Published in final edited form as:
Comput Med Imaging Graph. 2009 March ; 33(2): 131–139. doi:10.1016/j.compmedimag.2008.10.011.

Review of methods for functional brain connectivity detection using fMRI

Kaiming Li[a], **Lei Guo**[a], **Jingxin Nie**[a], **Gang Li**[a], and **Tianming Liu**[b,*]

[a] Department of Automation, Northwestern Polytechnical University, Xi'an, China

[b] Department of Computer Science and Bioimaging Research Center, the University of Georgia, Athens, GA 30602, USA

Abstract

Since the mid of 1990s, functional connectivity study using fMRI (fcMRI) has drawn increasing attention of neuroscientists and computer scientists, since it opens a new window to explore functional network of human brain with relatively high resolution. A variety of methods for fcMRI study have been proposed. This paper intends to provide a technical review on computational methodologies developed for fcMRI analysis. From our perspective, these computational methods are classified into two general categories: model-driven methods and data-driven methods. Data-driven methods are a large family, and thus are further sub-classified into decomposition-based methods and clustering analysis methods. For each type of methods, principles, main contributors, and their advantages and drawbacks are discussed. Finally, potential applications of fcMRI are overviewed.

Keywords

FMRI; Brain connectivity; Brain network

1. Introduction

The past two decades have witnessed the popularity of functional magnetic resonance imaging (fMRI) as a tool for mapping human brain functions. By measuring blood oxygen level dependent (BOLD) single changes [1–6], fMRI detects the active parts of brain. Recently, instead of identifying the isolated activated brain regions under certain conditions, increasing attention has been paid to how different parts of the brain connect, interact and coordinate with each other to perform certain kind of cognitive function [7–9].

Functional connectivity is defined as the "temporal correlations between spatially remote neurophysiological events" [10,11]. Unlike anatomical connectivity that describes the physical connections between two brain sites [12] and effective connectivity which characterizes the influence that a neural system may exert over another [10], functional connectivity examines regional interactions in the brain at a macro level, using datasets from electroencephalographic (EEG), magnetoencephalographic (MEG), local field potentials (LFP), positron emission tomography (PET) or functional MRI [14]. Compared with other imaging modalities, functional MRI provides investigators with a non-invasive yet in-vivo representation of brain

* Corresponding author. Tel.: +1 706 542 3478; fax: +1 706 542 2966. tliu@uga.edu (T. Liu).

state with high spatial resolution, and thus has drawn a lot of interest from researchers worldwide.

To stay close with the definition of functional connectivity, we here make a distinct discrimination between two types of fMRI studies. One type tries to find the spatial activation patterns of human brain. These studies are often done under a well-designed cognitive task, aiming to find the brain regions involved in this task. The other type, functional connectivity study with fMRI (fcMRI), tries to find the temporal correlations of spatially remote neurophysiological events. Unlike fMRI study, fcMRI study is often conducted under resting-state condition although there are methods using paradigm fMRI data.

From our perspective, methods used for functional connectivity analysis via fMRI are generally grouped into two types: model-based methods and data-driven methods. Model-based methods such as cross-correlation analysis (CCA) are based on prior knowledge. Since they are easy to implement and interpret, model-based methods are wildly used. Data-driven methods (either based on clustering or decomposition), however, need no prior knowledge. Thus, it is quite useful for resting-state fMRI studies where no prior information about the spatial or temporal pattern is known.

Although interesting research findings about functional connectivity detection with fMRI have been extensively reported in the literature, as far as we know, there are few dedicated reviews on methods for functional connectivity investigation with fMRI. Therefore, this paper aims to provide such a review. We will focus on the methods for detecting functional connectivity with fMRI, while review on methods for study of anatomical connectivity and effective connectivity is beyond the scope of this paper.

This paper is divided into four sections as follows: the first section opens with an introduction of fcMRI study and classification of the study methods. The second section explains these methods in detail, including their principles, main contributors, as well as their advantages and drawbacks. Discussion of problems for fcMRI study is provided in the third section. Finally, the fourth section concludes the paper, and points out the significance of fcMRI study meanwhile.

2. Methods for fcMRI study

After extensive study for more than a decade, scientists have come up with several methods for functional connectivity detection using fMRI. Generally, these methods can be classified into two categories (see Fig. 1): model-based methods and data-driven methods. Each category has its own merits and limitations, which will be our discussion focus in the following.

2.1. Model-based methods

Until now, many functional connectivity explorations are model-based. That is, these studies select some regions of interest (ROIs) as so-called “seeds”, and determine whether other regions are connected to these seeds by defining certain metrics, and thereby generate the connectivity map of human brain. These methods are typically based on strong prior neuroscience knowledge or experience.

According to the metrics used as connectivity measurement, these methods could be classified as follows.

2.2. Cross-correlation analysis

Cross-correlation analysis is a mature technique that has been widely used in many fields. Cao and Worsley introduced this technique into fcMRI study in Ref. [15]. Intrinsically, if one part

of brain is functionally connected to a certain seed, there should be correlation in terms of their BOLD time courses. For a fMRI BOLD time course $F_x(k)$and a seed $F_x(k)$ (which is also a time course), CCA estimates the correlation at lag μ as:

$$\mathrm{Corr}_{x,y}(\mu)=\frac{\mathrm{Cov}_{x,y}(\mu)}{\sqrt{\mathrm{Var}(x)\times\mathrm{Var}(y)}} \quad (1)$$

where $Var(x)$and $Var(y)$are the variances of $F_x(k)$and $F_y(k)$, respectively; $Cov_{x,y}(u)$is the cross variance of $F_x(k)$and $F_y(k)$ at lag μ:

$$\mathrm{Cov}_{x,y}(\mu)=E\left\{((F_x(k)-E(F_x))\times\left((F_y(k)-E(F_y)\right)\right\} \quad (2)$$

and E means the expected value, and $E(F_x)$ and $E(F_y)$ are the expectation or the mean of $F_x(k)$and $F_y(k)$, respectively. If $Cov_{x,y}(\mu)$ is above a certain threshold, we consider that the two BOLD time courses $F_x(k)$ and $F_y(k)$ are functionally connected.

