Time frequency analysis of functional MR images

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TIME FREQUENCY ANALYSIS OF FUNCTIONAL MR IMAGES

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Abstract

Functional Magnetic Resonance Imaging (fMRI) technique is used to evaluate and visualize human brain activity in a non-invasive manner. It measures blood-oxygenation-level-dependent (BOLD) changes induced by neural activity resulted in due to external stimuli. FMRI experiments result in time-series of BOLD signals from brain voxels, collected over stimulated and rest conditions. Artifacts related to subject's head movement and physiological processes confound the signal and low signal-to-noise ratio (SNR) of fMRI make its analysis difficult. Temporal autocorrelation of fMRI time-series and the contextual dependencies on brain activation also requires proper handling.

The motivation of this thesis is to propose frequency and time-frequency domain techniques to properly handle temporal autocorrelation, to enhance the detection of activated brain voxels and resting state brain networks. This thesis makes three major contributions and introduces: (i) a mixed spectrum analysis (MSA) method to remove the temporal autocorrelation effect in voxel time-series, in a model-free manner, while detecting activated voxels. It can also detect resting-state networks and physiological signals in fMRI data; (ii) two frequency domain methods, using higher harmonics of stimulus frequency, to enhance activation detection in event-related data. One of these selectively includes higher harmonics in analysis and the other is additionally extended in scale-space domain, and (iii) a time-frequency domain method to detect default-mode network in resting state fMRI data.

Chapter 1 gives an introduction to the thesis, motivation for this work, briefly describes the previous work and provides a summary of our major contributions. In Chap-

ter 2, we aim to remove the temporal autocorrelation effect from voxel time-series, in a model-free manner, while calculating the statistical significance of activation. A fixed model for temporal autocorrelation is restrictive because temporal autocorrelation structure is known to vary across brain regions. We propose a novel MSA method based on Priestley's $P(\omega)$ test that removes the temporal autocorrelation effect in voxel's time-series by determining its spectrum from appropriately truncated autocovariance series. Spatial correlation of activations is incorporated using a conditional random field (CRF). Subsequently, we apply Priestley's principle in detecting default-mode network in resting state fMRI data. This new perspective uses temporal autocorrelation values instead of the normally used low-frequency amplitude and seed-region time-series. Exploring further, we test the proposed method to detect other frequencies of interest in fMRI data, such as physiological process related frequency components. This method is easy to use as compared to the present methods that tend to be exploratory and cumbersome requiring good knowledge of anatomical brain regions. Additionally, we apply the random field principle to efficiently regularize the AR(1) parameters in model-based prewhitening methods. It can easily be extended beyond AR(1) model.

In Chapter 3, we intend to improve activation detection in periodic event-related data. We propose two ways of using higher harmonics of stimulus signal to achieve this. The first presented method, based on χ^2 random field, uses the fundamental frequency and its first higher harmonic. The second method, based on Hartley's F -test, evaluates the improvement in statistical significance values before including higher harmonics along with the fundamental frequency. We also extend the scale-space method based on χ^2 random field, to include higher harmonics, for providing important information on spatial extent of activation.

In Chapter 4, we aim to improve default mode network detection in resting state fMRI data. We propose a novel method based on Cohen's class of distribution for time-frequency analysis of the data's low-frequency components. It is thus able to use the

variation in the amplitude of various low-frequency components along the time and also the mutual information contained in these low-frequency components to its advantage. The proposed method is also less tedious than the other commonly used seed-based time-series analysis method, as it does not require pre-identification of brain seed regions. We also present in this chapter the results of using earlier mentioned Priestley's principle in detecting resting state networks.

The presented methods are extensively tested on both synthetic and real fMRI data and the results are also compared with the standard methods in each application.

Publications

- (i) A. Kumar and J.C. Rajapakse, Power spectral based detection of brain activation, Neural Computing and Applications (2007) 16: 551-557.
- (ii) A. Kumar and J.C. Rajapakse, Time-frequency method based activation detection in functional MRI time-series, Lecture Notes in Bioinformatics (2007) 4774: 368-377.
- (iii) A. Kumar and Lin Feng, Efficient Regularization of Temporal Autocorrelation Estimates in fMRI Data, In IFBME Proceedings of ICBME conference (2013) 43: 88-91.
- (iv) A. Kumar and J.C. Rajapakse, Scale-space analysis of event-related fMRI data using higher harmonics, In IEEE Conference Publications, Defense Science Research Conference and Expo (DSR), 2011, Singapore.
- (v) A. Kumar and J.C. Rajapakse, Activation detection in fMRI using Priestley's test, BIRC Student Symposium on Bioinformatics 2011, Singapore.
- (vi) A. Kumar and J.C. Rajapakse, Power spectral density based activation detection in functional MRI time-series, ICONIP 2006 conference, Hong Kong. (Paper was among five papers shortlisted for best paper award)
- (vii) A. Kumar, Y. Wang and J.C. Rajapakse, Hidden Markov model based analysis of single trial functional MRI data, IFMBE proceedings of ICBME conference 2005, Singapore, Vol. 12, ISSN 1727-1983.

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List of Abbreviation

AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
ALFF	Amplitude of Low-frequency Fluctuations
ANN	Artificial Neural Network
AR	Auto-regressive
ARMA	Autoregressive Moving Average
AUC	Area Under the Curve
BOLD	Blood Oxygen Level Dependent
BSS	Blind Source Separation
CCA	Clustered Component Analysis
CHH	χ^2 Random Field using Higher Harmonics
CRF	Conditional Random Field
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DSD	Delay Subspace Decomposition
dof	Degree of Freedom
EC	Euler Characteristic
EEG	Electroencephalogram
EPI	Echo-planar Imaging
fALFF	Fractional Amplitude of Low-frequency Fluctuations
FCA	Fuzzy Cluster Analysis
FLASH	Fast Low Angle Shot
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
FPF	False Positives Fractions
FWHM	Full Width at Half Maximum
GLM	General Linear Model
GM	Gray Matter
GRF	Gaussian Random Field
HRF	Hemodynamic Response Function
HSH	Hartley's F -test for Significant Harmonics
ICA	Independent Component Analysis
KL	Kullback-Leibler
MA	Moving-average
MAP	Maximum a Posteriori
MEG	Magnetoencephalogram
MFG	Middle Frontal Gyrus
MPFC	Medial Prefrontal Cortex

MRI	Magnetic Resonance Imaging
MRF	Markov Random Field
MS	Multiple Sclerosis
MSA	Multi-Spectrum Analysis
PACF	Partial Autocorrelation Function
PCA	Principal Component Analysis
PCC	Posterior Cingulate Cortex
pCS	Precentral Sulcus
PCu	Precuneus
PET	Positron Emission Tomography
PGLS	Pseudo-Generalized Least Squares
PRESTO	Principles of Echo-Shifting with a Train of Observation
psd	Power Spectral Density
REML	Restricted Maximum Likelihood
ROC	Receiver Operating Characteristic
ROI	Region of Interest
SBA	Seed-based Correlation Analysis
SCH	Scale-space χ^2 Random Field using Higher Harmonics
SEM	Structural Equation Modeling
sICA	Spatial Independent Component Analysis
SNR	Signal-to-Noise Ratio
SOM	Self-organizing Map
SPM	Statistical Parametric Mapping
STFT	Short-Time Fourier Transform
SVD	Singular Value Decomposition
TE	Echo Time
TR	Repetition Time
UFCA	Unsupervised Fuzzy Cluster Analysis
WM	White Matter

List of Notation

a	Activation label of a voxel
$\mathcal{F}$	Spatiotemporal fMRI data
h	Hemodynamic response function (time-domain)
h_k	Autoregressive model coefficients
H	Hemodynamic response function (frequency-domain)
i	Voxel number
J	Cumulative statistical value in Priestley's test
$\kappa_0 \dots \kappa_6$	Constants in hemodynamic response function
n	Number of cycles of stimulus ($=T/T_c$)
N	Number of voxels in each image
$\mathcal{N}$	Neighborhood voxels
ω_p	p th harmonic of stimulus frequency, $p = 1 \dots q$
$\omega_{\mathcal{P}}$	Highest harmonic of stimulus frequency
Ω	3D spatial domain of brain voxels
$p()$	probability value
$\wp()$	probability value
$P(\omega)$	Priestley's test value at frequency ω
Φ	Standard normal distribution
Q	Range of image intensities
q	Variable (Priestley's test)
$R(\tau)$	Autocovariance function
$\mathcal{R}$	Energy in a particular frequency component
$\mathbf{r}$	Radius
ρ	Autocorrelation function
ϱ	Euler characteristic intensity
s	FWHM (smoothing)
$s(t)$	Stimulus signal (time-domain)
$\mathcal{S}(\omega)$	Stimulus signal (frequency-domain)
S	Windowed estimates of spectrum
σ_i^2	Temporal variance of voxel time-series
σ_s^2	Spatial variance of image
$\mathcal{T}$	Scanning times
$\mathfrak{T}$	t-test value
T	Number of brain scans in a voxel time-series
T_s	Number of time-points in truncated autocorrelation function of voxel time-series
T_c	Number of brain scans in one cycle
T_p	Number of brain scans corresponding to activation duration in one cycle

t	Time
τ	Time lag
V_d	Search region of dimension d
V_i	Single voxel potential at voxel i
V_{ij}	Potential of voxel interaction between voxels i and j
W	Time Window function
x_i	Response due to input stimuli at voxel i (time-domain)
X_i	Response due to input stimuli at voxel i (frequency-domain)
y_i	Functional MRI time-series at voxel i
z_i	Temporal correlation component at voxel i

Chapter 1

Introduction

Human brain is one of the most complex organs anatomically and more so in its functionality. It is based on complementary principles of functional integration and functional specialization. Functional specialization means that a cortical area has a specialization for some aspects of neural functioning, and anatomically this specialization is distributed within the cortex. Hence the cortical structure associated with a single function generally consists of a number of specialized areas united by functional integration among them. A number of imaging modalities have been used to understand the functionality of the brain.

Until the 1990's nuclear medicine imaging particularly positron emission tomography (PET) was the main choice for imaging the functional part of the brain. This technique utilizes radiotracers that produce positron-electron pairs. The main disadvantage of PET is that it is invasive as it requires radioactive injections. Other problem is poor temporal resolution of PET images because of its slow image acquisition [53]. Computed tomography (CT) scanning is another technique that creates the brain image based on the differential absorption of x-rays. Images made using x-ray depend on the absorption characteristics of the tissue it passes through. Air, which has very low x-ray attenuation coefficient, appears black in the image; Bone, because of its high attenuation coefficient appears white and soft tissue appears somewhere in between. Radiation dosages are generally high in case of CT scan, hence they are not recommended for children and

pregnant women [1, 98]. For patients with implants (e.g., intracranial aneurysm clip) who are not allowed to enter the MR (Magnetic Resonance) room, CT scan is the best imaging alternative [98]. Other techniques include scalp recording of electrical field potentials i.e. electroencephalogram (EEG) and magnetoencephalogram (MEG). These techniques record and analyze electrical and magnetic fields generated by the nerve cells respectively. They provide good temporal resolution but the spatial resolution is not high enough and the signal is marred by ocular artifacts such as eye movements and blinks as well as muscular artifacts such as biting [53].

Magnetic resonance imaging (MRI) technique that gives vivid picture of the anatomy of brain has revolutionized the way we investigate the brain. Since 1992, this technique has been enhanced to capture images that can be processed to map changes in brain hemodynamics and hence detect neural activation [53]. This technique is known as functional magnetic resonance imaging (fMRI). The concept of MRI was discovered quite early in 1940's but it is only in past two decades that it has emerged to be an important diagnostic tool in a number of medical areas such as neurology. MRI's capability to observe brain function non-invasively has provided us with new opportunities in understanding the brain organization and also for assessing neurological status [37]. In comparison to PET, it does not require injections of any radioactive isotopes, scan time is remarkably shorter, resolution in terms of voxel size is comparatively much higher, and it is capable of obtaining images in any plane through the body. In comparison to CT scan, MRI provides better contrast between different soft tissues [98].

fMRI data generally consists of a series of images corresponding to a number of cycles of task related stimulation. The fMRI experiments can be block-based or event-related. In the block-based experiments, the stimulus condition is present for nearly half of the stimulus cycle while in event-related designs the stimulus condition exists for a much shorter period, mostly represented by a single stimulus. Other than the task related fMRI experiments, resting state fMRI experiments in which the subjects are not

required to perform any task are also useful. This data can be processed to detect the resting state brain networks which undergo specific changes in the case of certain brain ailments. fMRI data is generally affected by a number of noise sources and artifacts. Advanced statistical analysis methods are thus employed to analyze the fMRI data and also to detect activated brain voxels corresponding to the task.

In this thesis, we introduce a few novel frequency and time-frequency domain techniques for the analysis of fMRI data. Our first proposed mixed spectrum analysis technique, based on Priestley's $P(\omega)$ test, is able to handle the temporal autocorrelation present in voxel time-series, during the statistical analysis of fMRI data, in a very elegant and model-free method [82–84]. We apply this technique and its principle to detect activated voxels in task-related data, to detect default-mode network in resting state data and also to detect physiological process related frequency components in fMRI data. In its activation detection application, conditional random field (CRF) has been used for modeling the spatial correlation of activation. An additional application of random field analysis concept in efficient regularization of model-based prewhitening parameters has also been discussed. We also present frequency domain and scale-space domain techniques that use the spectral energy present in higher harmonics of stimulus frequency, to enhance activation detection in the case of event-related data. And finally we propose a time-frequency domain technique for network analysis in resting-state fMRI data.

1.1 Motivation and Objectives

The task related response in fMRI data is small in magnitude and its exact form is not known. This hemodynamic response is variable across brain regions, across subjects and during repeated trials on the same subject [2]. Analysis of fMRI data is confounded by many factors. Noise from the MRI equipment and subject's physiological artifacts related to cardiac signal and respiration are some of the undesired signals that affect the fMRI signal. Other important factors that need to be taken into account during fMRI data

analysis include the temporal autocorrelation of voxel time-series and spatial correlation of the likelihood of activated voxels. The temporal autocorrelation structure is known to vary across brain regions but the present methods assume a fixed model for temporal autocorrelation, resulting in them being restrictive in detecting activated voxels in the task-related fMRI data.

In the case of periodic event-related fMRI data, spectral energy gets distributed to higher harmonics of stimulus frequency. Since most of the prevalent frequency domain methods, use only the energy in fundamental frequency of the stimulus signal in their analysis and does not use the energy present in higher harmonics, they tend to lose some accuracy in activation detection.

In the case of resting state data, most of the prevalent methods of default state network analysis use the total sum of the amplitudes of low frequency components. These methods do not take into account the variation in the amplitude of various frequency components along the time and they also discard the information regarding mutual relationship of these low frequency components, thus losing some accuracy in detection of default state networks.

Specific problems that we are set to resolve in this thesis, are listed below in some detail, including the reasons as to why the present methods fail to be fully satisfactory.

- (i) Temporal autocorrelation present in voxel time-series is one of the major confounding problems in fMRI time-series analysis, with a number of methods proposed earlier. Most of these methods use a specific model for temporal autocorrelation. Temporal autocorrelation in voxel time-series has been modeled earlier with different types of models e.g. autoregressive (AR) models such as AR(1) model, AR(1) model with additional white noise component, AR(p) model and autoregressive moving average (ARMA) model in time-domain [16, 62, 64, 85, 112, 115] and $1/f$ noise model in frequency domain [120]. In a recent study on resting state fMRI

datasets, simpler models, such as AR(1) model, have been found to be inadequate in modeling the temporal autocorrelation structure present in voxel time-series [31]. Failure to accurately model the temporal autocorrelation results in erroneous statistical analysis results. In addition, the temporal autocorrelation in voxel time-series is likely to vary across the brain regions [26, 67], resulting in a fixed model based method to be restrictive. We are thus motivated to explore activation detection methods that do not depend on specific model for temporal autocorrelation. Our objective is thus to propose such a method and test it against the presently prevalent methods of activation detection.

We also explore to see if our proposed method has an additional advantage of being model-free in terms of hemodynamic response function (HRF). Most of the present methods rely on modeling of HRF with fixed parameters [37, 39, 95]. Experiments in which relatively long periods of neural activity are evoked, i.e., block-based designs, failure to correctly model the hemodynamic response will likely result in only small decrements in sensitivity. In comparison, for event-related designs failure to correctly model HRF may result in loss of statistical power.

- (ii) In the case of periodic event-related experiments, energy of brain activation gets distributed substantially to the higher harmonics of the stimulus frequency. This energy can thus be used to enhance the activation detection. In the present frequency domain methods this energy in higher harmonics is discarded and only the energy in fundamental frequency is used for activation detection [16, 111, 117]. At the same time, as the harmonics get high, they are more likely to be affected by the noise and they are also attenuated by the brain's hemodynamic response, which acts as a low-pass filter. Thus selecting and using appropriate number of harmonics in activation detection is a challenge.

