An Efficient Method for Independent component – Cross correlation – Sequential epoch analysis of Functional Magnetic Resonance Imaging

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Abstract

The analysis of functional MRI (fMRI) data is one of the most promising applications of independent component analysis (ICA) [8], [15]. Some of the spatially independent maps estimated by ICA correspond to independent brain functional units [19]-[21]. However, the problem of how to extract maps of physiological interest out of a vast number of statistically independent components remains. An fMRI procedure combining sequential epoch analysis (SEA) with ICA proposed by Nakada et al. to address this has been named *independent component - cross correlation - sequential epoch analysis* (ICS) [24]. Here, we describe an efficient method that embodies the concept of ICS, based on the fixed-point ICA algorithm proposed by Hyvärinen [13].

Introduction

A common approach to analyzing functional magnetic resonance imaging (fMRI) data is to test the statistical significance of a correlation between an analytical model and the time-series of every voxel. An activation map is presented as a contrast between two specified conditions. The contrast is given by a set of weights for the basis functions constituting a specific analytical model. The activation areas are constructed by the voxels that satisfy the predetermined criteria (e.g. $p < 0.01$) for statistics yielded to a given contrast.

Statistical parametric mapping (SPM) [9], [10] is an analytical tool that utilizes this type of hypothesis-driven approach and is frequently applied to fMRI and PET research. Although this type of method is useful for various fMRI studies, the functional resolution is insufficient for some studies. The power of hypothesis-driven methods is limited mainly by the following: (1) A set of basis functions representing signal components should be determined *a priori* so that it satisfies the completeness to measured data. However, fMRI data include various signal components besides task-related signals such as physiological noise, head movements and measurement noise, and accurately assuming all of such signal components is usually impracticable. Consequently, analytical errors are inevitable. (2) Similar bases share weights, and are not separated into different physiological components in principle.

Independent component analysis (ICA) is a novel statistical technique that can solve blind source separation (BSS) problems, and it should overcome the limitation of hypothesis-driven methods described above, since it is data-driven. Several algorithms have been proposed for performing ICA[1]-[5], [7]-[8], [11]-[13], [15]-[17], [25]-[26]. In parallel, the applications can be extended to research and industrial projects such as data communication, speech recognition and medical sciences. The application of ICA to fMRI analysis was originally introduced by McKeown et al. [19]-[21]. They proposed obtaining spatially, instead of temporally, independent components by transposing the data matrix. The fMRI data extends spatiotemporally, so that each blindly separated independent map has an associated time-series that can be referred to determine whether or not a map is of interest.

Sequential epoch analysis (SEA) investigated by Nakada et al. allows for experimental designs of fMRI comparable to neurophysiological techniques in primates[23]. Our experience indicated that a set of SEA patterns could be used to test the physiological significance of statistically independent components. We call this technique *independent component - cross correlation - sequential epoch analysis* (ICS) [24].

This technique incorporates a hypothesis-driven approach (correlation with SEA patterns) into the data-driven analysis (ICA). The results of ICS showed that the physiological resolution of fMRI was considerably increased compared with SPM.

The simplest way of executing ICS is to calculate the correlation of time-series with a reference pattern for all of the independent maps estimated by ICA beforehand. This is a quite inefficient way because only one or two percent of components are significant, yet several days are often required to perform ICA for the complete data set of a single fMRI experiment even with the latest high-performance workstation.

We propose an optimized technique for performing ICS that incorporates the optimal initial parameters with the deflation approach of the fixed-point ICA algorithm proposed by Hyvärinen [13]. A proper relationship between the correlation of the time-series and distance in the parameter space of unmixing vectors assures the validity of our technique. Our procedure remarkably improves the efficiency of ICS since the physiological components can be selectively and individually calculated.