The complete calculation of cross-correlation at all lags would be computationally expensive [16–17]. Fortunately, the hemodynamic response of blood makes full-lag-space calculation of cross-correlation unnecessary. Although the hemodynamic response function (HRF) varies across different subjects or even across different brain regions of the same subject, the duration of HRF is limited. That is, it will return to baseline after limited time which is a few dozen seconds in general [3,18–19]. Thus, people generally need to compute the correlation with a time window of a dozen time points or so (the exact number depends on the TR of fMRI scan). In fact, many cross-correlation studies compute only the correlation with zero lag.

2.3. Coherence analysis

Although CCA has been extensively used for fMRI data analysis on both paradigm-based and resting-state dataset, using correlation at zero lag as the connectivity measurement has been controversial [64]. On one hand, correlation is sensitive to the shape of HRF, which has been reported to vary cross different subjects and different brain regions [20–24]. On the other hand, high correlation can be detected between regions that actually have no blood flow fluctuations. Contaminations from noises such as cardiac activity and blood vessel activity in the brain would also lead to illusion of high correlation [25].

To overcome these problems, a new metric called coherence is proposed by Sun *et al*. [30]. Coherence is the spectral representation of correlation in frequency domain. For the same time courses $F_x(k)$ and $F_y(k)$ defined in Eq. (1), the coherence is expressed as:

$$\mathrm{Coh}_{x,y}(\lambda)=\frac{|F_{x,y}(\lambda)|^2}{F_{x,x}(\lambda)F_{y,y}(\lambda)} \quad (3)$$

where $F_{x,y}(\lambda)$ is the cross spectrum, defined by the Fourier transform of the cross covariance as follows:

$$F_{x,y}(\lambda)=\sum_u Cov_{x,y}(u)\times e^{-j\lambda u} \quad (4)$$

and $F_{x,x}(\lambda)$ is the power spectrum, so is $F_{y,y}(\lambda)$. They are defined as:

$$F_{x,x}(\lambda)=\sum_u Cov_{x,x}(u) \times e^{-j\lambda u} \quad (5)$$

$$F_{y,y}(\lambda)=\sum_u Cov_{y,y}(u) \times e^{-j\lambda u} \quad (6)$$

The expression of correlation in frequency domain enables researchers to study time course relationship in a natural and intrinsic way. For example, blood flow fluctuations usually have a period of 10 s or so. Thus, the coherence at low frequency below 0.1 Hz is particularly related to functional connectivity; while cardiac activity usually works at a frequency of around 1.25 Hz, thus, coherence at this frequency band may arise from the cardiac activity instead of really functional connectivity.

2.4. Statistical parametric mapping

Statistical parametric mapping (SPM) is a model-based method used to find the activation patterns induced by cognitive tasks in fMRI. Over the years, SPM has come to refer to the conjoint use of the general linear model (GLM) and Gaussian random field (GRF) theory to make classical inferences about spatially extended data through statistical parametric maps. SPM uses GLM to estimate the parameters that could explain the data and uses GRF to resolve the multiple comparison problems in making statistically powerful inferences.

Although generally considered as a method for paradigm fMRI study, SPM methodology recently has been used for functional connectivity detection with resting-state fMRI dataset by Greicius et al. [31]. After scaling and filtering steps across all brain voxels, this method averages the voxels in certain seed, and considers it as a covariate of interest in the first-level SPM analysis. Then contrast images corresponding to this regressor were determined individually for each subject and entered into a second-level random effect analysis, in order to determine the brain areas that show significant functional connectivity across subjects.

The essence of this method is to mimic a stimulus based on the selected seed, and uses it in the same way as the real stimulus in cognitive tasks is, since there is no designed cognitive activity in resting-state fMRI study. The modeling and statistical reference are the same with those in SPM. For more detailed SPM theory, please refer to [25].

Model-based methods, especially CCA, are widely used in the detection of functional connectivity [26–29], however, some concerns exist. Firstly, seeds-based methodology renders the detected functional connectivity sensitive to seed selection [32]. It is common that different seeds would lead to detection of different connectivity. Secondly, the requirement for prior knowledge constrains the exploration of possible functional connectivity. With priors-based method, one may only focus on brain regions related to the prior knowledge, and neglect other parts or functions of brain. Therefore, the full exploration of brain goes beyond the capability of this type of methods, and might need data-driven methods such as decomposition analysis and clustering analysis.

2.5. Data-driven methods

To overcome the limitations of model-based methods, analysis methods that are independent of prior information or assumed model have been developed. There are generally two types of data-driven methods for functional connectivity detection. The first type is based on decomposition techniques such as principal component analysis (PCA), singular value decomposition (SVD) and independent component analysis (ICA). This type tries to express

the original fMRI dataset as a linear combination of basis vectors (PCA/SVD) or statistically independent components (ICA). The second type is based on clustering analysis such as fuzzy clustering analysis (FCA) or hierarchical clustering analysis (HCA). This type tries to apply traditional clustering techniques to fMRI dataset. Both types of methods are explorative, and thus help to explore the functional connectivity of human brain as a whole.

2.6. Decomposition-based methods

2.6.1. Principal component analysis and singular value decomposition—

Principal component analysis and singular value decomposition are widely used techniques for data analysis. Since they are closely related theoretically, we consider them as one type here.

The core of PCA/SVD is to represent the observed fMRI time courses X with a combination of orthogonal contributors (see Fig. 2). Each contributor is made of a temporal pattern (a principal component) multiplied with a spacial pattern (an eigen map). Mathematically, the SVD of X (T time points × N voxels) is:

$$X=\mathrm{USV}^T=\sum_{i=1}^{p} S_i U_i V_i^T \tag{7}$$

where the S_i is the singular value of X; U_i is the ith principal component; and V_i is the corresponding eigen map; p is the number of chosen components. Usually, people will discard the vectors with small contribution to the data variance, and obtain much refined signal data which meanwhile preserves most of the signal energy.

The generated eigen maps reveal the connectivity of different brain regions: regions with high absolute values (either positive or negative) are considered correlated.