We are thus motivated to extend the frequency domain methods to include the energy in higher harmonics in their analysis of event-related data. Our objective is to show that careful inclusion of energy in higher harmonics does result in a better activation detection. We also intend to explore a scale-space method to use the energy in higher harmonics for activation detection. Scale-space methods have an additional advantage that they are also able to provide information about the spatial extent of activation [111, 117].

- (iii) Other than task-related fMRI experiments in which the aim is to detect task related brain regions, resting state experiments are also conducted for the analysis and detection of resting state brain networks, mainly the default mode network. A number of studies have found changes in the default mode network in the cases of patients suffering from Alzheimer's disease (AD) [56], multiple sclerosis (MS) [13], epilepsy [121] and attention deficit hyperactivity disorder (ADHD) [35, 119] as compared to the normal brain. The default mode network can thus be used as a marker of pathological changes in the brain. Most of the present methods used for detecting these networks are based on the selection of a seed brain region to start with [12], and hence are highly dependent on the accuracy of the seed region chosen. Some methods based on the sum of the amplitudes of frequency components in a certain frequency range (0.01Hz-0.1Hz) have also been suggested [119, 124, 125], but these methods ignore the variation in the amplitude of various low-frequency components along the time and also the mutual information contained in these low-frequency components.

We are thus motivated to explore if the use of mutual information among the various low-frequency components can result in a better detection of default state networks. Our objective is thus to propose a method that is able to use this mutual information in detection of default state network and compare its results with the standard method.

- (iv) Physiological noise related to the cardiac and respiratory functions is distributed throughout the brain, including the gray matter where the task related activation is mainly concentrated [53]. Presence of physiological noise related artifacts in the fMRI data can affect the statistical analysis results. Hence it is good to remove the effect of these physiological signals, when the statistical analysis of data is performed.

In the cases where physiological signals have been measured using extra sensors along with the acquisition of fMRI data [49, 53], methods such as image based correction method RETROICOR [45] or digital filters [10] are used to remove the effect of physiological signals from fMRI data. These techniques still require careful synchronization of fMRI data with externally measured physiological signals for the effective removal of physiological signal related artifacts from fMRI data and they also require a specialized pulse sequence.

When physiological signals are not measured, these signals need to be detected from fMRI data before their effect can be removed from fMRI data. In the cases where fMRI data has been captured at a very high sampling rate, i.e., at a short enough repetition rate ($TR < 0.5s$) to capture the unaliased physiological signals, these signals are identified from the frequency spectrum, using the knowledge of frequency range of these artifacts. When k -space fMRI data is available, physiological signals are removed in the k -space data itself [38, 52]. The k -space data is a spatial frequency domain data and is the raw data as captured by MRI equipment [52, 53]. Other methods include analyzing the signal in particular cortical areas such as ventricles [80] and reorganization of the time samples from CSF of various brain slices to get unaliased physiological signals [106]. All these techniques are effective but short repetition time ($TR < 0.5s$) fMRI data acquisition methods are generally applicable for only single brain slice imaging rather than the whole brain

[38, 118] and k -space data is generally not readily available in clinical applications.

When whole brain datasets have repetition times of $TR \sim 2s$, physiological signal related artifacts are aliased to the lower frequencies, hence are difficult to detect based on their known frequency ranges.

We are thus motivated to explore methods that can detect physiological signals from fMRI data with $TR \sim 2s$ and when the physiological signals are not captured along with the fMRI data. The effect of these signals can then be removed from the fMRI data during its statistical analysis. Our objective is thus to propose a method for physiological signal detection and compare the results with other standard methods.

1.2 Previous Work

In this section, we discuss about the currently applied methods in three categories of applications in fMRI. In the first of these categories, we include present methods of activation detection. In the second category, we present current methods of analysis of resting state data for detection of default mode networks. In the last category, we present current methods of detecting physiological signals from fMRI data and also of synchronization of these signals.

1.2.1 Activation Detection Techniques

The earliest techniques in detecting activation in fMRI time series were based on simple correlation between the response signal and the stimulus signal convolved with HRF in time-domain. The t -test has been used to detect the difference in mean between two conditions. Subsequently regression equation related methods based on general linear model (GLM) were introduced and are still one of the most popular methods of activation detection today. Frequency domain techniques have also been applied to fMRI data for activation detection. All these techniques belong to the category of hypothesis driven

techniques also known as model based techniques. The results of these techniques are generally enhanced by the application of random field analysis methods that incorporate contextual information of activation. Other than the spatial contextual information, these methods also need to consider the temporal autocorrelation present in voxel time-series and take it into account while calculating the statistical significance of activation.

The other main category of data analysis is based on data-driven exploration. Examples of exploratory analysis methods are Principal Component Analysis (PCA), clustering analysis, artificial neural networks, self-organising maps and Independent Component Analysis (ICA), which have been recently used successfully for the analysis of fMRI data. Scale-space domain methods such as wavelet analysis have also been used for fMRI analysis.

Presented below is the brief description of these methods.

Correlation Coefficient based Methods

In the earlier attempts of application of correlation in fMRI data analysis, Bandettini et al. in the year 1993 presented a method that involved thresholding according to the correlation of data with respect to the reference waveform followed by a formation of cross-correlation image [4]. For a given fMRI time series at voxel i , $y_i = (y_i(t))_{t=1}^T$, and stimulus $(s(t))_{t=1}^T$, with T time points, the cross-correlation is calculated as described below.

$$Corr(y, s) = \sum_{t=1}^T y_i(t) \times s(t) \quad (1.1)$$

Their method was an improvement on then prevalent method of creating activation pattern by subtraction of magnitude images obtained during resting state from the magnitude images of same brain area obtained during activation. Instead of using the reference stimulus signal, some of the techniques use the predicted hemodynamic response for correlation. A positive cross-correlation value indicates that the experimental data varies

in same manner as predicted response, negative values indicate that the experimental data varies in opposite manner as compared to the predicted response and zero values indicate that the experimental data is unrelated to the predicted response. The significance of correlation can be evaluated using statistical tables based on the degrees of freedom. The power of correlation analysis is based on having the maximum variability in signal of interest as compared to the noise in experiment. Gembris et al. presented an algorithm based on correlation analysis for real time mapping of brain activity during the on-going scan [44]. They used correlation coefficients between measured fMRI time-series data and a reference vector, in conjunction with detrending and a sliding window. For increased sensitivity in activation detection a fast and robust optimization of the reference vector was also proposed by them. Correlation based techniques are still being used with enhancements and Baudewig et al. suggested the use of correlation coefficients in plotting the statistical parametric maps [5]. They have demonstrated the disadvantage of thresholding with fixed correlation coefficients and have instead introduced thresholds as p -values which are defined with respect to the physiologic noise distribution of the individual maps. Another issue that they have addressed in their work is the improvement in sensitivity without essential loss of specificity. For detecting spatial extent of activation they have suggested addition of immediate neighborhood pixels provided their correlation coefficients comply with a second lower p -value threshold. Correlation has also been used with the signal averaging. In this case the various epochs are averaged before the correlation is calculated. In the case of low-frequency noise such as scanner drift this may be beneficial as such noise can reduce the correlation coefficient value quite significantly.

t -test

In the case of simple block based experiments with two conditions t -test can be used to

differentiate between the mean values of response with respect to their shared standard deviation [53]:

$$\mathfrak{T} = \frac{\bar{y}_{on} - \bar{y}_{off}}{sd} \quad (1.2)$$

where $\bar{y}_{on}$ and $\bar{y}_{off}$ represents the mean value of the signal during the two different conditions of the experiment in block-based design, with n_{on} and n_{off} being the respective number of samples and sd their joint standard deviation [53]. The resulting t -statistic can then be converted to a probability value, based on the degrees of freedom, to select the activated voxels.

As in the case of correlation, one of the main challenges in this test is to decide on the data points that belong to the either condition. The choice is made difficult as a result of delay in the hemodynamic response as compared to the stimulus function. Hence the data points for either condition may be selected based on a given HRF. Some variations in the selection of data points may include rejection of ambiguous points that appear during the change of stimulus condition. The drawback of t -test is its inability in providing the information about the timing of activity. The t -test can be used in any experiment involving evaluation of difference in mean values of response to two conditions, regardless of the experimental design. The only drawback is that this test is insensitive to the differences in variance of response to experimental test conditions. The test uses joint variance and ignores the individual variances.

General Linear Model

In time domain the regression equation method based on GLM is one of most popular methods. Friston et al. have expounded this technique in their book and papers [37, 39, 40]. The technique is commonly known as SPM (Statistical parametric mapping). In this method, the response variable $y_i = (y_i(t))_{t=1}^T$ is generally written in terms of stimulus signal $(s(t))_{t=1}^T$ and other model factors in the design matrix X .

$$y = \beta X + \epsilon \tag{1.3}$$

where β represents the unknown parameters corresponding to the stimulus signal and other model factors and ϵ represents the error terms. The GLM then selects the most suitable values for the variables β , for each voxel. A t -statistic or F -statistic is then used to test for the linear combination of certain effects (contrasts). F -statistic analysis can similarly be carried out in SPM, for the multiple contrast vectors written in the form of a contrast matrix. The t -statistic and F -statistic activation maps are thresholded using methods that account for the multiple comparisons problem. GLM analysis is conceptually quite similar to the correlation analysis, in that the significance is based on fitness of experimental data to the predicted hemodynamic response. If only one model factor, corresponding to expected hemodynamic response, is used in the design matrix then the GLM analysis is identical to the correlation analysis. The t -test can also be conducted with the GLM by having two levels in the model factor corresponding to two different experimental conditions. The basic assumption behind the use of GLM in fMRI data is that the raw data can be modeled as a sum of separate factors, each of which may vary independently across voxels.

A great amount of success in GLM depends on the valid design matrix, as created by the user. The design matrix contains one or more model factors that might have contributed towards the resultant fMRI response. Block-related design matrix has a model factor which indicates alternating periods of low and high activity convolved with the chosen HRF. Event-related design matrix has a factor for short duration hemodynamic response. Particularly in SPM package the event-related model factor in design matrix is mentioned as stimulus with zero duration [95]. In addition to the expected model factors, the design matrix may also contain factors associated with known non-experimental sources of variability. These are known as nuisance or confounding factors, e.g., linear

drift factor in the MR scanner. These nuisance factors are included to reduce the amount of residual variation included in the error term. Since the number of nuisance factors affects the degrees of freedom, their number is kept small. Inclusion of nuisance factors makes the statistical test more conservative but at the same time it improves the validity of the GLM. Care needs to be taken in excluding the factors that are correlated, as they can complicate the interpretation of results.

The GLM is one of the most widely used tools for fMRI data analysis, but its validity rests on a series of assumptions. Proper and only necessary factors needs to be included in the design matrix. The most important factor is the stimulus related factor, which is the predicted BOLD time course based upon hypothesized neuronal activity. Mostly an HRF with fixed parameters is used in these models. Since there is variation in the hemodynamic response across the subjects and from brain region to region, an HRF with fixed parameters is restrictive. Temporal and dispersion derivatives of the stimulus signal convolved with the HRF are used to reduce the effect of this drawback. Other drawback of GLM is that it assumes the amount of noise in a voxel to be same both during the presence and the absence of the task. Some research papers have indicated towards increase of noise during the BOLD activity as compared to the rest state. Yet another thing to be considered in GLM analysis is the assumption of a fixed model for temporal autocorrelation. Unless until included properly as the nuisance factors, scanner drift, thermal variation, head motion etc. can cause the MR signal to change dramatically across time points and hence influence the residual error. Residual error (ϵ) is the minimum error term left after solving the GLM Eq. (1.3). In conclusion the appropriate choice of design matrix factors is the most critical part in the GLM analysis, which if chosen inappropriately may lead to incorrect analysis.

Penny and Friston suggested a method based on mixtures of GLM, i.e., MGLM method with SPM as a special case of their proposed method [79]. The principle of their method is based on fundamental quantities of interest such as the location, shape, and

temporal signature of clusters of voxels showing task-related activity. Each cluster of activation is represented by a single time series which they propose may be useful in analyzing the effective connectivity that studies the interactions among different brain regions.

Frequency Domain Methods

The frequency domain approach to activation detection has also been used by a number of researchers [61, 69, 77, 120]. In the case of periodic block-based and event-related data, the periodic nature of the voxel time-series can also be quantified in the frequency domain. In the frequency domain, generally only the information pertaining to the stimulus frequency is sufficient. In comparison, in the time-domain accurate knowledge of time-instances of stimulus are required. Other than simple alternating block designs, more complex designs are also possible, such as the one in which one type of image e.g. faces appear at one fixed frequency and other types of images e.g. objects appear at another different fixed frequency, with both the types of stimulus interlaced together. The two types of stimulus can then be separated by using the spectral amplitude at respective stimulus frequencies [53]. As explained later, most of the frequency domain techniques differ in the way they remove or take into account the effect of temporal autocorrelation while calculating the statistical significance of activation of voxels.

The above mentioned methods generally involve some correction for spatial and temporal correlation effect in fMRI data. Next we discuss some of the aspects of evaluation and correction for temporal and spatial correlations in fMRI data, before we discuss the data-driven exploration techniques of activation detection.

fMRI data is degraded by a number of noise components, including random noise, noise related to MRI equipment, e.g., scanner drift, and noise related to subject, e.g., subject movement, physiological signal related artifacts. In addition to other factors, under-sampling of physiological signals is one of the factors that result in temporal autocorrelation present in fMRI data [63]. The fMRI time-series of a voxel, $y = \beta X + \epsilon$, X being the design matrix containing modulated stimulus signal, thus has noise component (ϵ) which is temporally correlated. Here we take it that the signal drift component has been removed as a part of preprocessing. It is important to take into account this temporal autocorrelation in noise when calculating the statistical significance of activation of the voxel otherwise the results may not be valid.

In addition to temporal correlation, fMRI data has spatial correlation because adjacent brain regions are functionally similar and also as a result of blurring caused by the vascular system [53]. A voxel is thus likely to contain some signal from the surrounding tissue [109]. The probability of activation of a voxel i , $p(a_i)$, hence will depend on the activation status of neighborhood voxel j , $p(a_j)$, i.e., $p(a_i) = f(p(a_j))$. This contextual information can thus be included in statistical analysis of fMRI data to enhance the activation detection results.

Some of the methods of evaluation and correction for spatial and temporal autocorrelation are mentioned below.

Evaluation and Correction for Spatial Correlation Effect

Contextual information of activation detection in data-driven methods is generally included using random field methods, such as Gaussian random field and Markov random field. Gaussian Random Field (GRF) theory controls the expected number of false positive regions, in comparison to the much stringent Bonferroni correction that controls the expected number of false positive voxels [37]. Based on the FWHM (full width at

half maximum) value of the Gaussian filter applied during the smoothing step in data pre-processing, the number of independent statistical tests is calculated as:

$$N_{resels} = \frac{V}{FWHM^D} \quad (1.4)$$

where N_{resels} is the number of independent statistical tests and V is the volume of D -dimensional search region. The variable N_{resels} (number of independent comparisons) also represents the number of resolution elements or resels. Based on the number of resels and the shape of the volume containing resels, number of clusters of activity to be found at a given statistical threshold can be computed [37]. This is known as Euler characteristic of the data. At low values the expected Euler characteristic is a good approximation of the probability of observing one or more blobs at that threshold. Hence one can select the alpha value starting with the required Euler characteristic value or given the number of resels one can calculate the threshold value at which there will only be alpha value chance of seeing a false positive cluster of activation. For smoothed data, this corrected value of threshold is much less conservative and more appropriate as compared to the Bonferroni correction.

One of the main drawbacks of GRF is related to its requirement of initial filtering of data, which suppresses high frequency information in fMRI data thus rendering small activated regions undetectable. Markov random field on the other hand models the brain activation patterns without smoothing and takes into account the interactions of the neighborhood voxels [89]. The global energy is given by the sum of the potentials of the cliques of the brain activation patterns based on the Hammersley-Clifford theorem. Generally only the first-order and second-order doubleton cliques are included. The prior probability of activation pattern is given by

$$p(a) \propto \left\{ - \sum_i [V_i(a_i) + \sum_{j \in \mathcal{N}_i} V_{ij}(a_i, a_j)] \right\} \quad (1.5)$$

where the initial summation is over the complete set of brain voxels, $a_i = 1$ when voxel i is activated and otherwise 0, $V_i(a_i)$ represents the single-voxel label potential at voxel i and $V_{ij}(a_i, a_j)$ the potential of voxel label interaction. The likelihood values are separately calculated using the observation values. In order to obtain the minimum of the posterior distribution, simulated annealing can be used, which iteratively considers the conditional probabilities on each site and accepts an increase of energy function randomly to escape from the local energy minima [89]. One of the main drawbacks of the MRF technique is that it does not take into account the data-dependent interactions within functional imaging data.