Independent Component Analysis

The discrete model of blind source separation (BSS) problems with a time-invariant linear mixture is represented as the transform

$$\mathbf{x}(n) = \mathbf{A}\mathbf{s}(n), \quad n = 1, \cdots, N \tag{1}$$

where n is the time index, $\mathbf{s}(n) = \{s_1(n), \cdots, s_K(n)\}^T$ is a set of unknown source signals, $\mathbf{x}(n) = \{x_1(n), \cdots, x_K(n)\}^T$ is a set of observations and $\mathbf{A} \in \mathbf{R}^{K \times K}$ is an unknown mixing matrix. The goal of ICA is to recover from observations both the mixing matrix and source signals without knowing their properties. The only assumption is that source signals are mutually independent. Practically, ICA seeks for an unmixing matrix $\mathbf{W}$ so that the vector

$$\mathbf{y}(n) = \mathbf{W}\mathbf{x}(n) \tag{2}$$

is an estimate of source signals $\mathbf{s}(n)$, except for a permutation, signs and amplitudes. In the learning process of ICA, the unmixing matrix (or transformation) $\mathbf{W}$ is iteratively updated to minimize dependence among the elements of $\mathbf{y}$. Most of the algorithms estimate the whole of $\mathbf{W}$ at a time. The fixed-point algorithm proposed by Hyvärinen[13] is an exception that individually extracts independent components, and thus is suitable for ICS. In the fixed-point ICA, an approximation of differential entropy is used for the measure of dependence. The contrast function to find one component is given by

$$J_G(\mathbf{w}) = \left[E\{G(\mathbf{w}^T\mathbf{x})\} - E\{G(\nu)\}\right]^2 \tag{3}$$

where $E\{\}$ denotes the expectation operator, $\mathbf{w} = (w_1, \cdots, w_K)^T$ is a weight vector under the constraint $E\{(\mathbf{w}^T\mathbf{x})^2\} = 1$, which is a certain row vector of $\mathbf{W}$, G is a non-quadratic function and ν is a normalized Gaussian variable. A single independent component, $y = \mathbf{w}^T\mathbf{x}$, would be found at a maximum of the function $J_G(\mathbf{w})$. If the data has been sphered (uncorrelated up to the second-order statistics) in advance, the maxima of $J_G(\mathbf{w})$ are obtained at optima of $E\{(\mathbf{w}^T\mathbf{x})\}$. The data can be sphered by principal component analysis (PCA), for example. The optima of $E\{(\mathbf{w}^T\mathbf{x})\}$ are solutions of the following equation:

$$\begin{aligned} &E\{\mathbf{x}G'(\mathbf{w}^T\mathbf{x})\} - \beta\mathbf{w} = 0 \\ \text{and} \quad &\beta = E\{\mathbf{w}_0^T\mathbf{x}G'(\mathbf{w}_0^T\mathbf{x})\} \end{aligned} \tag{4}$$

where G' is the derivative of G with respect to $y\,(=\mathbf{w}^T\mathbf{x})$ and $\mathbf{w}_0$ is the value of $\mathbf{w}$ at the optimum. According to [13], Newton's method can be applied to derive the following fixed-point algorithm:

$$\begin{aligned} \mathbf{w}^+ &= E\{\mathbf{x}G'(\mathbf{w}^T\mathbf{x})\} - E\{G''(\mathbf{w}^T\mathbf{x})\}\mathbf{w} \\ \mathbf{w}^* &= \mathbf{w}^+ / \|\mathbf{w}^+\| \end{aligned} \tag{5}$$

where $\mathbf{w}^*$ is the updated value of $\mathbf{w}$. Our technique uses (5) as its core.

An ICA model of fMRI data

The ICA model (1) assumes that the number of source signals (or channels) K is less than the number of samples in a time domain N. It is impossible to apply the model (1) directly to fMRI data because the size of time-series is usually much less than the number of channels, or voxels. To circumvent this problem, McKeown et al. proposed transposing the data matrix [19], [20]. Then the data model for fMRI is represented by

$$\mathbf{x}(k) = \mathbf{A}\mathbf{s}(k), \quad k = 1, \cdots, K \tag{6}$$

where k is the index of pixels, $\mathbf{s}(k) = \{s_1(k), \cdots, s_N(k)\}^T$ is a set of spatially independent images and $\mathbf{x}(k)=\{x_1(k),\cdots,x_N(k)\}^T$ is a series of acquired images. We call each element of $\mathbf{s}$ *an independent map*. Each column vector of $\mathbf{A}$ then represents a time-series of the corresponding map. Figure 1 is a pictorial expression of (6). It is the value of using ICA that the sets of a map and the associated time-series are obtained without any *a priori* information. However, some criteria for selecting significant components should be defined for each fMRI experiment.