Introduced into functional connectivity analysis by Friston et al. on PET data [10], PCA/SVD has been applied to fMRI dataset in several studies [33–35]. Despite the good performance on detection of extensive regions of correlated voxels, PCA/SVD seems to encounter some difficulties that constrain its use in functional connectivity study. For example, Baumgartner et al. [33] found PCA/SVD fails to identify activations at lower contrast-to-noise ratios (CNR) when other sources of signal variation (e.g. physiological noise) are present. Besides, there is no agreement on how many components are appropriate. In addition, PCA/SVD only diminishes second-order dependency between each component. Therefore, PCA/SVD is often used as a preprocessing step for dimensionality reduction for further analysis such as independent component analysis.

2.6.1.1. Independent component analysis: Independent component analysis is a recently developed popular method for functional connectivity detection using fMRI. Since it needs no prior information about the spatial or temporal patterns of source signals, ICA is well suited for resting-state fMRI study. Therefore, there is increasing interest in applying ICA algorithm to resting-state fMRI study for functional connectivity detection.

Like PCA/SVD, ICA seeks to find a linear combination of components. The difference is that ICA would find components that are as statistically independent as possible [36], while PCA/SVD would find orthogonal components (see Fig. 3). For fMRI data X (T time points × N voxels), the ICA model can be expressed as:

$$X=\mathrm{AC}=\sum_{i=1}^{N}A_iC_i \tag{8}$$

where C_i is the ith underlying signal source (IC component); A is the mixing matrix with a dimension of $T \times N$. Different sources are independent from each other:

$$P(C_1, C_2, \cdots, C_N)=\prod_{i=1}^{N}P(C_i) \tag{9}$$

Here, $P(C_i)$ is the probability of the ith underlying signal source. Denoting W as the pseudo reverse of A (W also called unmixing matrix), we can obtain the independent components (ICs) simply by:

$$C=\mathrm{WX} \tag{10}$$

As for the solution of ICA, there are two commonly used algorithms: the Infomax [37] and the Fixed-Point [38], both of which are through the minimization of mutual information of components C_i Informax achieved this goal by adaptively maximizing the output entropy of a neural network with as many outputs as the number of ICs to be estimated; whereas Fixed-Point used the concept of negentropy [39]. Esposito et al. compared the effect of these two algorithms on ICA result, and found that both algorithms can generate highly accurate results. However, each of them has its own advantages: Fixed-Point outperforms the Infomax in terms of spatial and temporal accuracy whereas Infomax is better in global model estimation and noise reduction [40].

Very similar to PCA/SVD, ICA decomposes the original time sources into independent component components that are statically independent and corresponding IC maps that measure the correlation. By thresholding these IC maps, one would obtain the connectivity maps with corresponding underlying sources (see Fig. 4).

According to whether to decompose the data into spatially independent components and spatially independent time course (sICA), or temporarily independent components and temporarily independent time course (tICA), ICA could be divided into spatial ICA (sICA) and temporal ICA (tICA). Then the question is which type one should choose for functional connectivity detection.

Since the introduction of ICA into fMRI study [44], both sICA and tICA have been widely used. However, the criterion for which one to use seems to be task dependent. Researchers reported that sICA and tICA can have diverging results, depending upon the characteristics of the underlying signals to be estimated [43]. If the underlying signals are spatial correlated but not temporarily, one may want to choose tICA instead of sICA since sICA would probably not yield the correct activation pattern if the null spatial correlation is strongly violated, and vice versa for tICA.

Despite the increasing popularity of applying ICA algorithm to fcMRI study, especially on resting-state fMRI data, there are some pitfalls that need mentioning.

Firstly, ICA is grounded on the assumption of components (signal sources) independence, whether spatially or temporally. Violation of this assumption would decrease the effectiveness of ICA considerably [43].

Secondly, how to choose the number of independent components and how to threshold the IC maps have become open questions. Ma et al. studied these questions and concluded that when the number of ICs is smaller than that of the source signals, ICA results become highly dependent on the number [32]. Actually, thresholding IC maps directly is difficult. In practice, it is common to convert an independent map with a non-Gaussian distribution into a z-map with a Gaussian distribution [44,45]. Ma et al.'s results show that the z-map conversion tends to overestimate the false-positive rate (FPR) [32]. This overestimation, however, is not very severe and may be acceptable in many cases.

Last but not least, ICA is a noise-free generative model. The observed fMRI datasets are completely explained by the source signals contained in matrix C and the mixing matrix *A*, and thus precludes the assessment of statistical significance of the source estimates within the framework of null-hypotheses. To solve this problem, Beckmann et al. recently developed a new model called probabilistic ICA or pICA, which assumes that the observed *p*-dimensional time series are generated from a set of q ($q < p$) statistically independent non-Gaussian sources (spatial maps) via a linear and instantaneous 'mixing' process corrupted by additive Gaussian noise $\eta(t)$:

$$X_i = AS_i + \mu + \eta_i \tag{11}$$

Here X_i refers to the *p*-dimensional column vector of individual measurements at voxel location i; A is mixing matrix; S_i denotes the q-dimensional column vector of non-Gaussian source signals contained in the data; μ is constant part; and η_i denotes Gaussian noise $\eta_i \sim N(0,\sigma^2 \Sigma_i)$. For more information about pICA, please refer to [46].

2.6.2. Clustering analysis—Clustering analysis methods have been wildly used in fMRI study to find the activity patterns. These methods include fuzzy clustering analysis, vector quantization, self-organizing maps, and neural gas network [47–52]. The primary goal of clustering analysis in fMRI study is to partition the data into different clusters based on the intensity proximity of the time course. Time courses that are close enough are considered to be in one cluster.

However, clustering analysis based on intensity proximity is not enough for functional connectivity detection in fcMRI study (see Fig. 5). Instead of characterizing the distance by intensity proximity, clustering methods in fcMRI study often use the similarity between time courses as the distance measurement [53].