Evaluation and Correction for Temporal Autocorrelation Effect

Temporal autocorrelation present in voxel time-series, if not taken into account, leads to incorrect statistical significance results of voxel activation. In the case of time-domain techniques, mostly a fixed model, e.g., an autoregressive model of order one, i.e., AR(1) is employed to fit the temporal correlations of residuals. This is generally implemented in multi-step manner to derive the parameter values [16, 112, 115]. Variations of AR(p) models, such as AR(1) model with an additional white noise component [85] and ARMA model [64] have been suggested. Since the temporal autocorrelation structure is known to vary across brain regions [26, 67], fixed model methods are restrictive in the removing the temporal autocorrelation effect.

Frequency domain approaches have also been used in fMRI analysis and their approaches to remove the temporal autocorrelation effect generally require an analysis of the spectrum of null distribution of no activation. The null distribution has been derived by smoothing the periodogram on log scale following the exclusion of stimulus frequency [69], by averaging of squared residuals around each of the fundamental and harmonic stimulus frequencies [61], by subtracting the adjacent epoch time courses [77]. In [120], the spectral power of the time-series has been modeled with the inverse frequency ($1/f$)

noise model for fitting the temporal autocorrelation. However, such methods suffer from shortcomings because smoothed periodogram may still retain some of the effect of the stimulus signal and subtracting adjacent epoch time courses may introduce spurious high frequency effects in the null distribution. Also, the presence of unknown significant noise frequencies adversely affects the null distribution in these cases.

Next we will discuss some of the present data-driven exploration techniques of activation detection.

Principle Component Analysis

PCA is a technique for multivariate analysis. The basic aim of PCA is to find those uncorrelated linear combinations (principal components) of a set of variables that retain the maximum possible amount of information from the original variables. Principal components are basically the directions of largest variance of input data and are derived based on the eigen structure of the data covariance matrix [23]. In PCA, the first principal component is the linear combination of the variables with maximal variance and the subsequent components are linear combinations of variables with decreasing variance and are also orthogonal to all the previous components. The total number of components generated is equal to the number of original variables. PCA is generally used for dimension reduction, wherein a small number of components that account for most of variability in data are retained and other components are rejected.

Thomas et al. proposed the use of component analysis (PCA or ICA) method to identify components contributing primarily to the noise rather than for identification of activation pattern [100]. Noise components, identified based on the Fourier decomposition of each component time series, were removed before subsequent reconstruction of the time series data. They compared PCA and ICA technique results for their method and found that ICA can better isolate and remove the structured noise whereas PCA can

better isolate and remove the random noise. Thirion and Faugeras proposed a method based on kernel PCA. Their proposed method takes into account the knowledge of experimental paradigm but at the same time retains the flexibility of exploratory methods. It is based on two steps, first they temporally model the time courses and then subsequently add up the voxel-based models to develop a global representation of the data [99]. Some work has also been done using the correlation matrix of fMRI data. Chen et al. reported a new delay subspace decomposition (DSD) algorithm, which as compared to canonical zero-delay correlation matrix, introduces a delay into the correlation matrix of the subspace decomposition to suppress noise in the data [19]. The second step in this technique involved subspace projection of the measured fMRI data using SVD (Singular value decomposition). It was reported that when the subspace is composed of the first principal component only, the method reduces to PCA otherwise the method performs better than PCA method. The results were also found to be comparable to ICA results. Daniel Rowe and Raymond Hoffman demonstrated the use of PCA in extracting common temporal response features of a region of interest (ROI) as well as differentiating the temporal response of groups of commonly responding ROI [27]. In this technique, the ROI was determined first by using the multivariate regression analysis for voxel activation detection.

The major drawback in PCA technique is that generally the first component accounts for maximum variance and other components account for little variance. This also results in PCA being unable to separate multiple signal sources and at the same time a signal source may be present in multiple components [11].

Independent Component Analysis

The ICA technique provides a linear representation of non-Gaussian data by generating statistically independent components. Aapo Hyvarinen and Erkki Oja described various algorithms and applications of ICA technique and presented the results of MEG data

analysis [54]. ICA has been used extensively in analysis of electrical recordings of brain activity, i.e., EEG data analysis. In recent years, ICA technique has been applied to fMRI signal to understand its spatio-temporal structure [8, 17, 54, 66, 70, 90]. In case of fMRI signal, ICA basically decomposes the data matrix into a product of spatial patterns and their corresponding time courses where either patterns or time courses are a priori independent. Esposito et al. compared the two spatial ICA algorithms: the Infomax and the Fixed-Point algorithms [33]. They tested these techniques for simulated motor, real motor and visual activation fMRI data. They found that although both algorithms produced highly accurate results, the Fixed-Point performed better than the Infomax in terms of spatial and temporal accuracy provided inferential statistics were employed as benchmarks, and the Infomax sICA was better at global estimation of the ICA model and at noise reduction. Moritz et al. proposed an ICA based method to objectively differentiate between task-related components and artifactually non-relevant components [74]. They applied this power spectrum ranked ICA method to analyze a periodic fMRI complex motor paradigm. They argued that power spectrum ranking is similar to correlation with an a priori hemodynamic response, and at the same time exact timing or extent of the fMRI response is not required. Reported results show the sensitivity of ICA to short-duration hemodynamics, and the efficiency of power spectrum ranking method in detecting task-related components. Wei Lu and Rajapakse have presented constrained ICA [66], which is a semiblind approach and is better than classical ICA methods when useful constraints are incorporated into the contrast function. A number of related techniques have been explored by researchers such as hybrid method proposed by Rajapakse et al., which combines ICA and structural equation modeling (SEM) to exploratory derive the functional connectivity without a prior model [90].

According to Calhoun [17], the application of ICA to fMRI data has been quite successful, but as yet this technique does not fully utilize the prior information about various

signal sources and their properties, e.g., fMRI properties, physiologic recording etc., during analysis. Authors of book Human Brain Function [37] have compared ICA and SPM techniques and found the qualitative results of ICA and SPM to be quite comparable, but they mention that SPM has the advantage of providing significance values to its results. Authors further argue that data-driven analysis techniques are considered to be best suited to the analysis of uncontrolled experiments and not that much for conventional experiments.

Clustering

Various kinds of clustering techniques have also been applied in fMRI analysis with good success. Clustering is basically a non-supervised classification which generates classes without a priori knowledge of prototype classification. Algorithms meant for clustering are mostly based on some kind of similarity measure, which is used to detect objects belonging to same category. A numerical value is generally derived to indicate the amount of similarity between patterns in a group. The most commonly used functions are Euclidean distance, Mahalanaobis function and Tanimoto coefficient, although others, such as inertia function and the fuzzy membership function have also been suggested. Most of the clustering techniques are based on heuristic approach and some of the commonly used techniques are k -nearest neighbor and adaptive sample set construction technique [14].

Baumgartner compared the results of paradigm independent fuzzy cluster analysis (FCA) in the time domain with paradigm based correlation analysis [7] and also with the PCA results [6]. They demonstrated that FCA does not require prior knowledge about the paradigm and its results were found to be quite comparable with correlation method results which use extensive prior knowledge. Fadili et al. have demonstrated the use of multistage unsupervised fuzzy cluster analysis (UFCA) method for fMRI data analysis [34]. Two similarity criterion used by them are the correlation coefficient on temporal

profiles and fuzzy overlap coefficient on membership degree maps. Based on the area under receiver operating characteristic (ROC) curves for False Positives Fractions (FPF) range of (0,0.01), as a value of merit in the comparison studies, they demonstrated that their proposed method can perform better than other methods such as classical FCA. Goutte et al. suggested a simple stochastic procedure to choose the initial set of cluster centers in the k -means method and have also presented the results for another hierarchical algorithm used in conjunction with the classical k -means method [48]. They used cross-correlation function as the feature space, rather than using the raw fMRI time-series and have shown that clustering can effectively identify regions of similar activation. Meyer-Baese et al. compared unsupervised clustering and ICA in a fMRI study [70], and found that fuzzy clustering based on deterministic annealing outperformed ICA in terms of classification results but required a longer processing time than the ICA methods. Chen et al. presented a technique which works in two steps, first step being dimensionality reduction followed by the step for clustered component analysis (CCA) [20]. Decomposition of data into harmonic components using least squares fitting was used for dimension reduction. It was followed by determination of signal subspace from the estimated signal and noise covariances and eigen decomposition followed by prewhitening before application of the CCA. Clustered components analysis is a amplitude-independent clustering method based upon an explicit statistical data model. CCA is shown to outperform ICA, PCA and FCM methods in both mean square error and accurate voxel classification.

Artificial Neural Networks

Artificial neural network is basically a method that follows the processing capabilities of biological neural systems. This system can perform complex processing tasks by interconnecting a large number of simple processing elements (neurons). The main feature of artificial neural network is their massive parallel processing architecture and capability

of learning from the presented inputs. Their two main categories of learning algorithms are supervised and unsupervised learning.

Chuang et al. proposed a cascade clustering method combining Kohonen clustering network and fuzzy c -means [22]. They mention that in comparison to their method, clustering algorithms like fuzzy clustering have difficulty in finding activation that occupies a small area, are sensitive to noise and initial values, and are computationally demanding. They show that their method can precisely detect the functional responses and active regions and is also able to distinguish between varied signal source responses, e.g., large venous vessels or varied activation patterns of motor cortex. Voultzidou et al. explored the use of neural networks for clustering and has mentioned the advantage of defining functional connections between voxels by thresholding the correlation matrix without the need of estimating probability distributions [105]. Misaki and Miyauchi demonstrated the use of artificial neural network (ANN) to detect correlations between event sequences and fMRI signals [72]. They proposed the use of a series of events as inputs and the fMRI signal as a supervised signal for ANN and hence perform a non-linear regression analysis. The results showed that the ANN was able to detect various responses with different time courses. They conclude that ANN regression analysis is beneficial for exploratory search of brain responses that have an unknown shape and unknown parametric relation with the stimulus.

Self-organizing Maps

Self-organizing map (SOM) belongs to the category of neural networks and is implemented by a 1D or 2D lattice of neurons. The weights of neurons that are closely located on the lattice are trained to represent similar input vectors. The resulting network preserves the neighborhood topology of the input space. SOM basically transforms a high-dimensional input space onto a low dimensional discrete map by an adaptive learning process which on convergence represents a topographic map of the input patterns.

In comparison to other techniques such as PCA, fuzzy clustering etc., computationally faster algorithms like SOM and k -means clustering has an advantage. PCA finds principal components that account for large variance in data and are also orthogonal, but fMRI data can violate orthogonality assumptions. Fuzzy clustering groups data into clusters of related time courses on the basis of membership of each time course in each cluster; but fuzziness may not be necessary in fMRI clustering.

Fisher and Henning proposed the use of SOM for clustering followed by ordering cluster centers on a two-dimensional projection plane [36]. The SOM is then able to summarize all dynamic effects of an experiment by means of data partitioning. They merged the neighborhood clusters to form superclusters and mention that SOM approach is useful in finding differently activated patterns resulting from complex stimulation or high temporal resolution, in visualizing dynamic experiments, and in automated fMRI analysis. Ngan and Hun also proposed the use of kohonens SOM for analysis of fMRI data [76]. They mention that tests like t -test and cross-correlation are effective in analyzing simple paradigm data, but are not in analyzing complicated neural response or unknown fMRI response. They modified SOM algorithm by incorporating spatial connectivity using probabilistic relaxation technique of image segmentation and notified an improvement in results over standard algorithm in detecting activation regions.

Wavelets

Time-scale domain based methods that have been investigated for fMRI data analysis, mainly employ wavelets [75, 91, 101, 102]. Wavelet transforms were basically developed as an alternative to short time Fourier transform (STFT), whereby the frequency information is available with the representation of time when this frequency content occurs in the signal. Wavelet transform is basically a time-scale representation as compared to STFT, which is a time-frequency representation and the basis functions in case of wavelets are all scaled versions of a common 'mother wavelet' whereas in case of STFT,

the basis functions are windowed sinusoids. Unser and Aldroubi mentioned that the main advantage of wavelet transform is that the spatially localized discriminative information gets concentrated into a relatively small number of coefficients, with the noise divided evenly among them [101]. Also as compared to the regression analysis, where one test per voxel is required, wavelet based analysis requires considerably lesser number of statistical tests carried out on few wavelet channels that contain significant differences. Ruttimann et al. demonstrated the use of wavelet analysis to differentiate between principles of echo-shifting with a train of observations (PRESTO) method and EPI method of fMRI data acquisition, based on a performance index characterizing the signal detection [91]. The wavelets form a basis, thus the transformation is non-redundant by default. Van De Ville et al. emphasize that although it is a beneficial property to limit the number of tests in the wavelet domain, non-redundancy also contributes to the shift-variance of the wavelet transform [102]. Therefore, the same, but shifted, activation clusters can influence the sensitivity of the detection. Karsten Muller et al. demonstrated a method that combines the wavelet and the GLM [75]. This method first estimates the variance-covariance matrix of the model and then spatial wavelet transform of contrast images is computed. Wavelet coefficients are statistically analyzed in a post processing step. They concluded that for fMRI inference, wavelet-based multiresolution methods are better than monoresolution filters.

1.2.2 Resting State Network Detection Methods

The resting state data can be analyzed to detect the default network, which can then be used as a marker of pathological changes in the brain. Various methods that have proposed earlier for this are as mentioned below.

Seed Based Analysis

The seed-based correlation analysis (SBA) method has been one of the most widely used

methods and it identifies brain activity pattern correlated to a seed-region that has been pre-defined by the user [12, 30, 46]. The main challenge in this method is in choosing the appropriate seed-region which requires an expert knowledge of brain's functional organization and in the case of group studies, consistent choice of same region as the seed-region proves to be much more challenging. The low frequency fluctuations ($<0.1\text{Hz}$) in resting state fMRI data were first identified by Biswal et al. [12] to be significantly correlated in the functionally connected parts of the brain.

Amplitude of Low-frequency Fluctuation based Methods

The amplitude of low-frequency fluctuations (ALFF) and fractional amplitude of low-frequency fluctuations (fALFF) techniques use the low-frequency components. The ALFF value is calculated as the sum of amplitudes of frequency components in the range of 0.01Hz to 0.1Hz [119, 125], whereas the fALFF value is the ALFF value divided by the amplitude of frequency components in the entire detectable frequency range [124, 125]. The fALFF is thus calculated as the fraction of the signal energy in the low frequency range (0.01Hz to 0.1Hz) in comparison to the total energy of the entire signal. The main drawback in this method is that it takes into account only the sum of frequency components in the low frequency range and ignores the mutual information contained in these frequency components.

Clustering Domain Methods

A spectral clustering method has been suggested by Venkataraman et al. for the detection of resting state brain networks [104]. In this method, eigen vectors of affinity matrix, calculated using pairs of voxels, is used for clustering. In another clustering based method, suggested by Cordes et. al., cross-correlation values between pairs of voxels in the low frequency range are used for clustering [25]. The main drawback is again that the mutual information contained in these low-frequency components is not used in analysis.

Independent Component Analysis

The ICA technique has also been successfully used for the resting state fMRI data analysis with the spatial ICA's ability to delineate independent resting state brain networks but the main limitation remains the selection of components of interest from the complete set of independent components [32, 68].

Time-frequency Domain Methods

Time-frequency analysis based on STFT [71] has also been used for resting state network analysis. The main drawback with the STFT is that it suffers from time and frequency trade-off.

1.2.3 Physiological Signal Detection Methods

In the cases of fMRI data acquisition, where physiological signals are measured using extra sensors along with the acquisition of fMRI data, image based correction method RETROICOR [45] or digital filters [10] are used to remove the effect of these signals from fMRI data. Hu et al. suggested another method related to the k -space data, in which relative phase of physiological cycle based on the time at which a k -space data point was measured is determined first, followed by the examination of temporal series of each sampled point in the k -space. These techniques are effective but require synchronization of fMRI data with externally measured physiological signals and design of specialized pulse sequence. In cases where, physiological signals are not measured along with fMRI data acquisition, a number of methods have been deployed to detect these signals from fMRI data and thereby remove their effect before statistical analysis. The physiological signal detection methods that have been proposed earlier are mentioned below.

Frequency Domain Methods

When the fMRI data has been captured at very high sampling rate, i.e., at a short repetition rate ($TR < 0.5s$), unaliased physiological signals are identified from the frequency spectrum, using the knowledge of frequency range of these artifacts. Cardiac pulsations have generally been found to be around 1Hz [38, 73, 118] and specified to be in the range of 0.75-1.5Hz [21]. The respiratory signal frequency has similarly been found to be around 0.25Hz [38, 73] and specified to be in the range of 0.1-0.5Hz [21]. These identified frequency components are then removed from fMRI data [21, 73].

The main drawback of this method is that short repetition time ($TR < 0.5s$) fMRI data acquisition methods are generally applicable for only single brain slice imaging rather than the whole brain [38, 118].