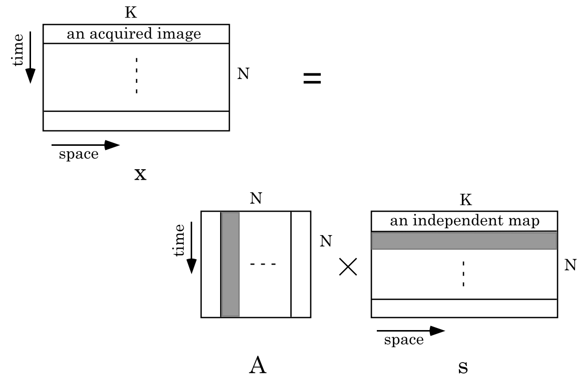

Figure 1: fMRI data model

Sequential epoch analysis

The basic idea of state-related fMRI analyses is subtraction on a specified combination of two states for data of a multiple-state experiment. We describe here the human hand motion paradigm used in [23] as an example to explain the idea in brief. Figure 2 shows the paradigm schematically. The letters *r*, *R*, *L* and *B* correspond to rest, right hand motion, left hand motion and bilateral hand motion, respectively. The duration of each segment (or epoch) is fixed to 30 seconds. The inter-scan interval is one second for each slice. The following three contrasts are considered fundamental for the paradigm: (*R* – *r*), (*L* – *r*) and (*B* – *r*).

r	r	R	L	B	r	R	L	B	r

time →

Figure 2: Sequential epoch hand motion paradigm

Sequential epoch analysis (SEA) was proposed to elucidate the specific functional area of interest by combining the statistical images of fundamental contrasts into a single SEA display [23]. This analysis has the advantage of identifying brain functions over conventional state-related analyses. The hand motion paradigm has six possible SEA patterns as shown in Fig. 3: (A) right hand M1, (B) left hand M1, (C) non-specific, (D) right hand exclusive, (E) left hand exclusive and (F) bilateral exclusive.

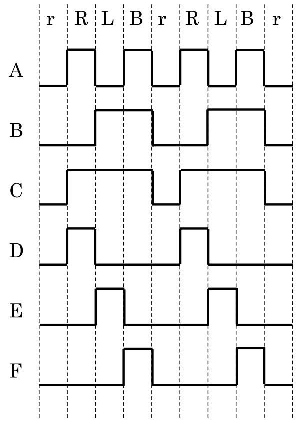

Figure 3: Possible SEA patterns

Concept of ICS

Since SEA patterns were actually observed in the raw fMRI data of our sequential epoch paradigm with an acceptable level of pixel misalignment using a high-field (3 Tesla) MRI system, Nakada et al. proposed ICS that uses an SEA pattern for the reference time-series with intent to extract activation maps out of spatially independent maps obtained by ICA [24].

The correlation of a time-series with an SEA pattern is calculated to identify the activation maps by a given threshold. The time-series vector of a map can be denoted by $\mathbf{a}=(a_1,\cdots,a_N)$ and one of the SEA patterns by $\mathbf{b}=(b_1,\cdots,b_N)$. If these vectors are normalized so that $\sum a_i=\sum b_i=0$ and $\|\mathbf{a}\|^2=\|\mathbf{b}\|^2=1$, the correlation r between these two vectors is simply represented by their inner product:

$$r=\langle\mathbf{a}|\mathbf{b}\rangle\equiv\sum_i a_i b_i\ . \tag{7}$$

Around two percent of the components were selected by the empirical condition, $r\geq 0.7$, for all the SEA patterns of our hand motion paradigm.

An efficient technique for ICS

We discuss here a direct way of extracting the activation maps. The time-series $\mathbf{a}$ of a single independent map estimated by the fixed-point ICA (5) is given by a psuedo-inverse of the corresponding unmixing vector $\mathbf{w}$. Since $\mathbf{w}$ is normalized to have unit norm $\|\mathbf{w}\|^2 = \mathbf{w}^T\mathbf{w} = 1$, $\mathbf{a}$ is equal to $\mathbf{w}^T$, and the nearest $\mathbf{w}$ to a given initial vector is obtained by (5). Thus the relationship between the correlation and the distance of two vectors should be examined first. Euclidean distance, or the squared norm of difference of two vectors, is used to measure the distance d:

$$d = \|\mathbf{a}-\mathbf{b}\|^2 \equiv \sum_i (a_i - b_i)^2 . \quad (8)$$

If the effects of sphering are not taken into account, the distance (8) is directly related to correlation r in (7) according to the following derivation:

$$\begin{aligned} d &= \sum_i (a_i - b_i)^2 \\ &= \sum_i \left(a_i^2 + b_i^2\right) - 2\sum_i a_i b_i \\ &= 2(1-r) \end{aligned} \quad (9)$$