2.6.2.1. Fuzzy clustering analysis: Fuzzy c-means (FCA) is a clustering analysis method which allows fuzzy partition of the dataset. The main idea behind it is the minimization of an objective function, which is usually defined as the total distance between all patterns and their cluster centers:

$$J(M,C) = \sum_{i=1}^{i=N} \sum_{j=1}^{j=K} M_{ij}^{\varphi} D_{ij}^{2} \tag{12}$$

Here, M_{ij} is a metric which measures the probability of voxel i belongs to cluster j; D_{ij} is the distance between voxel i and the centroid C_j of cluster j; N is the number of voxels of brain;

K is the number of initial clusters; φ is a weighting component. The objective function is subject to:

$$\sum_{j=1}^{j=K} M_{ij}=1, i=1,2,\cdots,N; \tag{13}$$

$$\sum_{i=1}^{i=N} M_{ij}=1, j=1,2,\cdots,K; M_{ij}\in[0,1]; \tag{14}$$

Bezdek provided a solution for the membership matrix M and cluster centroids C [54]:

$$M_{ij}=\frac{D_i^{\frac{2}{\varphi-1}}}{\sum_{l=K}^{l} D_{il}^{\frac{2}{\varphi-1}}}, \quad \begin{cases} i=1,2,\cdots,N; \\ j=1,2,\cdots,K; \end{cases} \tag{15}$$

$$C_j=\frac{\sum_{i=1}^{i=N} M_{ij}^{\varphi} X_i}{\sum_{i=1}^{i-N} M_{ij}^{\varphi}}, \quad j=1,2,\ldots,K; \tag{16}$$

where X_i is a vector that contains the coordinates of cluster centroid i. With an iterative procedure, we could obtain the membership matrix M and centroids.

For fcMRI study, Golay et al. [53] proposed two distance metrics $D_{cc}{}^1$ and $D_{cc}{}^2$ based on Pearson's correlation coefficient $CC_{x,y}$ between two time courses $F_x(k)$ and $F_y(k)$:

$$D_{cc}{}^1=\left(\frac{1-CC_{x,y}}{1+CC_{x,y}}\right)^{\beta} \tag{17}$$

$$D_{cc}{}^2=2(1-CC_{x,y}) \tag{18}$$

where $CC_{x,y}$ is the cross-correlation of $F_x(k)$ and $F_y(k)$ at lag zero. These distances characterize the degree of correlation between two fMRI time courses. Brain regions whose distance is under a certain threshold are considered functionally connected.

Golay et al. compared three distance metrics: Euclidean distance, $D_{cc}{}^1$ and $D_{cc}{}^2$, and found that fuzzy clustering analysis based on time course similarity generates effective connectivity results, while results using distance metric $D_{cc}{}^1$ outperforms the other two.

A potential question for FCA might be how many clusters should be chosen. It has been reported that different number of clusters significantly affects the connectivity results, especially when the number of underlying function networks are more than that of initially selected clusters [55]. Golay et al. recommended using a large number of clusters initially, which may help to

obtain a clear yet complete description of the clusters without redundancy or acquisition of insignificant cluster centers. However, cluster selection problem is intrinsic for FCA and might not be completely solved within the framework of FCA.

Besides the cluster initialization issue in FCA, the distance metrics proposed by Golay et al. might be contaminated by structured noises such as human heart beat and respiration. These noises contribute to the distance metrics $D_{cc}{}^{1}$ and $D_{cc}{}^{2}$ at a relative high frequency domain (around 1 Hz), while the distance contributors we are interested are low frequency oscillations (<0.1 Hz) that represent synchrony in cerebral blood flow and oxygenation between different brain regions.

To alleviate the above problems, Cordes et al. [56] introduced a hierarchical clustering analysis method using a new distance measurement based on frequency analysis.

2.6.2.2. Hierarchical clustering analysis: Different from FCA which uses an empirically chosen number of initial clusters, hierarchical clustering analysis considers each voxel as one cluster at the beginning, and merges the close clusters based on certain distance measurement. Closeness could be measured by different ways, which distinguishes single-linkage from complete-linkage and average-linkage clustering. For HCA details please refer to [57].

Cordes et al. adopted a single-linkage HCA algorithm, and defined a new distance by combining correlation analysis and frequency decomposition. The Pearson's correlation coefficient $CC_{x,y}$ between two time courses $F_x(k)$ and $F_y(k)$ can be decomposed as

$$CC(x,y) = \frac{N\Sigma_f \mathrm{Re}(\omega_f)\mathrm{Re}(\varphi_f) + \mathrm{Im}(\omega_f)\mathrm{Im}(\varphi_f)}{S} = \Sigma_f \frac{N(\mathrm{Re}(\omega_f)\mathrm{Re}(\varphi_f) + \mathrm{Im}(\omega_f)\mathrm{Im}(\varphi_f))}{S} = \Sigma_f CC_f(x,y) \tag{19}$$

where ω_f and φ_f are complex frequency component of $F_x(k)$and $F_y(k)$, respectively; Re(*) and Im(*) refer to the real and imaginary component of signal *; S is defined as

$$S = \sqrt{\sum_{k=0}^{N-1} F_x{}^2(k) \sum_{k=0}^{N-1} F_y{}^2(k)} \tag{20}$$

Cordes et al. defined the distance $D(x,y)$ between $F_x(k)$ and $F_y(k)$ as [56]:

$$D(x,y) = 1 - \sum_{f=0}^{0.1\,\mathrm{HZ}} CC_f(x,y) \tag{21}$$

Intuitively, this distance applies a low-pass filter to Pearson's correlation coefficient and then builds a reverse increase function to map the output into distance. This filtering process extracts from correlation coefficient the information that reflects synchrony in cerebral blood flow and oxygenation between different brain regions.

Experiments based on both simulated data and human brain data show that structured contaminations such as respiratory or cardiac noises are generally well removed [56].

Hierarchical clustering analysis is often computationally expensive, and is thought to be more severe when applied to 3D human brain data. For whole human brain connectivity analysis

using this method, improvements in the theoretical methods and more careful studies are needed [56].

3. Discussions

3.1. Studies on macroscopic level

Although fMRI can provide human brain data from cortical areas with a comparatively high spatial resolution, and is considered a direct way for investigating how different brain regions interact [58], fcMRI studies still stay at a macroscopic level on regional cerebral blood flow since the resolution is far from enough to directly represent dynamic neuronal activity at the microscopic level. This resolution limitation inevitably results in significant consequences [59], which can be summarized as follows: (1) each voxel in fMRI images contains multiple neuronal populations, thus BOLD signal is an integration of a variety of neuronal activities; (2) the temporal resolution (often a few seconds) of fMRI makes the transient component of neuron activity (a few milliseconds) undetectable; (3) increases in both excitatory and inhibitory synaptic activity can lead to increased metabolic activity [60]. The above limitations motivate scientists to pursue higher-resolution functional magnetic resonance imaging techniques on one hand, and on the other hand remind researchers to be cautious while interpreting the results from fcMRI studies.