Analysis of Signal from Specific Cortical Areas

Perlberg et. al. suggested a method that is based on analysis of regions where the physiological signals are known to be significant, such as areas around the ventricles and major blood vessels [80]. The signals from the voxels in these regions were then clustered together to give a smaller number of time-courses representative of physiological noise. In parallel, they also performed spatial ICA on data and then selected the temporal components that matched the earlier found time-courses from clustering. The signals and their associated spatial components that influenced most of the identified brain regions, i.e., areas around the ventricles and major blood vessels, were then considered to be those related to physiological noise.

Wang et. al. suggested another method which is also based on the knowledge of regions with significant physiological signals [106]. The data was segmented into various brain regions i.e. gray matter (GM), white matter (WM), cerebrospinal fluid (CSF) and background regions. The CSF signal in each brain slice was averaged to get a single time-course of CSF. Respiratory and cardiac noise related frequency components were

then derived from the temporally reordered time course of CSF in image space. In-order to avoid the spectrum from being dominated by slice-to-slice variations, they removed the mean value of the reordered time courses of CSF. The main idea being reducing the time-difference between each sample, from TR value (time to scan whole brain), to time taken to image one single brain slice.

The main drawback of these methods is that the target areas need to be identified very accurately.

Methods based on k -space Analysis

When k -space fMRI data is available, physiological signals are removed in the k -space data itself [38]. Frank et al. suggested a method, whereby multi-slice data from center of k -space data is reorganized temporally, rather than spatially, to effectively give physiological signals at higher sampling rate than the TR value. Their main concept behind this idea is that the physiological fluctuations are rather global, hence likely to be present in the center of the k -space data. This method is slightly similar to the idea mooted by Perlberg et al. [80], whereby data from ventricles and CSF from multiple brain slices was organized temporally, but locating the data in the center of k -space is relatively easier.

The main drawback of this method is non-availability of k -space data in clinical applications.

1.3 Major Contributions

In this thesis we propose a number of methods belonging to frequency and time-frequency domains, motivated by the problems and desirable solutions mentioned earlier. Most of these methods are aimed at providing a model-free analysis of temporal autocorrelation in voxel time-series and at improving activation detection in fMRI data. In addition, some of these methods are meant for detection of default state networks in resting-state

fMRI data and others for detection of physiological signals in fMRI data. The specific contributions of this thesis are as follows:

- (i) We present a mixed spectrum analysis (MSA) method, which is based on Priestley's $P(\omega)$ test, for activation detection in fMRI data. The main advantage of the proposed method is that it is able to account for temporal autocorrelation present in voxel time-series, while calculating the statistical significance of activation, in a model-free manner. This method is also able to detect other unknown prominent noise frequencies during this analysis. This being a frequency domain method, it does not require a fixed parameter model for the HRF. Spatial correlation of activations is incorporated using a CRF. Compared to Markov random field (MRF), CRF models the spatial correlations in a probabilistic discriminative framework using the posterior distribution over labels given the observations, which relaxes the strong independence assumption and captures neighborhood interactions among observations. Also, in comparison to linear filtering, CRF does not suppress high frequency information in fMRI data thus rendering even small activated regions detectable.

We compare the results of the presented method with the standard GLM method and test it on synthetic data and two types of task-related data. For the synthetic data results, based on the ROC curves, we find that despite being a model-free method for temporal autocorrelation, our proposed method has lower error rates as compared to the standard GLM method. For two sets of task-related data, i.e., memory task and visual task datasets, our proposed method results are found to be comparatively more focal and localized to the cortical areas.

We also apply this MSA technique's principle to detect default-mode network in resting state datasets. The novelty of this method is that it uses temporal autocorrelation values, instead of the prevalent use of low frequency amplitude or seed

region time-series, in detecting the resting state networks. We test this method on synthetic data and four sets of resting state datasets and compare the results with the standard fALFF method. We find that the MSA method results better match the known cortical areas of default mode network.

In addition, we use this MSA technique to detect physiological signals from fMRI data, for the cases when this data has not been captured with additional physiological sensors and also when the captured fMRI data has $TR \sim 2s$ thus causing these signals to be aliased and rendering them difficult to be identified directly. Here we use Priestley's method in two ways. In the first case, spatial ICA (sICA) is used to find time-series related to the spatial components that match the target brain locations and Priestley's $P(\omega)$ test is then used to analyze these time-series. In the second case, all the voxel time-series in the chosen brain slices are directly analyzed using Priestley's $P(\omega)$ test, for significant frequency components. Spatial ICA based method, is slightly complex as it requires careful selection of spatial components based on the knowledge of brain areas where physiological signals are prominent [26]. In our analysis, results from this sICA method are taken as a benchmark against which the results from direct application of Priestley's $P(\omega)$ test are compared. We test our method on two sets of memory retrieval task related data, and find that the results from direct application of Priestley's method are quite consistent with the sICA method results, for detection of physiological signal frequency components.

In yet another application, we use CRF principle for efficient regularization of AR(1) values in model-based pre-whitening methods. In this method, residuals of voxel time-series after regression analysis, are fitted with an AR(1) model to calculate autocorrelation coefficients. A number of researchers have proposed to spatially smooth these autocorrelation estimates, with a spatial smoothing filter, to reduce

their variance before using them in a restricted maximum likelihood (REML) process to perform prewhitening [42, 112]. On the other hand, some researchers have found that smoothing these autocorrelation estimates with spatial smoothing filters prevents the successful modeling of negatively correlated and approximately white spectra [62]. Smoothing was also found to result in underestimation of positive correlations when weakly correlated or white spectral residuals bordered these positively correlated residuals [62]. We propose and apply random field analysis based regularization, with a modified CRF, rather than a smoothing filter. We test it on synthetic and memory-task related data and find that it provides the necessary reduction in variance of AR(1) coefficients by taking into account the neighborhood autocorrelation estimates and at the same time preserves the borders between the positive, negative and white spectral residuals. This method can easily be extended to regularize the parameter values for any model other than AR(1) also.

- (ii) We present two frequency domain methods that use the energy present in higher harmonics along with the fundamental frequency, for activation detection in the case of periodic event-related fMRI data. In the case of periodic event-related data, other than the fundamental frequency, higher harmonics of stimulus frequency also contain substantial energy. At the same time, as the harmonics get high, they are more likely to be affected by the noise and they are also attenuated by the brain's hemodynamic response, which acts as a low-pass filter. Thus selecting and using appropriate number of harmonics in activation detection is a challenge. In the first presented method, based on χ^2 random field, we use one higher harmonic along with fundamental frequency. In the second presented method, we use Hartley's F -test to select the prominent harmonics along with the fundamental frequency. The main advantage of these methods is that they are able to use the energy available in higher harmonics of periodic event-related data for more efficient activation detection.

Both the methods are tested on synthetic data as well as event-related memory retrieval task data. For the synthetic data, based on the ROC curves, we find that in most cases Hartley's F -test based proposed method has lower error rates as compared to the standard GLM method, whereas the proposed χ^2 random field based method has better results only in some specific cases. For the memory-task related dataset, Hartley's F -test based proposed method results are found to be comparatively more focal and localized to the cortical areas.

We have also extended a scale-space method based on χ^2 random field to include higher harmonics of stimulus frequency in its analysis. This method is able to provide better information about the spatial extent of activation. The results of this method are compared with the wavelet analysis results.

- (iii) We present a time-frequency domain method to detect default mode network in resting state fMRI data. Default mode networks are important, as changes in this network indicate changes in the pathological condition of the brain; hence it can be used as a diagnostic tool for certain brain ailments. The Rihaczek-Margenau distribution of Cohen's class [24], which produces the least amount of cross terms, is used in this method for calculating the time-frequency values of voxel time-series. The main advantage of this method is that it takes into account the variation in the amplitude of various frequency components in the range of 0.01Hz-0.1Hz along the time axis, as well as the mutual information contained in these frequency components.

The presented method is tested on synthetic data and four sets of resting state datasets and its results are compared with the fALFF technique results. We find the proposed method results better match the known cortical areas of default mode network.

1.4 Outline

In Chapter 2, we present a mixed spectrum analysis method, based on Priestley's $P(\omega)$ test for activation detection in fMRI data. This method removes the effect of temporal autocorrelation in voxels BOLD time-series, in a model-free manner, while calculating the statistical significance of activation. Spatial correlation of activations is incorporated using a CRF. Since the presented method is able to detect all the significant frequency components in a voxel time-series, in addition to activation detection, we demonstrate its application in detecting physiological signals in fMRI data. We also include in this chapter the results of application of random field analysis for more effective regularization of AR(1) parameters in model-based prewhitening, instead of widely used smoothing filter.

In Chapter 3, we present two methods of usage of higher harmonics of stimulus frequency in activation detection of event-related fMRI data. The first method is based on χ^2 random field and the second method is based on Hartley's F -test. Hartley's F -test based method selects the higher harmonics to be used in activation detection, whereas χ^2 random field based method uses fixed number of higher harmonics. We also present in this chapter, the scale-space χ^2 random field analysis method with the inclusion of higher harmonics. This scale-space method provides us with an indication of the spatial extent of activation in fMRI data.

Chapter 4, presents a method based on Cohen's class of distribution for time-frequency analysis of resting state fMRI data. The time-frequency distribution, corresponding to low frequency components, is shown to be able to detect efficiently the default mode network in resting state fMRI data. Here we also employ the MSA principle, as discussed in Chapter 2, to detect default-mode network in resting-state fMRI data.

Finally, in Chapter 5, we summarize, provide future directions to our work and conclude our thesis.

Chapter 2

Mixed Spectrum Analysis of Task-related Data

Temporal correlation present in fMRI data poses challenges to the data analysis, as it manifests itself in the form of temporally correlated noise. This leads to invalidation of statistical analysis results of voxel time-series, if the temporal dependence of error terms is not taken into account. The existing approaches handling autocorrelation in fMRI time-series often use a specific fixed model of autocorrelation. They presume that the autocorrelation structure is invariant over the brain although different brain regions have been found to have different hemodynamic responses and temporal and spatial correlations [26, 67, 115]. In this chapter, we propose MSA method that assumes a mixed spectrum consisting of a discrete component corresponding to input stimuli and a continuous component carrying temporal autocorrelation of fMRI time-series. A method based on Priestley's $P(\omega)$ test is proposed, which identifies significant peaks of the spectrum and removes autocorrelation from fMRI time-series. Unlike the existing models, the MSA does not assume any prior model of autocorrelation function or require knowledge of hemodynamic response function. Brain activation is detected by predicting the likelihood of activation by the filtered time-series and modeling spatial correlations among the likelihood with a CRF. The method is demonstrated on synthetic data as well as task-activated fMRI datasets. In addition, we demonstrate the capability of the MSA method in detecting physiological signals in task-activated fMRI datasets and apply random field

analysis for efficient regularization of autoregression values. An additional application of Priestley’s technique in detecting resting state networks is discussed in Chapter 4, along with other proposed resting state analysis technique.

2.1 Motivation and Contributions

Two types of strategies namely, prewhitening [115] and coloring [41], have mainly been proposed to account for temporal autocorrelation of fMRI time-series. Prewhitening refers to a technique whereby the effect of temporal autocorrelation is removed from the time-series before its further analysis and coloring refers to a technique whereby a known autocorrelation is imposed on the data using filters before its further analysis. The pseudo-generalized least squares (PGLS) method has been proposed to fit regression models of time-series and then temporal correlations of residuals are fitted with a first-order AR model [16]. In the ReML approach, temporal autocorrelations were spatially smoothed to reduce their variability and then fitted with the Yule-Walker equations to obtain $AR(p)$ parameters [112, 115]. This method was found to have adverse effect on the classification of voxels having either approximately white or negative autocorrelation, which was overcome by a non-regularized $AR(2)$ model [62]. Variations of $AR(p)$ models, such as $AR(1)$ model with an additional white noise component [85] and ARMA model [64] have been suggested. Coloring strategies shape up intrinsic autocorrelation of data, usually with band pass filters consisting of a low pass smoothing filter and a high pass filter specified by the minimum period [41, 114]. Filtering imposes an autocorrelation structure on the error terms. An $AR(1)$ model is then fitted to the altered correlations, which coefficients are assumed to be invariant over the brain [41].

Frequency domain approaches have also been used to handle temporal autocorrelation in fMRI time-series. In these techniques, detection of brain activation is usually performed by evaluating the null distribution of no activation of the spectrum. Zarahn et al. (1997) modeled the spectral power of the time-series with the inverse frequency

($1/f$) noise model for fitting the temporal autocorrelation [120]. The null distribution has also been derived from the smoothed periodogram on log scale excluding stimulus frequency [69], by averaging the squared residuals around each of fundamental and harmonic stimulus frequencies [61], and by subtracting the adjacent epoch time courses [77]. In above-mentioned frequency domain approaches, smoothing of the periodograms may retain some of the effects of the stimuli and subtraction of adjacent epochs may introduce spurious high frequency effects in the null distribution, adversely affecting the null distribution.

A major drawback common to above methods is that most methods fit a time-series into a specific model and then remove autocorrelation by using an iterative scheme such as ReML or PGLS. For detection of brain activation, PGLS technique with AR(1) model and the inverse frequency model are found to be inadequate to model both intermediate or long-range autocorrelations [41]. Coloring methods are found to be less attractive unless the specified deconvolution matrix exactly matches the actual covariance structure whereas prewhitening methods are generally found to be less accurate [110]. Furthermore, they presume that the autocorrelation structure is invariant over the brain although different brain regions have been found to have different hemodynamic responses and temporal and spatial correlations [26, 67, 115].

Spatio-temporal techniques that concurrently deal with spatial and temporal correlations have also been suggested for fMRI data analysis. Woolrich et al. used temporally fixed spatial AR(1) model together with a spatially varying temporal AR model for short term correlated processes in addition to a high pass filter in pre-processing stage to remove large scale temporal variations [109]. Descombes et al. proposed a 3D spatio-temporal MRF model with two spatial dimensions and one temporal dimension [29]. Gossel et al. used a Bayesian framework in which they combine the spatial and temporal random field priors as a Kronecker product of their respective precision matrices [47]. One major drawback of this technique is the use of deterministic model for drift with the assumption

that the remaining noise is white [109]. Bayesian spatio-temporal technique has also been suggested by Bowman [15] but they still lack an optimized model fitting procedure [63].

In this chapter, we aim to remove the temporal autocorrelation effect from voxel time-series, in a model-free manner, while calculating its statistical significance of activation. At the same time, despite being model-free we expect our method to be efficient in activation detection. We propose the MSA method for fMRI data analysis. The spectrum of fMRI time-series is presumed to be the sum of a discrete spectrum due to task-related activation and a continuous spectrum carrying the autocorrelation of the signals. Our proposed method, based on Priestley's $P(\omega)$ test, removes the effect of temporal autocorrelation without a presumed model, selects significant frequencies in each voxel time-series, and thereby detect activations due to input stimuli. The earlier frequency domain approaches used only a discrete spectrum to model fMRI time-series and autocorrelations were removed by fitting a specific model such as AR(1) model [16, 73, 77]. The advantage of MSA is that it does not require explicit knowledge of autocorrelation function or the hemodynamic response function [82–84]. Therefore, it is capable of handling complex autocorrelations, such as those found in high-field fMRI [43]. Priestley's test has been applied successfully in harmonic analysis of time-series for meteorology and econometric applications [3, 9, 97]. In the cases where characteristic equation of continuous spectrum has complex roots near the unit circle, this method has got mixed results, regarding its capability of accurately predicting future values [3, 108]. However, we demonstrate the applicability of Priestley's test by analysis of complex roots of characteristic equation related to power spectrum of real fMRI data.

In Section 2.2, we describe how fMRI time-series are modeled with a mixed spectrum and Priestley's $P(\omega)$ test is used to identify significant frequency components in each voxel time-series. Brain activations are detected by using filtered time-series and modeling of spatial correlation of brain activation is done with CRF. In Section 2.3, we present the results of detecting activation on synthetic data as well as real fMRI gathered in a

visual task and in a memory retrieval task. In addition, we demonstrate the application of the proposed MSA method in detecting physiological signals and the application of random field analysis in efficient regularization of autoregression values. An additional application of Priestley’s principle in detecting resting state networks is discussed in Chapter 4. Section 2.5 concludes the chapter.

2.2 Models and Methods

In this section, we present our novel method of mixed spectrum analysis of fMRI data, which consists of two parts, i.e., Priestley’s test to remove temporal autocorrelation effect when calculating statistical significance of activation and a CRF to incorporate spatial correlation of activation into this statistical analysis of activation. This method is novel as present methods used in fMRI for removing temporal autocorrelation effect are based on a fixed assumed model either in time domain, e.g., AR(1) model, or in frequency domain, e.g., $1/f$ noise model, whereas the proposed method does not need to assume any such fixed model. The proposed method is advantageous as autocorrelation structure in resting state fMRI datasets has been found to be more complex than the generally assumed simpler fixed models [31], such as AR(1) model, and the temporal autocorrelation in voxel time-series is likely to vary across the brain regions [26, 67], resulting in a fixed model based method to be restrictive.