This linear relationship laid the foundation of our optimized technique. Figure 4 plots the relationships between r and d observed for the right hand M1 pattern (denoted by A in Fig. 3) in our hand motion study as circles together with the theoretical relationship (9) shown by a solid line.

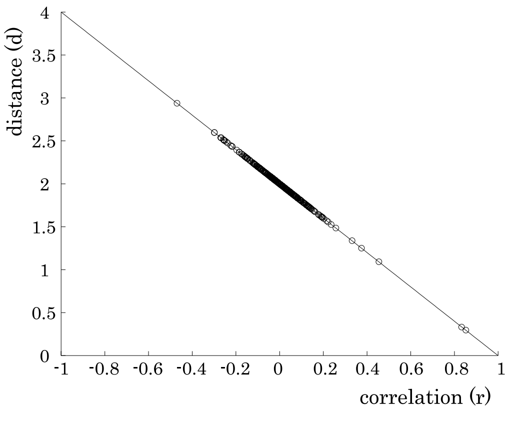

Figure 4: Correlation vs. distance relationship observed in the original ($\mathbf{w}$) space.

Sphering should now be considered. The Jacobian matrix of the left side of (4) becomes diagonal if the data are sphered [13]. Therefore, the Euclidean distance can still be a practical measure of closeness. A transfer matrix $\mathbf{B}$ for sphering is estimated by PCA as

$$\mathbf{B} = \mathbf{D}^{-1}\,\mathbf{E} \quad (10)$$

where $\mathbf{E}$ denotes the (transposed) eigenvector matrix and $\mathbf{D}$ denotes the diagonal matrix whose elements are the square root of the corresponding eigenvalues. Sphered data $\boldsymbol{\chi}$ and the unmixing vector $\boldsymbol{\omega}$ for one component in a sphered space are given by

$$\begin{aligned} \boldsymbol{\chi} &= \mathbf{B}\,\mathbf{x} \\ \text{and}\quad \boldsymbol{\omega} &= \left(\mathbf{w}^T\,\mathbf{B}^{-1}\right)^T \end{aligned} , \quad (11)$$

respectively. A time-series $\mathbf{a}$ in the original data space relates to $\boldsymbol{\omega}$ as

$$\mathbf{a} = \left(\mathbf{B}^{-1}\boldsymbol{\omega}\right)^T . \quad (12)$$

As expressed in (11), the relationship (9) is generally broken in the space of $\boldsymbol{\omega}$. Because $\mathbf{E}$ is an orthogonal matrix, distance is preserved by the transformation of $\mathbf{E}$ alone. It is $\mathbf{D}$ that disperses the relationship by multiplying imbalance weights with the elements of $\boldsymbol{\omega}$. However, components having a high correlation should still have a relatively short distance. This was validated by the actual relationships observed in the sphered data of our hand motion study shown in Fig. 5. The observations support the notion that a normalized SEA pattern can be used as an appropriate initial value of $\mathbf{w}$ for the criterion, $r \geq 0.7$.

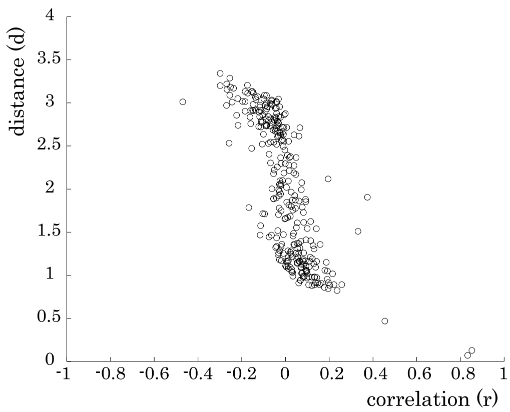

Figure 5: Correlation in the original ($\mathbf{w}$) space vs. distance in the sphered ($\boldsymbol{\omega}$) space.