3.2. Model-based methods or data-driven methods

Whether to choose model-based or data-driven methods has been in long time discussion. A number of researches have done comparison [35,61]. Generally, no one outperforms the other in an all around way. The preference to model-based methods or data-driven methods is scenario dependent and study dependent. One has no reason to give up one's precious experience and knowledge, and pick up data-driven methods when both kinds of methods would do; at the same time, using CCA instead of ICA to detect extensive regions of correlated voxels seems unreasonable.

3.3. Resting-state data or task-induced data

Currently, many studies on fcMRI are based on resting-state fMRI data. That is, no external cognitive tasks are performed while the subjects are being scanned. Such a requirement for fMRI datasets is incompatible with those paradigm-based fMRI datasets.

To tackle this problem, Arfanakis et al. [62] proposed a method that combines ICA and CCA to detect connectivity using task-induced fMRI datasets. The core of this method relies on the evaluation of task-induced effect on BOLD signal using ICA. With this effect removed, the left fMRI data could be considered as resting-sate. Beside of using task activated data residuals, one can also uses interleaved resting-state epoch data, as proposed by Fair et al. in Ref. [63]. This method takes "interleaved" resting blocks from blocked or mixed blocked/event-related sets and considers these data as taken under resting state. Others select as seeds the regions that are not influenced by the cognitive task, and use CCA to detect functional connectivity [7]. This method seems to be well justified since even scanned under resting state, subjects still have complex brain activities. Real resting state may not even exist. Experiments have provided that these procedures may be useful for fcMRI study [63]. However, as Fair et al. suggests, results should be interpreted with care.

3.4. Functional connectivity vs. effective connectivity

FcMRI analysis aims to find temporal correlations between spatially remote neurophysiological events [3,4]. The results show the synchronization, e.g. co-activation or contra-activation of brain regions, which gives people an image of coordination of different

brain regions to perform a certain cognitive task. However, this image does not show how this coordination comes into operation, or rather, how one brain region exerts effects on other parts of human brain. The causality on coordination is usually called effective connectivity [10].

Graphically speaking, functional connectivity study gives results as an un-weighted and undirected graph, whereas effective connectivity study yields a directed graph. Apparently, effective connectivity study would help people explore the brain mechanism behind, and thus is a hot issue though it is challenging at the same time. Details on effective connectivity are referred to [13].

4. Conclusion

In this paper, we reviewed the state-of-the-art methods that were developed to detect functional connectivity using functional MRI. In the discussion of each method, its advantages and possible pitfalls are also discussed.

According to whether or not seeds are used, these methods are categorized into two classes: model-based methods and data-driven methods. Model-based methods mainly include cross-correlation analysis, coherence analysis (CA), and statistical parameter mapping. Although prior knowledge and experience are needed, this kind of methods is widely used in fcMRI study because it is conventionally simple and has a direct and precise research goal.

Different from seeds-based methods, data-driven methods need no seeds selection, and are ready to detect extensive connectivity network. This kind of methods can be divided into two sub categories: data decomposition and clustering analysis. Data decomposition-based methods such as PCA/SVD and ICA try to represent the original data using several components which have certain statistical features (for PCA, orthogonal and make up most of the signal power; for ICA, statistically as independent as possible). Clustering-based methods (FCA or HCA) try to classify similar brain regions into one cluster. The distance definition is a key issue for this type of methods. Distances used in clustering methods introduced previously mainly result from Pearson's correlation coefficient. Therefore, they stay close to the definition of functional connectivity. At last, the selection of data and methods for fcMRI study, as well as interpretation of study results, are discussed.

FcMRI studies have generated abundant achievements in both basic neuroscience research and clinical applications [7–9]. With the help from complex network theory and graph theory, and combined with other imaging modalities such as EEG and diffusion weighted MRI, fcMRI studies may have more significant findings and more clinical applications in brain disorders such as Alzheimer's disease and Schizophrenia.

Acknowledgement

K Li, L Guo, J Nie and G Li were supported by NWPU Foundation for Fundamental Research. T Liu was supported in part by the U.S. National Institutes of Health under Grant NIH NIBIB K01 career award K01 EB 006878.

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Biographies

Kaiming Li Mr. Li is a PhD student at the Department of Automation, Northwestern Polytechnic University, Xi'an, China. He is working on algorithm development for human brain mapping.

Jingxin Nie Mr. Nie is a PhD student at the Department of Automation, Northwestern Polytechnic University, Xi'an, China. He is working on human brain mapping, cortical surface reconstruction and mapping, deformable surface model, hybrid volume and surface registration, and statistical inference.

Gang Li Mr. Li is a PhD student at the Department of Automation, Northwestern Polytechnic University, Xi'an, China. His research interests include deformable registration and warping, neuroimaging, and human brain mapping.

Lei Guo Dr. Guo is a Professor at the Department of Automation, Northwestern Polytechnic University, Xi'an, China. He has been working in the area of computer vision, neural networks, machine learning, and pattern recognition for over 20 years.

Tianming Liu Dr. Tianming Liu is an Assistant Professor of Department of Computer Science and Bioimaging Research Center in the University of Georgia. His research interests include biomedical image analysis, computational neuroscience, and biomedical informatics. Before he moved to UGA, Dr. Liu was a faculty member in Weill Medical College of Cornell

University (2007–2008) and Harvard Medical School (2005–2007). Dr. Liu was trained as a postdoc in neuroimaging in the University of Pennsylvania (2002–2004) and Harvard Medical School (2004–2005). Dr. Liu received his PhD in computer science from Shanghai Jiaotong University in 2002. Dr. Liu is the recipient of the Microsoft Fellowship Award (2000–2002) and the NIH NIBIB K01 Career Award (2007–2011).