2.2.1 Modeling fMRI Time-series with a Mixed Spectrum

An fMRI experiment consists of taking a series of three-dimensional (3D) brain scans while the subject is performing a functional task. Let the spatiotemporal fMRI data be $\mathcal{F} : \Omega \times \mathcal{T} \rightarrow Q$ where $\Omega \subset \mathbf{N}^3$ denotes the 3D spatial domain of brain voxels, $\mathcal{T}$ represents the scanning times, and Q the range of image intensities. Considering a series of brain scans taken at regular intervals, scanning times are indexed by $\mathcal{T} = \{t\}_{t=1}^T$ where T denotes the total number of brain scans, representing the total scan time.

Changes of blood-oxygenated-level-dependent (BOLD) signal over an fMRI experiment define the hemodynamic time-series response at a brain voxel. Let the fMRI time-series at voxel $i \in \Omega$ be $y_i = (y_i(t))_{t=1}^T$ which is presumed to be the sum of signals due to task-related activity and autocorrelation:

$$y_i(t) = x_i(t) + z_i(t) \quad (2.1)$$

where $x_i(t)$ represents the response due to input stimuli and $z_i(t)$ represents the temporally correlated noise. This temporally correlated noise is a result of human physiological processes and also found to be contributed by external factors, e.g., equipment [62, 120]. The signal $x_i(t)$ has a discrete spectrum of stimulus frequency and the component $z_i(t)$ has a continuous spectrum. The task-related signal generated by periodic stimuli, can be written as

$$x_i(t) = \sum_{p=1} A_{ip} \cos \omega_p t + B_{ip} \sin \omega_p t \quad (2.2)$$

where ω_p denoted the p th harmonic of the stimulus frequency ω_1 , and A_p and B_p denotes the amplitude of Fourier series [97].

2.2.2 Priestley's Test for Mixed Spectrum Analysis

For notational simplicity, the subscript indexing the voxel is omitted in this section. The autocovariance $R_y(\tau)$ of time-series $y(t)$ at a time lag τ is given by

$$R_y(\tau) = R_x(\tau) + R_z(\tau) \quad (2.3)$$

where $R_x(\tau)$ and $R_z(\tau)$ represent the autocovariance functions of $x(t)$ and $z(t)$, respectively.

In the absence of a stimulus, $R_y(\tau) = R_z(\tau)$ and the autocovariance $R_y(\tau)$ dampens out to zero as $|\tau|$ gets large. Therefore, consideration of the spectrum of $R_y(\tau)$ beyond a certain values of τ suffices to remove the effect of temporal autocorrelation. Priestley's mixed spectrum test or $P(\omega)$ test was thus used to identify significant frequency components in the truncated autocovariance function $R_y(\tau)$ [57, 83].

First, the truncation point τ_1 of time-lag beyond which the autocovariance function is of interest, i.e., the point beyond which the autocovariance $R_y(\tau)$ is free from the effects of $z(\tau)$, is determined [84]. The value of τ_1 is estimated based on Eq. (2.4) and its relationship with AR(k) and moving average (MA(k)) models is as given below.¹ For long time-series, rather than using the complete autocovariance from point τ_1 onwards, an upper truncation point $\tau_2 (\leq T)$ is also suggested. This gives an upper bound of τ to perform spectrum analysis of $R_y(\tau)$. Generally, $\tau_2 \geq 2\tau_1$ [9, 84]. As is commonly used in all the lag window based spectrum estimation methods, this upper bound in autocovariance series results in lowering the variance of spectral estimates [18]. Let $S_1(\omega)$ and $S_2(\omega)$ denote the windowed estimates of the spectrum of autocovariances $R_y(\tau)$ for time lags up to τ_1 and τ_2 , respectively, and W_1 and W_2 denote the corresponding window functions for time lags up to τ_1 and τ_2 , respectively. Priestley's $P(\omega)$ function is thereby computed within this interval :

$$\begin{aligned} P(\omega) &= \frac{1}{2\pi} \sum_{\tau=-(T-1)}^{T-1} (W_2(\tau) - W_1(\tau)) R_y(\tau) \exp^{-j\omega\tau} \\ &= S_2(\omega) - S_1(\omega) \end{aligned} \quad (2.6)$$

¹In the Priestley's $P(\omega)$ test, lag value τ_1 is required, beyond which the autocovariance function is used to calculate the spectral density of time-series. In case, $z(t)$ is an AR(k) process with an exponential damping function: $|R_z(\tau)| \leq K\rho^{|\tau|}$ where ρ is the damping factor and K a constant. The truncation point τ_1 beyond which $R_y(\tau)$ is free from modulation by $z(\tau)$ is given by [84]:

$$\tau_1 = \frac{\log T}{\log(1/\rho^2)} + \frac{\log(1 - \rho^2)/(1 + \rho^2)}{\log(1/\rho^2)} \quad (2.4)$$

where T is the total number of brain scans. AR(1) or AR(2) model is usually assumed for fMRI time-series, so for $z(t)$:

$$\begin{aligned} \text{AR}(1) : \quad & z(t) = h_1 z(t-1) + \epsilon(t) \\ \text{AR}(2) : \quad & z(t) = h_1 z(t-1) + h_2 z(t-2) + \epsilon(t) \end{aligned} \quad (2.5)$$

where h_1 and h_2 are the model coefficients and the noise $\epsilon(t)$ is assumed to be zero mean white noise. For AR(1) model, $\rho = h_1$ and for AR(2) model, $\rho = \sqrt{h_2}$. For an AR(2) signal with coefficients $h_1 = h_2 = 0.4$ [115], $\tau_1 = 4$, for a signal with 100 scans. Similarly, if $z(t)$ is assumed to be of type MA(k), value of $\tau_1 = k$ [84]. We have used the value of τ_1 equal to number of scans in one stimulus cycle for our analysis, which adequately covers the time-series with higher-orders of AR(k) and MA(k) coefficients than are typical of fMRI data.

at $\omega = 2\pi k/T$ for $k = 0, 1, \dots, [T/2]$.

Finding significant frequencies in voxel time-series is performed in an iterative manner in a two-step procedure. First, positive peaks of $P(\omega)$ function are identified, which provide a set of frequencies that are likely to be significant under the null hypothesis of no brain activation. Second, a significance test is performed on each of these frequencies in a sequential manner, starting with the lowest frequency, to confirm if a particular frequency component is significantly present or not.

Let $u(\neq 0, \pi)$ be the frequency of a positive peak in $P(\omega)$, i.e., $\omega = u$, which is to be tested for significance under the null hypothesis and J_u be its cumulative statistics. To compute J_u , a value δ_u is chosen such that $u = (2\pi q/\tau_1) + \delta_u$ for some integer q in the range $\{0, \tau_1/2\}$. By rewriting the autocovariance function $R_y(\tau)$ as an autocorrelation function $\rho_y(\tau) = R_y(\tau)/R_y(0)$, and transforming $P(\omega)$ by using $R_y(0)$ as $P^*(\omega) = P(\omega)/R_y(0)$, $J_u = \max_q(J_{uq})$ is based on a random walk model where J_{uq} is given by [84]:

$$J_{uq} = \sqrt{\frac{2\pi T}{\tau_1 g(\pi) W_{1,2}}} \sum_{s=0}^q P^*\left(\frac{2\pi s}{\tau_1} + \delta_u\right) \quad q = 0, 1, \dots, [\tau_1/2] \quad (2.7)$$

where $g(\pi) = (\sum_{\tau=-\tau_1}^{\tau_1} \rho_y^2(\tau) - 2 \sum_{\tau=\tau_1+1}^{\tau_2} \rho_y^2(\tau)) / 4\pi$.

We use Bartlett window for calculation of $S_2(\omega)$ and also for $S_1(\omega)$ instead of the rectangular window. That is, $W_2(\tau) = 1 - |\tau|/\tau_2$ for $|\tau| \leq \tau_2$ and zero, otherwise, and $W_{1,2} = 2\tau_2/3 - 4\tau_1/3 + 2\tau_1^2/3\tau_2$ [9]. For $s \in \{0, \dots, q\}$, $2\pi s/\tau_1 + \delta_u$ corresponds to frequency values that are sufficiently well apart and $P^*(\omega)$ values are approximately independent at these frequencies. The term $\sum_{s=0}^q P^*\left(\frac{2\pi s}{\tau_1} + \delta_u\right)$ in (2.7) is thus a cumulative sum of asymptotically independent terms and is converted into a 'standardized' cumulative sum by the term $\sqrt{TW_{1,2}^{-1}/\tau_1}$. The term $\sqrt{2\pi/g(\pi)}$ in (2.7) causes $\max_q(J_{uq})$ to form a standardized normal $N(0, 1)$ distribution. This, $J_u = \max_q(J_{uq})$, is the significance value of the frequency u under the test. The corresponding probability value of significance at

this frequency is then calculated using, $p = 2\Phi(J_u) - 1$, where Φ represents the standardized normal distribution. This probability is compared at a user specified significance value α to confirm whether the frequency component under the test is significant or not.

For the set of peak frequencies on $P(\omega)$, the significance test under the null hypothesis is performed by one frequency at a time and in the order of increasing frequency. Once the peak frequency is found to be significant, that frequency component is removed from voxel time-series. The $P(\omega)$ value is recalculated from the filtered time-series and the procedure is repeated to find the next significant frequency component, and so continues. This process is repeated until all the significant frequencies are identified in the time-series. The procedure is given in Algorithm 1 and effectively removes autocorrelation during statistical significance calculation.

Algorithm 1 Selection of significant frequency components

```

begin
  for voxels  $i \in \Omega$  do
     $y(t) = y_i(t)$ 
     $k = 1$ 
    Compute  $P(\omega)$  values for  $y(t)$ 
    Find the set  $u$  of positive peaks of  $P(\omega)$ 
    for each  $u$  do
      Compute  $J_{uq}$ ,  $q = 0, 1, \dots, [\tau_1/2]$ 
      if  $2\Phi(\max_q(J_{uq})) - 1 > 1 - \alpha/k$  then
        Note that this frequency is significant
         $\hat{A}_u = \frac{2}{T} \sum_{t=1}^T y(t) \cos(ut)$ 
         $\hat{B}_u = \frac{2}{T} \sum_{t=1}^T y(t) \sin(ut)$ 
         $y(t) = y(t) - \hat{A}_u \cos(ut) - \hat{B}_u \sin(ut)$ 
        Recompute  $P(\omega)$  values for  $y(t)$ 
        Find the set of positive peaks  $u$  of  $P(\omega)$ 
         $k = k + 1$ 
      end if
    end for
  end for
end
  
```

2.2.3 Conditional Random Field for Contextual Information

Significant frequency components in voxel time-series are detected with Priestley's $P(\omega)$ test as described in Algorithm 1. Activation patterns are then detected by using the

cumulative statistics, J_{ω_1} , at the stimulus frequency ω_1 from the filtered time series. If $a = (a_i)_{i \in \Omega}$ denotes the brain activation pattern where $a_i = 1$ when voxel i is activated and otherwise 0, the probability of activation of voxel i is given by

$$p(a_i = 1|y) = 2\Phi(J_{\omega_1}) - 1 \quad (2.8)$$

where $J_{\omega_1} = \max_q(J_{uq})$ (refer Eq. (2.7)), evaluated at $u = \omega_1$, are the cumulative statistics of harmonics at the stimulus frequency ω_1 , measured at the voxel i .

In the brain, neighboring voxels are likely to have the same function, so spatial correlation exist among the activated voxels and need to be taken into account when determining the activation patterns of the brain. The aim is to find the optimal activation pattern a^* by using the maximum a posteriori (MAP) estimator:

$$a^* = \arg \max_a p(a|y) \quad (2.9)$$

In order to estimate the brain activation pattern, the pair (y, a) is assumed to form a CRF [60]. Then,

$$p(a_i|y, a_j, j \in \Omega, j \neq i) = p(a_i|y, a_j, j \in \mathcal{N}_i) \quad (2.10)$$

where $\mathcal{N}_i$ represents the neighborhood of voxel i .

From the fundamental theorem of random fields [50], the above distribution is given by a Gibbs distribution:

$$p(a|y) \propto \exp \left\{ - \sum_i \left(V_i(a_i|y) + \sum_{j \in \mathcal{N}_i} V_{ij}(a_i, a_j|y) \right) \right\} \quad (2.11)$$

where $V_i(a_i|y)$ represents the single-voxel potential at voxel i and $V_{ij}(a_i, a_j|y)$ the potential of voxel interaction with the neighborhood voxels $j \in \mathcal{N}_i$ [107].

The single-voxel potential V_i in (2.11) is decomposed as

$$V_i(a_i|y) = V_1(a_i) + V_1(a_i|y) \quad (2.12)$$

which consists of $V_1(a_i) = -\ln p(a_i)$ representing the prior information of activations and $V_1(a_i|y) = -\ln p(a_i|y)$ representing the data-dependent single-voxel potential. Let the

prior potential $p(a_i = 1) = \alpha_0$ be a constant over the brain. The data-dependent term $p(a_i|y)$ is calculated using (2.8).

The pairwise potential term V_{ij} in (2.11) is then given by

$$V_{ij}(a_i, a_j|y) = V_2(a_i, a_j) + V_2(a_i, a_j|y) \quad (2.13)$$

where $V_2(a_i, a_j)$ represents the data-independent joint potential and $V_2(a_i, a_j|y)$ represents the data-dependent joint potential. For spatial interactions, we use twenty six nearest neighbors in 3D and assume that the potentials are constant over the image.

The data-independent interaction term is set to encourage contiguous voxels of the same class:

$$V_2(a_i, a_j) = \beta_0 (1 - \delta(a_i - a_j)) \quad (2.14)$$

and the data-dependent term

$$V_2(a_i, a_j|y) = \beta_1 |p(a_i|y) - p(a_j|y)| \delta(a_i - a_j) \quad (2.15)$$

where $p(a_i|y)$ and $p(a_j|y)$ represent the probability of voxel time-series, given the state of activation of the voxels i and j respectively, and are determined using (2.8). And β_0 and β_1 are positive constants.

From (2.9)-(2.11), the MAP estimate of the activation pattern is given by

$$a^* = \arg \max_a \sum_i \left(V_i(a_i|y) + \sum_{j \in \mathcal{N}_i} V_{ij}(a_i, a_j|y) \right) \quad (2.16)$$

However, computing the optimal activity pattern by using the above equation and potential values is a computationally intensive task. We used the mean field approximation to efficiently compute the optimal solution. The derivation of the mean field approximation to the above estimate is as given below.

The CRF model to compute the posterior probabilities of voxel labels, as described in (2.11)-(2.15), is effectively implemented using the variational mean field approach. The posterior probability is approximated by a much simpler distribution $\varphi(a|y) = \prod_i \varphi(a_i|y)$

through the minimization of Kullback-Leibler (KL) divergence to determine the approximate distribution [78]. The term $\wp(a_i = 1|y)$ denotes the approximated probability that the voxel i contains an activated brain signal.² This finally leads to the iterative update rule:

$$\wp^{\text{new}}(a_i|y) = e^{(1+\gamma_i)} e^{-V_i(a_i|y)} e^{-2 \sum_{j \in \mathcal{N}_i} \sum_{a_j} \wp(a_j|y) (V_{ij}(a_i, a_j|y))} \quad (2.21)$$

where the normalization constant $e^{(1+\gamma_i)}$ ensures that $\sum_{a_i} \wp^{\text{new}}(a_i|y) = 1$ and

$$V_i(a_i|y) = V_1(a_i) + V_1(a_i|y) \quad (2.22)$$

$$V_{ij}(a_i, a_j|y) = V_2(a_i, a_j) + V_2(a_i, a_j|y) \quad (2.23)$$

2.3 Results

In this section, we include our activation detection results based on the proposed method. Tests have been conducted on both the synthetic as well as task-related fMRI data. But before the activation detection results, we analyze the fMRI data to determine its autocorrelation structure and to show the applicability of Priestley's test on fMRI

²The K-L divergence is defined as

$$D(\wp(a|y)||p(a|y)) = \sum_a \wp(a|y) \log \left(\frac{\wp(a|y)}{p(a|y)} \right) \quad (2.17)$$

where the summation is taken over the presence and absence of stimulated voxel time-series: $a_i \in \{0, 1\}$. Substituting the values from (2.11)-(2.15),

$$\begin{aligned} D(\wp(a|y)||p(a|y)) &= \sum_i \sum_{a_i} \wp(a_i|y) \log(\wp(a_i|y)) + \sum_i \sum_{a_i} \wp(a_i|y) V_i(a_i|y) \\ &+ \sum_i \sum_{j \in \mathcal{N}_i} \sum_{a_i} \sum_{a_j} \wp(a_i|y) \wp(a_j|y) V_{ij}(a_i, a_j|y) \end{aligned} \quad (2.18)$$

which needs to be minimized based on the constraint $\sum_{a_i} \wp(a_i|y) = 1$. Using Lagrange multipliers, the above optimization problem can be written as

$$\begin{aligned} J(\wp(a)) &= \sum_i \sum_{a_i} \wp(a_i|y) \log(\wp(a_i|y)) + \sum_i \sum_{a_i} \wp(a_i|y) (V_i(a_i|y)) \\ &+ \sum_i \sum_{j \in \mathcal{N}_i} \sum_{a_i} \sum_{a_j} \wp(a_i|y) \wp(a_j|y) V_{ij}(a_i, a_j|y) + \sum_i \gamma_i \sum_{a_i} (\wp(a_i|y) - 1) \end{aligned} \quad (2.19)$$

Differentiating with respect to $\wp(a_i|y)$ and by setting the derivatives equal to zero:

$$\wp(a_i|y) = e^{(1+\gamma_i)} e^{-V_i(a_i|y)} e^{-2 \sum_{j \in \mathcal{N}_i} \sum_{a_j} \wp(a_j|y) V_{ij}(a_i, a_j|y)} \quad (2.20)$$

time-series. These tests have been conducted on resting state and task-oriented fMRI datasets. At the end of this section, we demonstrate the application of MSA method for the detection of physiological signal related frequency components and the application of random field analysis for efficient regularization of autoregression values.