The following procedure is proposed for extracting components related to a (normalized) target SEA pattern, $\mathbf{b}$.

1. Sphere the data.
2. Prepare the initial vector $\boldsymbol{\omega}_{init}$ so that
$$\boldsymbol{\omega}_{init} = \left(\mathbf{B}\mathbf{b}^T\right)^T$$
$$subject\ to\ \left\|\boldsymbol{\omega}_{init}\right\| = 1$$
3. Execute the iteration (5) with its initial value $\boldsymbol{\omega}_{init}$ to calculate the single unmixing vector $\boldsymbol{\omega}_0$.
4. Recover the raw time-series $\boldsymbol{\alpha} = (\alpha_1, \cdots, \alpha_N)$ of an estimated component by using (12) and put the normalized vector into $\mathbf{a}$.
5. Calculate the correlation r between $\mathbf{a}$ and $\mathbf{b}$ using formula (7).
6. If $r \geq 0.7$, then the component $y = \boldsymbol{\omega}_0^T \mathbf{B}\mathbf{x}$ is considered an activation map of the target SEA pattern. To search the next component, subtract its time-series $(\alpha_1 y, \cdots, \alpha_N y)^T$ from the original data $\mathbf{x}$, then repeat from step 1. If $r < 0.7$, then stop searching.

The above procedure sequentially retrieves one every desired component.

Results

An fMRI experiment was conducted to examine the validity of our method. A right-handed normal volunteer (18-year) participated in our sequential epoch hand motion study. Gradient echo echo-planar images (EPI) were obtained using a General Electric SIGNA 3.0 Tesla system equipped with an Advanced NMR EPI module. The following parameters were used for data acquisition: FOV 40×20 cm; matrix 128×64; slice thickness 5 mm; TR 1 sec. Spatial smoothing was applied by convolving with a 5 mm full width at half maximum (FWHM) Gaussian kernel to minimize the effects of pixel misalignment due to brain motion during the experimental session. The optimized ICS technique was tested for the right hand M1 pattern. The third power was selected for the non-linear transfer function G' in (4) through our experience. The first thirty images of the fMRI time-series were not used for the analysis to avoid the effects of initial decay. Figure 6 shows all of the extracted maps and the associated time-series with their correlation values. The broken line in the time-series represents the normalized SEA pattern taken for reference.

The estimated components were precisely physiological independent units. The two time-series are so similar that these cannot be separated into different physiological components by model-based approaches such as SPM. The time efficiency of performing ICS was remarkably improved by our technique. A Sun Microsystems Ultra 60 workstation required only a few minutes to extract all of the significant components.

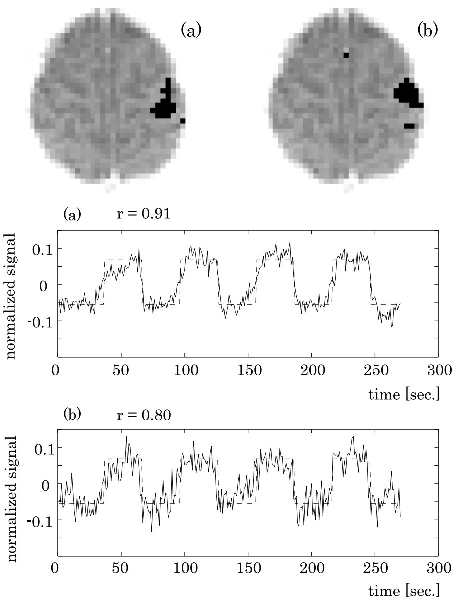

Figure 6: Activation maps and the associated time-series extracted by optimized ICS.

Concluding remarks

We proposed a validated and efficient technique for ICS that extracts singular and all significant activation maps from measured data. The direct search was achieved by incorporating appropriate initial parameters into the iteration rule of fixed-point ICA [13]. Our investigations into the relationship between correlativity in a time domain and distance in the parameter space of ICA assure the iteration process of convergence upon a desired target. The optimized technique can be utilized generally for fMRI analyses as far as a temporal reference function can be set for physiological units that have an objective task-related function. We emphasize that our technique embodies the concept of ICS itself in its algorithm.

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