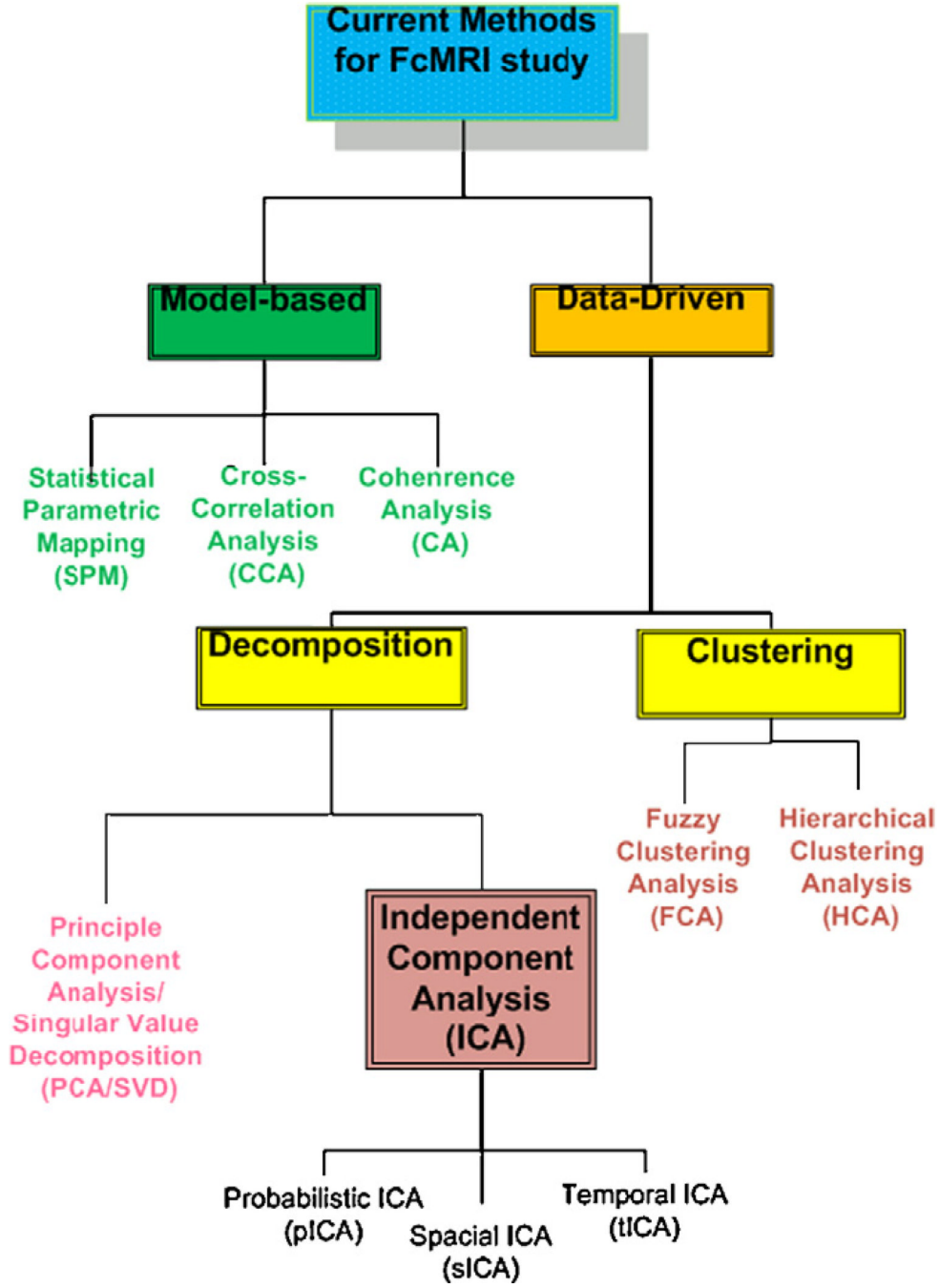

Fig. 1.
Current methods developed for FcMRI Study.

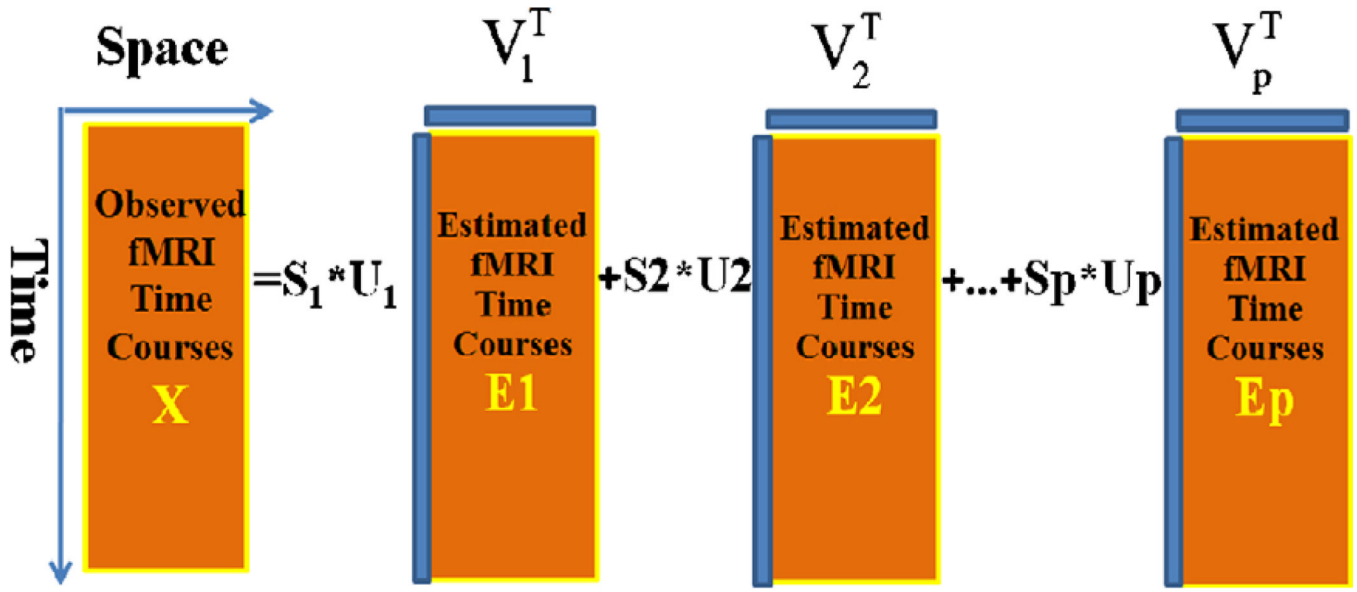

Fig. 2.