2.3.1 Applicability of the Priestley's Test on fMRI data

In order to study the validity of the Priestley's test, the complex roots of characteristic equation related to power spectrum of fMRI data were studied. Location of complex roots near the unit cycle results in a behavior similar to a non-stationary process. Absence of roots near the unit cycle prevents time-series from mistakenly being labeled as being generated by a non-stationary process [18]. Location of complex roots near the unit cycle may also result in Priestley's $P(\omega)$ test being less effective in forecasting the future values of process, as required in some meteorological and econometric applications, as shown by [108]; at the same time it has been applied successfully for harmonic analysis by [3, 9, 97] in meteorology and econometric applications.

In order to find the behavior of complex roots of characteristic equation related to power spectrum, the appropriate autoregression model order was first determined by evaluating the partial autocorrelation function (PACF) of the fitted model. The PACF value refers to the p th coefficient value in the $AR(p)$ model and denotes excess autocorrelation at lag p which is not accounted by an $AR(p-1)$ model [18]. This value thus is a useful aid in determining the correct order of the AR process. For this analysis, we fitted $AR(p)$ models to the time-series and analyzed their PACF values to check the fitness of model with 99% confidence level, followed by the analysis of the location of complex roots for each voxel time-series. PACF values outside the range of $[-2.58/\sqrt{T}, +2.58/\sqrt{T}]$ where T is the total number of brain scans are taken to be significantly different from zero at 99% confidence level [18]. At 95% confidence level, this interval is $[-1.96/\sqrt{T}, +1.96/\sqrt{T}]$

For the first resting-state dataset, brain voxels from sixteen brain slices were analyzed and PACF values were evaluated for various models and AR(2) model was found to be the most appropriate at 99% confidence level. The limits of PACF values, for 99% confidence level are ± 0.16 for 248 time-points (TR=1s) and as shown in (Figure 2.1a) some of the voxels have values outside this limit. For the models with order higher than the AR(2) model, PACF values were found to be within the limit. Once the model order was determined, locations of complex roots were determined with respect to the boundaries of the unit circle and the results are as shown in Figure 2.1c. As is clear from the figure, all the complex roots are well within the unit circle. A higher model, i.e., AR(3) model can be fitted when the PACF values are considered with confidence level below 99%. For example, at 95% confidence level, limits for PACF values are ± 0.12 , making it possible to fit AR(3) model as shown in Figure 2.1b. Locations of complex roots were again determined, for AR(3) model, with respect to the boundaries of the unit circle and the results are as shown in Figure 2.1d. In conclusion, although a different model may be fitted based on the different confidence level, the complex roots in either case were found to be well within the unit circle.

We also tested another resting-state dataset, whereby brain voxels from sixteen brain slices were analyzed and PACF values were evaluated for various models and AR(2) model was again found to be the most appropriate 99% confidence level. In this dataset also, for 248 time-points (TR=1s), the limits of PACF values for 99% confidence level are ± 0.16 and as shown in (Figure 2.2a) some of the voxels have values outside this limit. For the models with order higher than the AR(2) model, PACF values were found to be within the limit. Once the model order was determined, locations of complex roots were determined with respect to the boundaries of the unit circle and the results are as shown in Figure 2.2c. As is clear from the figure, all the complex roots are well within the unit circle. A higher model, i.e., AR(3) model can be fitted when the PACF values are considered with confidence level below 99%. Again at 95% confidence level, with PACF

value limits being ± 0.12 , we found that AR(3) can be fitted as shown in Figure 2.2b. Locations of complex roots were again determined, for AR(3) model, with respect to the boundaries of the unit circle and the results are as shown in Figure 2.2d. The findings in case of this second resting-state dataset were also similar to the first case as mentioned above, i.e., although different model may be fitted based on the different confidence level, the complex roots in either case were found to be well within the unit circle

Other than resting-state datasets, we also tested two task-related datasets, i.e., visual task dataset and memory retrieval task dataset. In a similar manner as mentioned above, AR(1) model was found to be the best for the visual task data at 99% confidence level. Since there can be no complex roots in AR(1) model, we tried fitting a higher model, i.e., AR(2) model, at a confidence levels lower than 99%, in order to observe the behavior of complex roots. The PACF value limits for this dataset (block-based dataset) are ± 0.24 for 64 time-points and 95% confidence interval. The results of PACF values are as shown in (Figure 2.3a). The complex roots for AR(2) model were found to be within the unit circle as shown in Figure 2.3c. For the memory retrieval task data, again AR(1) model was found to be the best fit at 99% confidence level. Again we tried fitting a higher model, i.e., AR(2) model, at a confidence levels lower than 99%, in order to observe the behavior of complex roots. The PACF value limits for this dataset are ± 0.21 for 90 time-points and 95% confidence interval. The PACF values for AR(2) model are as shown in (Figure 2.3b). The complex roots were also found to be within the unit circle as shown in Figure 2.3d.

2.3.2 Activation Detection in fMRI Data using MSA and CRF

Methods were applied to synthetic as well as real fMRI data. Synthetic data was used to quantitatively evaluate the performance and robustness of the method on different correlation structures, lengths of time series, noise etc. Functional MRI data gathered

Figure 2.1: The behavior of complex roots of characteristic equation related to power spectrum of resting-state dataset1: PACF values with (a) AR(2) model, and (b) AR(3) model; The locations of complex roots (c) AR(2) model, and (d) AR(3) model.

Figure 2.2: The behavior of complex roots of characteristic equation related to power spectrum of resting-state dataset2: PACF values with (a) AR(2) model, and (b) AR(3) model; The locations of complex roots (c) AR(2) model, and (d) AR(3) model.

Figure 2.3: The behavior of complex roots of characteristic equation related to power spectrum: PACF values with (a) AR(2) model for visual task data, and (b) AR(2) model for memory retrieval task data; The locations of complex roots (c) visual task data, and (d) memory retrieval task data.

from two different tasks - a memory retrieval task and a visual task - were used in the experiments.

For Priestley's $P(\omega)$ test, τ_1 value was chosen to be equal to number of scans in one cycle of stimulus, and τ_2 to be the total number of scans available minus number of scans in one cycle of stimulus. For CRF, the prior probability $\alpha_0 = 0.05$ was used for activated voxels as the usual range of activated voxels is 2 – 5% in real fMRI data. Small changes in α_0 do not affect the results notably. Values of β_0 , β_1 between 1 and 2 were empirically found to give optimal results for detection of activation from fMRI data. The results are compared with those obtained from the SPM method.

2.3.2.1 Synthetic Data

Two-dimensional synthetic fMRI datasets of 64×64 pixels per scan with 16 images per epoch and 2s interscan interval for both event-related and block-related data were generated. For event-related data, a stimulus cycle contained 4s of stimulations and 28s of rest time. And for the block-related data, a stimulus cycle contained 16s of stimulations and 16s of rest. FMRI time-series response of the activated pixels was obtained by convolving the stimulus with a hemodynamic response function $h(t)$ defined by a mixture of two gamma functions [95]:

$$h(t) = \frac{1}{\Gamma\left(\frac{\kappa_1}{\kappa_3}\right)} \left(\frac{\kappa_0}{\kappa_3}\right)^{\frac{\kappa_1}{\kappa_3}} w(t)^{\frac{\kappa_1}{\kappa_3}-1} e^{-\frac{\kappa_0}{\kappa_3}w(t)} - \frac{1}{\kappa_5 \Gamma\left(\frac{\kappa_2}{\kappa_4}\right)} \left(\frac{\kappa_0}{\kappa_4}\right)^{\frac{\kappa_2}{\kappa_4}} w(t)^{\frac{\kappa_2}{\kappa_4}-1} e^{-\frac{\kappa_0}{\kappa_4}w(t)} \quad (2.24)$$

where $\kappa_0 = 1/8s$, delay of response $\kappa_1 = 6s$, delay of undershoot $\kappa_2 = 16s$, dispersion of response $\kappa_3 = 1s$, dispersion of undershoot $\kappa_4 = 1s$, ratio of response to undershoot $\kappa_5 = 6$, the length of kernel $\kappa_6 = 32s$, $\Gamma(\cdot)$ represents the gamma function and $w(t) \in \{0, 1/\kappa_0, \dots, \kappa_6/\kappa_0\}$. A random variation of κ values, with standard deviation of 0.1κ , was used to simulate varying HRF conditions [2, 51]. In addition, synthetic datasets with canonical HRF were also generated and tested. The non-activated pixels were left unchanged at zero amplitude [122]. Spatially correlated Gaussian noise was added to all the brain pixels.

In order to test the robustness of the method, synthetic data was generated by assuming temporal correlation at different complexities. That is, by using AR models at various orders: $z(t) = \sum_{k=1}^K h_k z(t-k)$. That is, by assuming AR(1) models with $h_1 = 0.4$, AR(2) with $\{h_1, h_2\} = \{0.4, 0.4\}$, and AR(3) with $\{h_1, h_2, h_3\} = \{0.3, 0.3, 0.3\}$. Temporal correlation in noise also affects its variance and hence the signal to noise ratio (SNR) values.³ We have used the variance σ_z^2 instead of σ_ϵ^2 to calculate the SNR of signal affected with temporally correlated noise. The experiments were performed at two levels of signal-to-noise ratios, SNR = 0.9 and 1.2. The results of MSA were compared

³Let us consider the AR(2) model as given below:

$$z(t) = h_1 z(t-1) + h_2 z(t-2) + \epsilon(t) \quad (2.25)$$

where $\epsilon(t)$ represents the uncorrelated noise with zero mean and σ_ϵ^2 variance. Multiplying both sides of (2.25) with $z(t)$ and taking expectation values

$$\begin{aligned} E[z(t)z(t)] &= h_1 E[z(t-1)z(t)] + h_2 E[z(t-2)z(t)] + E[\epsilon(t)z(t)] \\ R(0) &= h_1 R(1) + h_2 R(2) + \sigma_\epsilon^2 \end{aligned} \quad (2.26)$$

Multiplying both sides of (2.25) with $z(t-1)$ and taking expectation values

$$\begin{aligned} E[z(t)z(t-1)] &= h_1 E[z(t-1)z(t-1)] + h_2 E[z(t-2)z(t-1)] + E[\epsilon(t)z(t-1)] \\ R(1) &= h_1 R(0) + h_2 R(1) \\ R(1) &= \frac{h_1}{1-h_2} R(0) \end{aligned} \quad (2.27)$$

Multiplying both sides of (2.25) with $z(t-2)$ and taking expectation values

$$\begin{aligned} E[z(t)z(t-2)] &= h_1 E[z(t-1)z(t-2)] + h_2 E[z(t-2)z(t-2)] + E[\epsilon(t)z(t-2)] \\ R(2) &= h_1 R(1) + h_2 R(0) \end{aligned}$$

Substituting value for $R(1)$ from (2.27)

$$R(2) = \frac{h_1^2}{1-h_2} R(0) + h_2 R(0) = \left[\frac{h_1^2}{1-h_2} + h_2 \right] R(0) \quad (2.28)$$

Substituting values for $R(1)$ and $R(2)$ from (2.27) and (2.28) in (2.26)

$$R(0) = \frac{h_1^2}{1-h_2} R(0) + h_2 \left[\frac{h_1^2}{1-h_2} + h_2 \right] R(0) + \sigma_\epsilon^2 \quad (2.29)$$

Since $R(0)$ is the variance of the autocorrelated noise, i.e., σ_z^2 , it can be written in terms of σ_ϵ^2 as shown below

$$\begin{aligned} \left[1 - \frac{h_1^2}{1-h_2} - h_2 \left[\frac{h_1^2}{1-h_2} + h_2 \right] \right] \sigma_z^2 &= \sigma_\epsilon^2 \\ \sigma_z^2 &= \sigma_\epsilon^2 / \left[1 - \frac{h_1^2}{1-h_2} - h_2 \left[\frac{h_1^2}{1-h_2} + h_2 \right] \right] \end{aligned} \quad (2.30)$$

with the SPM method which implements a GLM on fMRI time-series [95]. The ROC method was chosen for the performance and efficacy assessment of these two methods as it has been found to be useful in objective comparison of activation detection methods in fMRI [78, 107, 122, 123]. The ROC curves were plotted by varying the threshold probability value for detecting activation. In these curves, *sensitivity* = $(\text{true positives} / (\text{true positives} + \text{false negatives}))$ and *specificity* = $(\text{true negatives} / (\text{true negatives} + \text{false positives}))$. The ROC results are shown in Figures 2.4-2.6 and the area under ROC curve values are given in Tables 2.1-2.6.

In reference to the block-based data results, as seen in Figure 2.4, the MSA method performed better compared to the GLM method for both the SNR=0.9 and SNR=1.2 and also for both AR(1) and AR(2) temporal autocorrelations. Block-based datasets were generated with the canonical HRF and as the results for MSA were found to be better than GLM even for canonical HRF, HRF with deviation was not tested in this case. Canonical HRF is generated with the standard values of κ parameters of HRF [95], whereas HRF with deviation uses random variation of κ values, with standard deviation of 0.1κ to simulate varying HRF conditions [2, 51]. As is clear from the accompanying area under the ROC curve (AUC) values, as shown in Tables 2.1 and 2.2, margin of improvement increases slightly with the decrease in SNR value. These margin values are: 0.39 (SNR=1.2) and 0.58 (SNR=0.9) for AR(1) data and 0.65 (SNR=1.2) and 0.74 (SNR=0.9) for AR(2) data. The AUC values for AR(1) data are 99.99 and 99.60 for SNR=1.2, for MSA and GLM respectively. Corresponding AUC values for SNR=0.9 are 99.98 and 99.40. The margin of improvement also increases with the increase in order of temporal autocorrelation. As shown in these tables, for AR(2) data with SNR=1.2, AUC values are 99.98 and 99.33 for MSA and GLM respectively. Corresponding AUC values for SNR=0.9 are 99.60 and 98.86. The margin of improvement in AUC value increases from 0.39 to 0.65 in going from AR(1) to AR(2) temporal autocorrelation for SNR=1.2 and it increases from 0.58 to 0.74 for SNR=0.9.

In the case of event-related data, datasets were generated for three orders of temporal autocorrelation, i.e., AR(1), AR(2) and AR(3) for both SNR=1.2 and SNR=0.9. Also the datasets were generated for both the canonical HRF as well as HRF with deviation. The ROC results for all these datasets are shown in Figures 2.5-2.6 and the area under ROC curve values are given in Tables 2.3-2.6. These tables also list the values for area under the ROC curves in the specificity range of 0.95 to 1.00 [123], as it was observed in case of MSA method that the greater improvement is generally in region of the curve which has higher sensitivity (lower false positive) and also higher specificity (lower false negative results). In the case of SNR=1.2, the MSA method shows significantly better results as compared to the GLM method for the HRF with deviation, whereas for canonical HRF results are only slightly better (mainly in the specificity range of 0.95 to 1.00). In the case of SNR=1.2, with canonical HRF, AUC values in specificity range of 0.95-1.00 are 94.71 and 97.79 for AR(1) data, 93.71 and 95.68 for AR(2) data, 93.73 and 96.17 for AR(3) data, for GLM and MSA method respectively. In the case of SNR=0.9, the MSA method shows significantly better results as compared to the GLM method for the HRF with deviation, whereas for canonical HRF results are similar for AR(2) data and only marginally lower for AR(3) data. In the case of SNR=0.9, with canonical HRF, AUC values in specificity range of 0.95-1.00 are 91.57 and 95.48 for AR(1) data, 89.52 and 89.87 for AR(2) data, 87.95 and 84.57 for AR(3) data, for GLM and MSA method respectively. The GLM method does have an advantage in the case of datasets generated with canonical HRF because the same HRF is also assumed when the analysis is performed, whereas in the case of MSA method this advantage is missing. Still in most of the cases with canonical HRF, MSA performs marginally better than the GLM method, especially in the specificity range of 0.95 to 1.00. In the case of datasets generated with HRF with deviation, results for both SNR values and all three temporal autocorrelation orders (AR(1), AR(2) and AR(3)) were better for MSA method as compared to the GLM method. In the case of SNR=1.2, HRF with deviation, AUC values for full ROC

Table 2.1: The AUC Values for ROC Curves Comparing MSA and GLM Results: Block-based Data (SNR=1.2)

AR Model	GLM	MSA
AR(1)	99.60	99.99
AR(2)	99.33	99.98

curves are 99.16 and 99.98 for AR(1) data, 99.12 and 99.97 for AR(2) data, 99.27 and 99.68 for AR(3) data, for GLM and MSA method respectively. In the case of SNR=0.9, HRF with deviation, AUC values for full ROC curves are 98.73 and 99.87 for AR(1) data, 98.07 and 99.28 for AR(2) data, 98.32 and 99.16 for AR(3) data, for GLM and MSA method respectively. The AUC values in specificity range of 0.95 to 1.00 for these datasets also show a similar trend, i.e., better values for MSA method as compared to the GLM method. Figure 2.7, shows the activation detection results for AR(1) and AR(2) datasets, for MSA method (with and without CRF), and also the corresponding results of GLM method. The true image is also shown for comparison. As can be seen from these images, small areas of activation and boundaries are in general less accurately detected in the case of GLM method.

