde{w}_p} (SA_p - \overline{SA_p})^2}} \tag{4}$$

where $SA_p = \{SA_p(s) = -(s - \tilde{w}_p/2)^2 : s = 0, 1, \ldots, \tilde{w}_p\}$.
(4) Time ratio at peak amplitudes of QHC:

$$F_4^p(i) = \arg\max_{s \in [0, \tilde{w}_p]} A_p(i,s)/\tilde{w}_p \tag{5}$$

(5) Time ratio at lowest amplitude for QHC:

$$F_5^p(i) = \arg\min_{s \in [0, \tilde{w}_p]} A_p(i,s)/\tilde{w}_p \tag{6}$$

Two QHC were normalized to within $[0, 1]$ before correlation computation in feature 3 for easy comparison among voxels. Since the shapes of QHC of activated and non-activated voxels