Illustration for decomposition of a fMRI dataset X using SVD. S_i is the singular value of X; U_i is the ith principal component; and V_i is the corresponding eigen map; p is the number of chosen components.

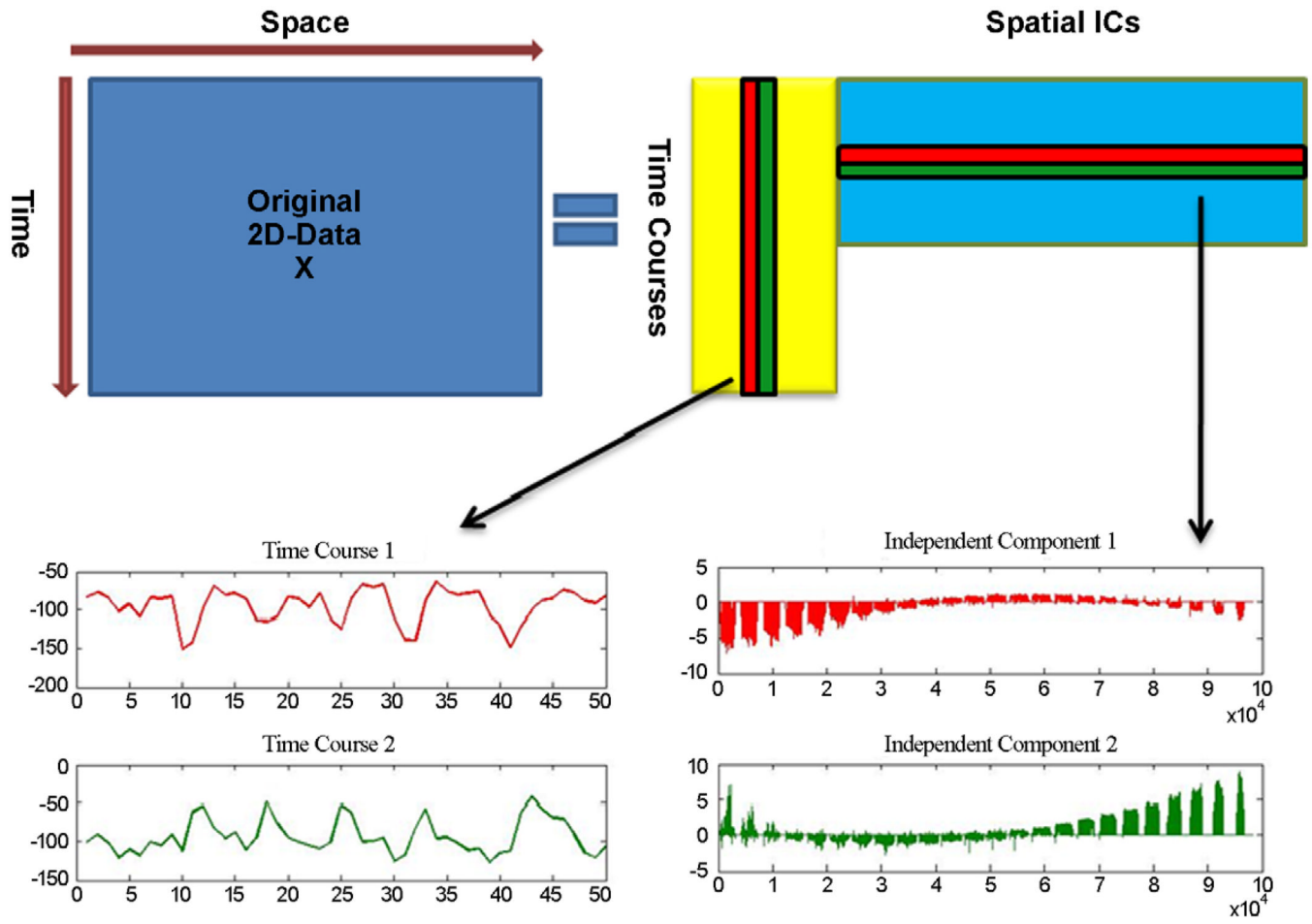

Fig. 3.
This figure illustrates the decomposition of a fMRI dataset using a certain type of ICA (spatial ICA to be exact. See the following several paragraphs for more information about sICA). Here, the independent components are spatially independent.