Simulations were carried out to test the MSA method for varying number of time-points. As seen in Figure 2.8a, the results were found to be similar to SPM results for up to 10 cycles of stimulus but beyond this, the results of MSA method improved considerably over the SPM results. In other words, the present approach requires a less number of time points compared to time-domain techniques to achieve higher accuracies. The present method also handles jittered event-related data. In order to show the capability of MSA method in handling jittered event-related data, such data was simulated and analyzed. The method could handle data with random jitter of up to ± 2 scan intervals, as shown in Figures 2.9a and 2.9b.

(a)

(b)

Figure 2.4: Detection of activation by using MSA and GLM (SPM) methods on synthetic data: block-based experiment data with AR(1) and AR(2) temporal autocorrelations with (a) SNR=0.9 and (b) SNR=1.2

Table 2.2: The AUC Values for ROC Curves Comparing MSA and GLM: Block-based Data (SNR=0.9)

AR Model	GLM	MSA
AR(1)	99.40	99.98
AR(2)	98.86	99.60

(a)

(b)

Figure 2.5: Detection of activation by using MSA and GLM (SPM) methods on synthetic data: event-related experiment data with AR(1), AR(2) and AR(3) temporal autocorrelations with SNR=0.9 and using (a) canonical HRF (b) HRF with deviation

Table 2.3: The AUC Values for ROC Curves Comparing MSA and GLM Results: Event-related Data (SNR=1.2, Canonical HRF)

AR Model	GLM (Full curve)	MSA (Full Curve)	GLM (Partial Curve with Specificity Range: 0.95-1.00)	MSA (Partial Curve with Specificity Range: 0.95-1.00)
AR(1)	99.71	99.96	94.71	97.79
AR(2)	99.30	99.54	93.71	95.68
AR(3)	99.67	99.48	93.73	96.17

(a)

(b)

Figure 2.6: Detection of activation by using MSA and GLM (SPM) methods on synthetic data: event-related experiment data with AR(1), AR(2) and AR(3) temporal autocorrelations with SNR=1.2 and using (a) canonical HRF (b) HRF with deviation

Table 2.4: The AUC Values for ROC Curves Comparing MSA and GLM Results: Event-related Data (SNR=1.2, HRF with deviation)

AR Model	GLM (Full curve)	MSA (Full Curve)	GLM (Partial Curve with Specificity Range: 0.95-1.00)	MSA (Partial Curve with Specificity Range: 0.95-1.00)
AR(1)	99.16	99.98	85.67	99.33
AR(2)	99.12	99.97	88.20	99.09
AR(3)	99.27	99.68	88.33	97.80

Figure 2.7: Illustration of detected activation on synthetic event-related data at SNR=1.2: Results on data with temporal autocorrelation AR(1) model with $h_1 = 0.4$ by MSA results (a) before and (b) after application of CRF, and (c) by GLM (SPM) method; Results on data with temporal auto-correlation AR(2) model with $\{h_1, h_2\} = \{0.4, 0.4\}$ (d) by MSA method and (e) by GLM (SPM) method; and (f) the ground truth of data.

Table 2.5: The AUC Values for ROC Curves Comparing MSA and GLM Results: Event-related Data (SNR=0.9, Canonical HRF)

AR Model	GLM (Full curve)	MSA (Full Curve)	GLM (Partial Curve with Specificity Range: 0.95-1.00)	MSA (Partial Curve with Specificity Range: 0.95-1.00)
AR(1)	99.40	99.72	91.57	95.48
AR(2)	99.30	98.14	89.52	89.87
AR(3)	99.05	97.48	87.95	84.57

Table 2.6: The AUC Values for ROC Curves Comparing MSA and GLM Results: Event-related Data (SNR=0.9, HRF with deviation)

AR Model	GLM (Full curve)	MSA (Full Curve)	GLM (Partial Curve with Specificity Range: 0.95-1.00)	MSA (Partial Curve with Specificity Range: 0.95-1.00)
AR(1)	98.73	99.87	83.71	97.37
AR(2)	98.07	99.28	78.32	93.70
AR(3)	98.32	99.16	80.77	91.64

(a)

(b)

Figure 2.8: Effects on the number of time points on detecting activation in event-related experiments. ROC curves for (a) varying number of cycles and (b) non-integral number of cycles. One cycle is equivalent to 16 samples.

(a)

(b)

Figure 2.9: The performance of MSA algorithm on jittered event-related data: (a) illustration of time courses of jittered stimuli, and (b) ROC curves indicating the performance on jittered data (± 2 scans).

2.3.2.2 Visual Task Data

This fMRI data was obtained on a 3.0 Tesla Medspec 30/100 scanner (Bruker Medizintechnik GmbH, Ettlingen, Germany) at the MRI Centre of the Max-Planck-Institute of Cognitive Neuroscience. A visual-stimulation experiment using fast low angle shot (FLASH) protocol was carried out to obtain these images (TR=80.5ms; echo time (TE)=40ms; matrix=128×128; spatial resolution=1.953mm×1.953mm; slice thickness=7mm). Each slice in this FLASH dataset was obtained separately by repeated application of the stimulation. The ON and OFF stimuli were presented at a rate of 5.16s per sample. Each stimulation period had four successive stimulated ON scans followed by four rest scans or OFF scans. There were eight cycles of stimulation and total time for experiment was 5.5min. For more details of this experiment, the reader is referred to [87].

Figure 2.10 shows the detected activation on two representative brain slices by using the MSA and SPM methods. Both methods detected activation in the expected cortical areas of visual cortex [87]. Visually, more focal activations in the cortical regions were detected by the MSA method than those detected by the SPM method.

2.3.2.3 Memory Retrieval Task Data

In a memory retrieval task, subjects learned three different sets (sizes 4, 6, and 8) of letters prior to the actual experiment with a corresponding cue for each set. During each trial of the experiment, a cue for the set and a letter were presented visually and the subject decided whether the letter corresponds to the indicated set. A delay of 2.0s was maintained between the presentation of the cue and the probe. Fourteen slices were acquired with 19.2cm field of view (FOV), 7mm thickness, and 64×64 matrix using single shot gradient echo-planar imaging (EPI) sequences (TE = 46ms and TR = 1700ms). Ten cycles of data were used for analysis. Details of the experiment are available in [88].

Brain processes involved in this memory retrieval task experiment are: encoding of the cue and probe, retrieval of information from the secondary memory, scanning of the

Figure 2.10: The detected activation of visual task for representative two brain slices by using the (a) GLM (SPM) technique (b) MSA method

primary memory, selection and execution of response [88, 89]. Brain activation was detected using the MSA and SPM methods [95]. Figure 2.11 shows activation detected on three representative slices by the two methods. The cue and the probe both generated activation in the brain at same frequency but with an interval of 2.0s apart. The temporal differences in stimulus presentation appear as differences of the phases in frequency domain. In the MSA method, brain regions corresponding to the probe and cue were thus separated based on the phase of autocorrelation function of voxel time-series. In SPM method, activations corresponding to cue and probe were found by properly designing the design matrix, separately taking into account the cue and the probe stimuli.

Both the methods detected activation in the expected cortical areas of inferior precentral sulcus (pCS) and posterior middle frontal gyrus (MFG) following cue and in regions of posterior parietal cortex following the probe [81, 88, 89]. Inferior pCS and posterior MFG are generally involved in the retrieval of information from secondary memory and also in

maintaining this information for search following the presentation of the cue, hence are also activated during the probe. The activation patterns detected by the non-parametric MSA method were quite similar to those detected by the SPM method.

2.4 Additional Applications of MSA and Random Field in fMRI

2.4.1 Detection of Physiological Signal Frequency Components using MSA

Priestley's $P(\omega)$ test as described above, can be used along with the knowledge of localization of physiological signal in the brain slices, to detect the physiological signal related frequencies. Cardiac pulsation generally is associated with a number of effects in the brain that includes the blood vessel pulsation, CSF movement and tissue deformation. Specific brain areas, such as those near to the major blood vessels are strongly influenced by these effects. These include regions along vertebrobasilar arterial system near the medial areas of the brain, along middle cerebral artery near the anterior temporal lobes and the insula and those along the anterior cerebral artery in the anterior interhemisphere fissure in the medial frontal lobes [26]. These areas have been found to contain the cardiac pulsation related artifacts, consistently among a number of subjects. Hence in our proposed method, we restrict our analysis to the brain slices that contain the carotid artery, middle cerebral artery (main trunk and branch), posterior cerebral artery and circle of Willis structure as shown in Figure 2.12. In earlier studies, regions that had been selected for such analysis were the brainstem and the ventricles [80], but we found that the physiological signals near the major arteries that we have selected for analysis are much more consistent and stronger. Also as per [26], the effect of physiological signals near the major arteries is supposed to be stronger, whereas those near to the CSF pools and the third and fourth ventricle is likely to be smaller.

We use Priestley's method in two ways for detecting physiological signals. In the first case, sICA is used to find time-series related to the target brain locations and Priestley's

Figure 2.11: The detected activation of memory task (a) GLM (SPM) results for cue (b) GLM (SPM) results for probe (c) MSA results for cue and (d) MSA results for probe

Figure 2.12: Brain slice with area of interest (white ellipse) for detection of physiological signals

$P(\omega)$ test is used to analyze these time-series. In the second case, all the voxel time-series in the chosen brain slices are directly analyzed using Priestley's $P(\omega)$ test, for significant frequency components. We also tested the earlier reported methods that work based on analyzing the signal in particular cortical areas such as ventricles to get pure physiological signals [80] and the methods that are based on reorganization of the time samples from CSF of various brain slices to get unaliased physiological signals from fMRI data with $TR \sim 2s$ [106], but the results of these methods were not consistent.

ICA is able to solve the blind source separation (BSS) problem, by separating the underlying sources in a signal that are mutually independent from their linear mixtures. Spatial ICA decomposes the fMRI data into a linear combination of independent spatial maps and their corresponding time courses as shown below⁴. From this complete set of independent spatial components, components present in the target brain areas as shown in Figure 2.12 are selected. The time courses corresponding to these selected spatial

⁴Consider fMRI data, $\mathcal{F} : \Omega \times \mathcal{T} \rightarrow \mathbb{Q}$, which can be decomposed in sICA as:

$$\mathcal{F} = MC \tag{2.31}$$

where $C = [c_1 c_2 \dots c_k]^T$ denotes the matrix of size $\Omega \times k$ of spatially independent sources and $M = [m_1 m_2 \dots m_k]$ denotes the mixing matrix of size $k \times T$ for corresponding time courses. We have used the FMRLAB software to perform sICA for our data [93].

components are then analyzed using the Priestley's $P(\omega)$ test to detect the prominent frequencies and these frequencies are the one that are likely associated with the physiological signals.

Memory Retrieval Task Data 1: Three independent components related to the physiological signals were selected visually, as shown in Figure 2.13, based on the knowledge of the location in the brain of strong physiological signals [26]. All the three components showed prominent presence in the main trunk of middle cerebral artery, component 1 (Figure 2.13a) is also significant in the branch of middle cerebral artery and component 3 (Figure 2.13c) in posterior cerebral artery. Based on the $P(\omega)$ test for component 1, frequency 0.1176Hz was found to be significant with a p -value of 0.03 as shown in Figure 2.13a. For component 2, the frequency 0.2092Hz was found to be significant with p -value of 0.07 as shown in Figure 2.13b. For component 3, the frequency 0.1176Hz was found to be significant with a p -value of 0.01 as shown in Figure 2.13c. Among all the components lowest p -value for 0.1176Hz was 0.01 and the best p -value for 0.2092Hz was 0.07.

Priestley's $P(\omega)$ test was also applied directly on the voxel time-series of an inferior brain slices, as shown in Figure 2.14, which are likely to have significant physiological signals [26]. All the significant frequencies (p -values<0.05) were recorded in each voxel time-series. Quite a large number of voxels had no significant frequencies at all and some of the voxels had more than one prominent frequency. The histogram results showing the various frequency components that are prominent in these brain slices is as shown in Figure 2.14. Stimulus related frequencies and their harmonics are removed to show the other frequency components clearly. The most prominent frequency (significant frequencies present in most number of voxels) corresponds to 0.1176Hz.

Memory Retrieval Task Data 2: Another dataset belonging to the same experiment was also tested. Three components from spatial ICA were selected, based on their localization, to be related to the physiological signals. All the three components showed

Figure 2.13: Spatial ICA components related to physiological parameters: (a),(c) and (e) show location of these components on structural scans (b),(d) and (f) show temporal variations of these components (top) and Priestley's $P(\omega)$ test results (bottom) - Dashed lines indicate stimulus signal harmonic locations

Figure 2.14: Memory dataset 1 results: Significant frequency components in the inferior brain slices. Dashed lines show the location of stimulus frequency and its harmonics

prominent presence in the main trunk of middle cerebral artery, branch of middle cerebral artery and posterior cerebral artery. Based on the $P(\omega)$ test for component 1, frequency 0.2876Hz was found to be significant with a p -value of 0.01 as shown in Figure 2.15a. For component 2, the frequency 0.0915Hz was found to be significant with p -value of 0.06 as shown in Figure 2.15b. For component 3, the frequency 0.2876 Hz was found to be significant with a p -value of 0.04 and frequencies 0.0915Hz and 0.2941Hz with a p -value of 0.05 as shown in Figure 2.15c. Among all the components best p -value for 0.2876Hz was 0.01, for 0.0915Hz was 0.04 and for 0.2941Hz was 0.05.

Priestley's $P(\omega)$ test was again applied directly on the voxel time-series of an inferior brain slices, as shown in Figure 2.16, which are likely to have significant physiological signals [26]. The histogram results showing the various frequency components that are prominent in these brain slices is as shown in Figure 2.16. Stimulus related frequencies and their harmonics are removed to show the other frequency components clearly. The most prominent frequency (significant frequencies present in most number of voxels)

Figure 2.15: Spatial ICA components related to physiological parameters: (a),(c) and (e) show location of these components on structural scans (b),(d) and (f) show temporal variations of these components (top) and Priestley's $P(\omega)$ test results (bottom) - Dashed lines indicate stimulus signal harmonic locations

Figure 2.16: Memory dataset 2 results: Significant frequency components in the inferior brain slices (as shown above the histogram). Dashed lines show the location of stimulus frequency and its harmonics

corresponds to 0.2876Hz. Other prominent frequencies are 0.0915Hz and 0.2941Hz.

In both the datasets, the results of direct application of Priestley's $P(\omega)$ test in detecting physiological signal components were found to be similar to those involving more complex spatial ICA method.

2.4.2 Efficient Regularization of AR(1) Values using Random Field

Earlier in this chapter we have proposed Priestley's method as a model-free approach to remove the effect of temporal autocorrelation while detecting activated voxels. Among the proponents of model-based pre-whitening methods, there is a disagreement which we feel that we can resolve with the application of random field analysis method. This disagreement is about the regularization of voxel based sample autocorrelation coefficient values. As mentioned earlier, a number of researchers have proposed to spatially smooth these autocorrelation coefficient value estimates, with a spatial smoothing filter,

to reduce their variance before using them in an REML process to perform prewhitening [42, 112]. On the other hand, some researchers have found that smoothing these voxel based autocorrelation coefficient value estimates with spatial smoothing filters prevents the proper modeling for voxels that have negatively correlated residuals (with negative correlation coefficient value) and for voxels that have approximately white spectra residuals (with nearly zero correlation coefficient value), when they are bordered with voxels having positively correlated residuals (with positive correlation coefficient value) [62]. In our method, we propose to use random field analysis based regularization, with a modified CRF, rather than a smoothing filter. It provides the necessary reduction in variance of AR(1) coefficients by taking into account the neighborhood voxel autocorrelation estimates and at the same time preserves the borders between the voxels having positive, negative and white spectral residuals. Shown below is the application of our proposed method on AR(1) model values and it can easily be expanded to regularize values for any model other than AR(1) also.