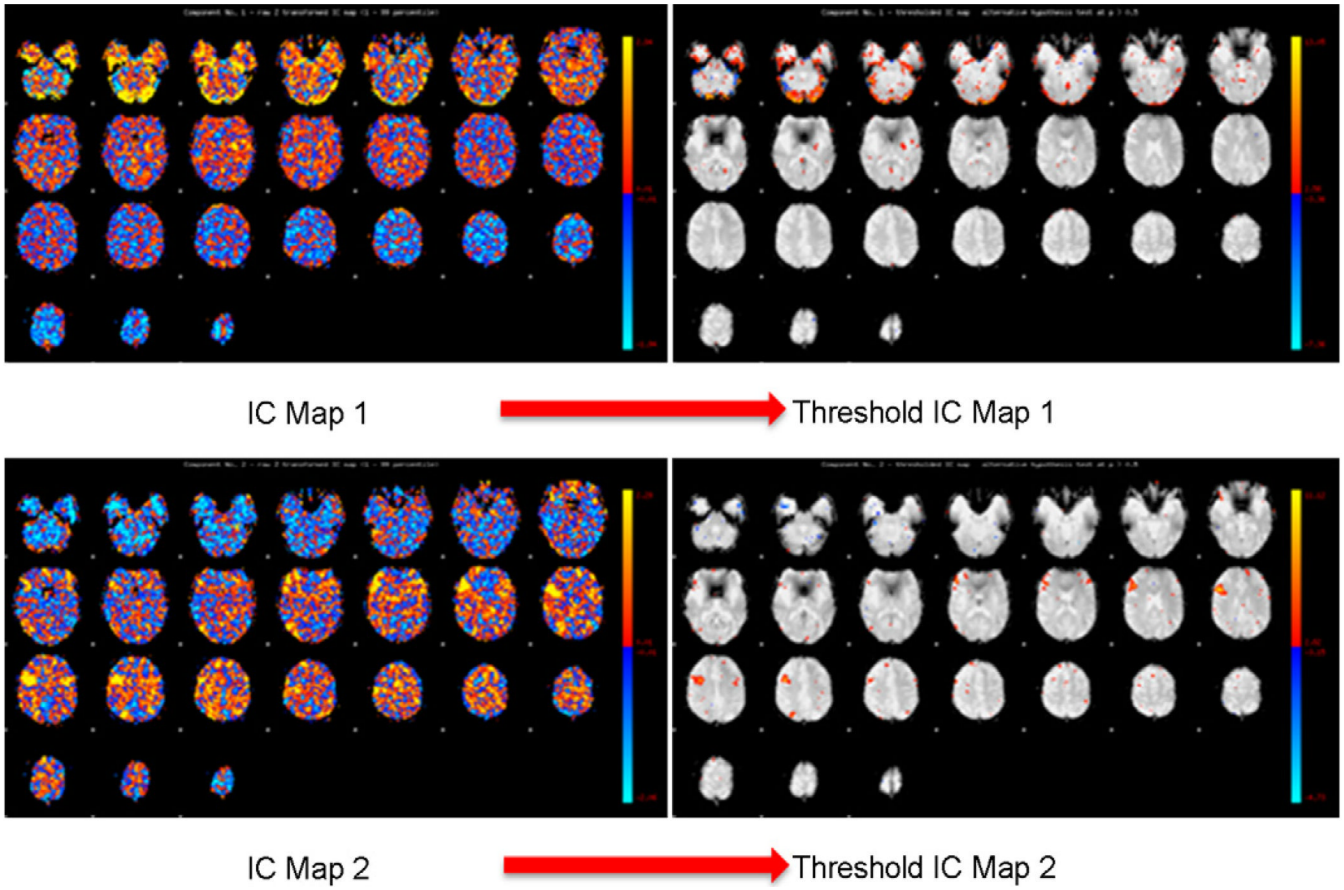

Fig. 4.
Illustration for independent component (IC) maps thresholding. IC map1 and IC map2 are 3D representation of IC 1 and IC 2 in Fig. 3.

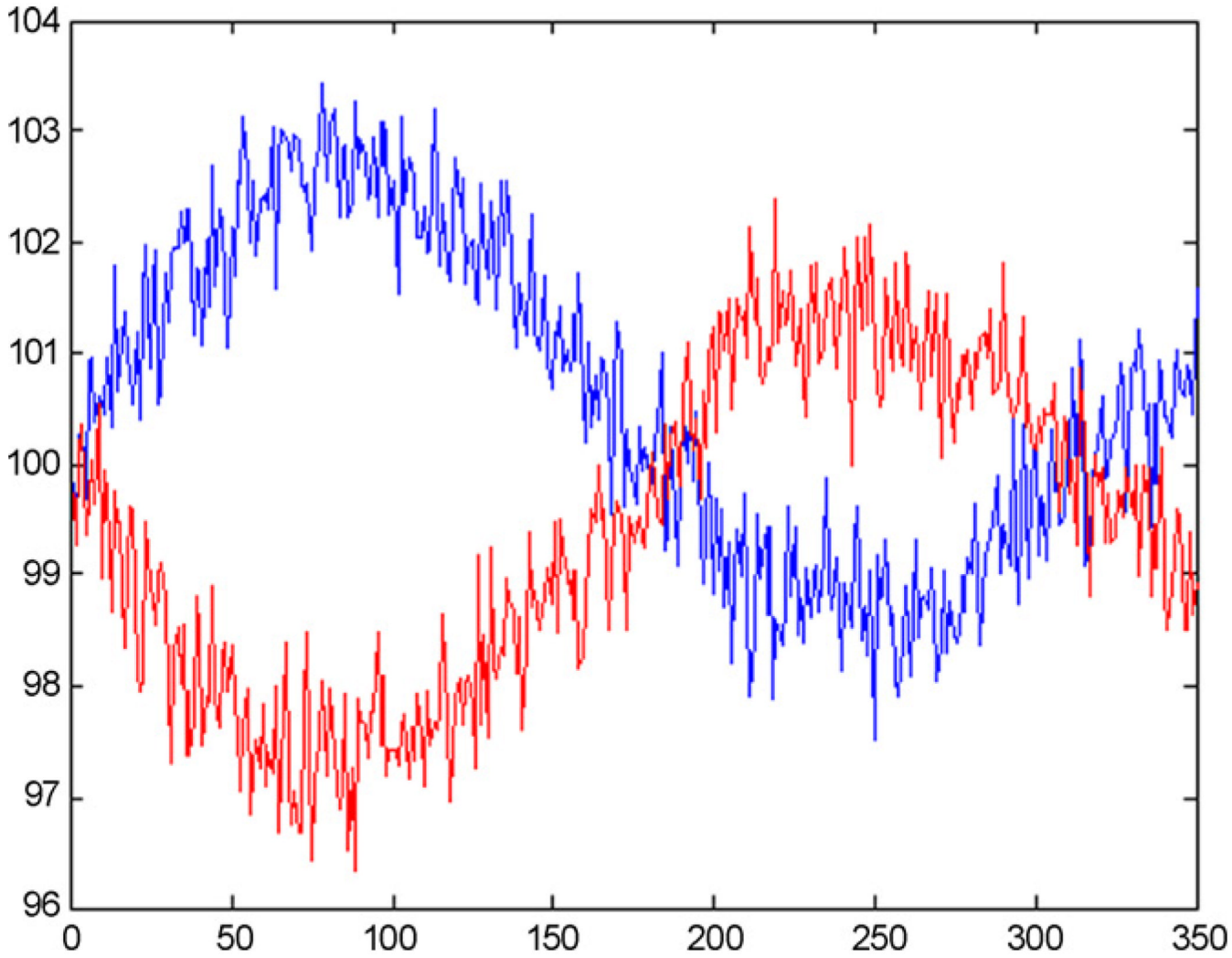

Fig. 5.
Two illustrative signals that are highly correlated (the correlation coefficient is −0.8824). However, the intensity distance is considerable.