Let $\tilde{h}_{1i}$ be the calculated (and noisy) AR(1) coefficient and h_{1i} be the actual (and unknown) AR(1) coefficient values for a voxel i , i.e.,

$$\tilde{h}_{1i} = h_{1i} + \epsilon_i(t) \quad (2.32)$$

where, ϵ_i , is considered to be the Gaussian random noise. The energy function, $V(h_1/\tilde{h}_1)$, for fMRI data can then be defined by the quadratic likelihood value and a neighborhood interaction prior as shown below:

$$V(h_1/\tilde{h}_1) = \sum_i (h_{1i} - \tilde{h}_{1i})^2 + \sum_{j \in \mathcal{N}_i} \lambda_j (h_{1j} - h_{1i})^2 \quad (2.33)$$

where, $\mathcal{N}_i$, represents the neighborhood of voxel i , and coefficient λ_j is available to control the tradeoff between the data fitting and neighborhood site interaction. In order to find the optimal values for h_1 , we need to minimize the energy $V(h_1/\tilde{h}_1)$ (and thereby

maximize the log posterior $p(h_1/\tilde{h}_1)$. Hence, we can take the derivative of the $V(h_1/\tilde{h}_1)$ with respect to h_{1i} and equate it to zero, and it provides us:

$$2(h_{1i} - \tilde{h}_{1i}) - 2 \sum_{j \in \mathcal{N}_i} \lambda_j (h_{1j} - h_{1i}) = 0 \quad (2.34)$$

$$h_{1i}(1 + \sum_{j \in \mathcal{N}_i} \lambda_j) = \tilde{h}_{1i} + \sum_{j \in \mathcal{N}_i} \lambda_j h_{1j} \quad (2.35)$$

$$h_{1i} = \frac{1}{1 + \sum_{j \in \mathcal{N}_i} \lambda_j} (\tilde{h}_{1i} + \sum_{j \in \mathcal{N}_i} \lambda_j h_{1j}) \quad (2.36)$$

This equation (2.37) is then used in an iterative manner to update the h_{1i} values, until the h_{1i} values stabilize and there is not much change in the subsequent updated values.

$$h_{1i}^{t+1} = \frac{1}{1 + \sum_{j \in \mathcal{N}_i} \lambda_j} (\tilde{h}_{1i} + \sum_{j \in \mathcal{N}_i} \lambda_j h_{1j}^t) \quad (2.37)$$

In case same fixed value is used for λ_j for the whole image, i.e., $\lambda_j = \lambda, \forall j$, results will be similar to the smoothing filter and the boundaries will not be protected, hence we propose to use the λ_j values based on the $\tilde{h}_{1j}$ and $\tilde{h}_{1i}$ values. We propose and have tested the following two modes, named as *simple delta* and *complex delta* respectively, of calculating λ_j :

$$\lambda_j = 1 - \text{abs}(\tilde{h}_{1i} - \tilde{h}_{1j}) \quad (2.38)$$

$$\lambda_j = 1 - \left\{ \frac{(\tilde{h}_{1i} - \tilde{h}_{1j})^2}{0.25 + 10(\tilde{h}_{1i} - \tilde{h}_{1j})^2} \right\} \quad (2.39)$$

The fixed values in the second model (complex delta model) for λ_j , were set empirically, based on the autocorrelation coefficient values generally found in the fMRI data.

In order to test the proposed random field analysis method, synthetic images were generated images with fixed AR(1) values, as shown in Figure 2.17e, where white corresponds to AR(1) value of 0.4 and black corresponds to value zero. Gaussian random noise was then introduced in these AR(1) values, as shown in Figure 2.17a. The AR(1) value image was then smoothened as advocated by present methods and was also processed (without smoothing) using modified CRF as per our proposed method. As is clear from Figure 2.17, the AR(1) values are preserved better in the case of the proposed method. We further analyze these images and as shown in Figure 2.18, smoothing results in increase in number of voxels with low deviation, but at the same time it also results in a slight increase in the number of voxels that have deviation higher than 0.15. In the case of the proposed method, although the number of voxels with very low deviation (around 0.0) does not go as high as in the case of smoothing, but the number of voxels with high deviation (around 0.15) are much lower as compared to smoothing. Effectively, smoothing results in a dual peak in the deviation histogram, increasing both very low and very high deviations, whereas random field analysis results in shifting the histogram towards zero deviation. As shown in Figure 2.19, the outlier values following smoothing have reduced as compared to the noisy data, but the random field based method is more effective in reducing the outlier values. Results of application of this method on actual fMRI data, memory related task data, are as shown in Figure 2.20. As can be seen clearly, the autocorrelation coefficient values in the frontal cortex of the right most brain slice are reduced significantly in the case of smoothing, but not by the proposed method.

2.5 Discussion

In this chapter, we presented the MSA method for fMRI data analysis and its use in handling temporal autocorrelation. The fMRI time-series was modeled with a mixed spectrum: a component having a discrete spectrum relating to task-related stimuli and a component having a continuous spectrum comprising of temporal autocorrelation. With

Figure 2.17: AR(1) Values (a) Noisy (b) After smoothing (c) After CRF processing (Using simple delta function) (d) After CRF processing (Using complex delta function) (e) True image (White=0.4 and Black=0.0)

Figure 2.18: Histogram of absolute deviation of AR(1) Values from the nominal values
 (a) Noisy (b) After smoothing (c) After CRF processing (Using simple delta function)
 (d) After CRF processing (Using complex delta function)

Figure 2.19: Boxplot of absolute deviation of AR(1) Values from the nominal values for noisy data, after smoothing, after CRF processing (Using simple delta function) and after CRF processing (Using complex delta function)

Figure 2.20: Memory task related fMRI data: AR(1) autocorrelation coefficients (a) Noisy (b) After smoothing (c) After CRF processing (Using simple delta function) (d) After CRF processing (Using complex delta function)

this model, the Priestley’s test was used to find the significant harmonics present in the fMRI voxel time-series and predict the likelihood of activation at a particular brain voxel. As shown, Priestley’s test can be successfully used for detection of significant frequencies in the spectrum of fMRI data. On testing the applicability of Priestley’s test for fMRI data, the complex roots of the characteristic equation related to fMRI time-series fitted with an AR model, were found to be well within the unit circle, both for two sets of resting-state data and two sets of task-related data. Presence of roots near the unit circle results in processes being nearly non-stationary and is harder to be distinguished from non-stationary processes having roots on the unit circle.

Spatial correlation among the likelihood of activated brain voxels was modeled with a CRF. Compared to Gaussian random fields [95] and MRF [78, 89], CRF accounts for data-dependent nature of neighborhood interactions of activations and significantly improves the detection of activation [107].

An advantage of MSA method is that it is not necessary to assume an *a priori* model of temporal autocorrelation or any form of hemodynamic response function. The method handles the autocorrelation in a unique way by separating it from the discrete spectra related to input stimuli. In the experiments with synthetic data, the MSA method performed better in particular for temporally correlated event-related data with higher order correlation compared to the SPM method. It is expected if the structure of the correlation is different from AR, i.e., MA or ARMA, the proposed method is likely to perform better than the existing techniques [84]. In a similar manner, the method could remove slow varying artifacts and noise.

This method was tested on the periodic block-based and periodic/jittered event-related data. In the experiments, it handled jittered data up to $\pm 12.5\%$ of the cycle. The method could be extended for aperiodic stimuli by first taking the smallest interval between two successive events and then using the trend analysis to reduce all the other time-intervals in between the other successive events to this smallest time-interval, thus

rendering the data to be periodic. This approach is also robust to the spatially varying temporal autocorrelation order within the brain. Another advantage of this approach is that it can detect voxels that are activated at a frequency different from stimulus frequency e.g. at twice the stimulus frequency. With real fMRI data gathered from a memory-related task and a visual task, the results from the MSA method were visually similar to SPM method; and the activations were more focal and localized to the cortical areas. In the cases, where the trial length is not an integral number of the stimulus cycles, the spectral amplitude will be spilled over to the adjacent frequency components. In such a case, we discard the samples that are over and above the integral number of cycles. However, this will not result in significant dilution of base frequency and loss of signal as shown by simulation results in Figure 2.8b. Other alternative to avoid the spill over is by padding the series with zeroes to make up the length of complete periodic design [69].

We also applied the approach based on Priestley's $P(\omega)$ test to detect default-mode networks in resting-state datasets, results of which are included in Chapter 4 with other resting state data methods. Another extension of this approach was to detect the physiological signal related frequency components in brain data and results are compared with the spatial ICA based technique. The main advantage of the proposed method over spatial ICA is it does not require going through all the independent components to select the relevant ones. We also successfully applied the random field analysis method in efficient regularization of sample autocorrelation values in model based prewhitening cases.

Chapter 3

Higher Harmonic Analysis of Event-related Data

In event-related experiments, the stimulus condition exists only for a very short duration within a cycle in comparison to block-based experiments, which is generally represented by a single stimulus. Event-related designs are particularly useful for experiments studying the transient phenomenon triggered by cognitive and sensory stimuli. This includes experiments related to memory, for example, where we need to explore the incidents of remembering and forgetting. Event-related designs have also been found to be useful in investigating the dynamics and time-courses of neural activity.

Since the stimulus exists for a short time in event-related experiments, the spectral energy of brain activation is distributed substantially to the higher harmonics of the stimulus frequency. At the same time, as the harmonics get high, they are more likely to be affected by the noise and they are also attenuated by the brain's hemodynamic response, which acts as a low-pass filter. Thus selecting and using appropriate number of harmonics in activation detection is a challenge. Frequency-domain methods that consider only the energy embedded in fundamental frequency of stimulus, have been used successfully for fMRI analysis mainly for block-based data. But in the case of event-related data, consideration of only the spectral energy in fundamental frequency and ignoring the spectral energy in higher harmonics, leads to deterioration in activation detection results. The analysis of event-related data is further complicated by the variation in shape and

amplitude of hemodynamic responses across different cortical regions [122]. Frequency-domain methods are found to perform comparatively or better than the other techniques [16, 69, 111] when the HRF and/or the stimulus timings are not exactly specified.

In this chapter, we intend to use the spectral energy present in higher harmonics of stimulus frequency in order to improve activation detection in event-related fMRI data. The main difference between frequency contents of block-based data and event-related data in frequency-domain is highlighted.

3.1 Motivation and Contributions

The spectral energy of brain activation is distributed substantially to higher harmonics of stimulus-frequency in event-related fMRI because activation is restricted to only a small part of the stimulus cycle. Frequency-domain methods that consider only the spectral energy embedded in the fundamental frequency are efficient in detecting activation in block-based data but are not very effective in the case of event-related data. We are thus motivated to work on methods that use the energy present in higher harmonics to enhance activation detection in event-related data.

Therefore, we present frequency-domain techniques for event-related fMRI data analysis, which take into account the energy distributed to higher harmonics of the stimulus frequency. The two proposed methods are χ^2 random field [111, 117] of higher harmonics (CHH) method and Hartley's F -test [97] of significant harmonics (HSH) method. The χ^2 random field analysis has been used previously for periodic block-based fMRI data analysis [111, 117]. Since in the case of block-based data nearly all of the activation related information is contained in the fundamental frequency, the basic χ^2 random field analysis method using only the fundamental frequency is sufficient. However, this basic approach is not efficient for event-related data as substantial amount of information contained in higher harmonics remains unutilized. We thus modify this technique to include higher

harmonics, thereby generating and analyzing χ^2 random field with higher degrees of freedom as compared to the method using the fundamental frequency components only for analysis. In HSH technique, we automatically determine the optimal number of harmonic components, which distinguishes activated brain voxels from the others. In this method, we iteratively include higher harmonics and perform Hartley's F -test to identify the appropriate number of harmonics for each voxel time-series. We then generate a statistical parametric map based on the final Hartley's F -test values. The contextual information of brain activation is accounted by a conditional random field [107]. Results of these two methods are compared with the GLM (SPM) technique.

Finally, in order to determine the spatial spread of activation in the event-related designs, we present the scale-space χ^2 random field of higher harmonics (SCH) method that uses higher harmonics of stimulus frequency in its analysis. Results of this method are compared with the wavelet technique.

This chapter is organized as follows: In the next section, we represent the fMRI signal in frequency domain and present our methods using higher harmonics. In the Results section, we present the results of application of our proposed methods on synthetic as well as actual fMRI data. We end this chapter with a discussion on our results.

3.2 Models and Methods

3.2.1 Frequency-Domain Representation of fMRI Data

Let n denote the number of stimulus cycles in the experiment, and T be the total number of scans. Changes in BOLD signal define the hemodynamic response at a brain voxel, measured by the fMRI experiment. Let the stimulus induced signal $x_i(t)$ at voxel $i \in \Omega$ be given by the convolution of the stimulus signal $s(t)$ and hemodynamic response $h_i(t)$, $d_i(t)$ be the drift signal and $z_i(t)$ be the correlated noise. The signal $y_i(t)$ at a voxel i is given by:

$$y_i(t) = x_i(t) + z_i(t) + d_i(t) \quad (3.1)$$

$$x_i(t) = s(t) * h_i(t) \quad (3.2)$$

By taking the Fourier transform of (3.2):

$$X_i(\omega) = \mathcal{S}(\omega)H_i(\omega) \quad (3.3)$$

where $X_i(\omega)$, $\mathcal{S}(\omega)$ and $H_i(\omega)$ represent the frequency-domain signals of $x_i(t)$, $s(t)$ and $h_i(t)$, respectively. The above equation suggests that experimentally induced signals convolve with the HRF only for activated voxels as there is no hemodynamic response at non-activated voxels. The hemodynamic response at activated voxels acts as a low-pass filter having a cut-off frequency near to 0.2Hz [37]. The physiological signal frequencies and drift signal $d_i(t)$ are removed from voxel time-series as a part of preprocessing.

3.2.2 Harmonic Analysis of fMRI Data

Consider a periodic stimulus signal $s(t)$ composed of a rectangular pulse train having a duration of T_p of activation in a cycle of period T_c . The k th harmonic $\mathcal{R}_k$ of the signal is given by

$$\mathcal{R}_k = \frac{2A}{k\pi} \left| \sin\left(k\pi \frac{T_p}{T_c}\right) \right| \quad (3.4)$$

where A is the amplitude of the pulse train. And, the ratio between the energies of k and l th harmonics is given by

$$\frac{\mathcal{R}_k^2}{\mathcal{R}_l^2} = \frac{l^2}{k^2} \left| \frac{\sin\left(k\pi \frac{T_p}{T_c}\right)}{\sin\left(l\pi \frac{T_p}{T_c}\right)} \right|^2 \quad (3.5)$$

For block-designed data, often $T_p = T_c/2$ and therefore, the amplitudes of even harmonics are zero. The ratio of amplitude of the third harmonic to the first harmonic is 0.33 and the ratio of the fifth to the first harmonic is 0.2. That is, $\mathcal{S}(\omega)$ and therefore

Figure 3.1: The energy contained in up to the sixth harmonic, relative to the first harmonic of event-related stimulus. T_p is the activation and T_c the period of the stimulus cycle.

$X_i(\omega)$ of activated voxels will have the most of the signal energy concentrated in the first harmonic of the stimulus, followed by a small amount of energy in the third harmonic.

For event-related data, $T_p \ll T_c/2$ and the energy of higher harmonics becomes significant. Figure 3.1 shows that the relative energies of higher harmonics to the first harmonic vary with the width of stimulus relative to the period. For event-related data, as the size of the stimulated segment becomes smaller compared to the period of the stimulus cycle, the relative energy of the higher harmonics increases. Hence, it is necessary to use higher harmonics for the detection of brain activation in event-related data. However, since the hemodynamic response function $H(\omega)$ is a low-pass filter with a cut-off frequency near to 0.2Hz [37], the measured fMRI response at the activated voxels will have energy distributed only up to that frequency range.

3.2.3 χ^2 Random Field of Higher Harmonics

χ^2 random fields have been used for analysis of fMRI data [111, 117]. However, application has been mainly concentrated on block-based design. In this chapter, we propose this technique for the analysis of event-related fMRI data. The novelty of the proposed

method is the use of higher-order harmonics of fundamental frequency in a χ^2 random field setup for the analysis of event-related data. The higher harmonics of fundamental frequency have significant magnitude in periodic event-related data, warranting their use in combination with the fundamental frequency for a χ^2 random field analysis. The resultant χ^2 random field has higher degrees of freedom as compared to the one using the fundamental frequency components only.

The fMRI signal is fitted in a regression equation at stimulus frequency and its higher harmonics.

$$y_i(t) = \sum_p (A_{ip} \cos \omega_p t + B_{ip} \sin \omega_p t) + \epsilon_i(t) \quad (3.6)$$

where ω_p represents p th harmonic of fundamental frequency of the stimulus ω_1 ; A_{ip} and B_{ip} are the Fourier coefficients of p th harmonic at voxel i . The least square solution of this equation gives the estimates of the coefficients:

$$A_{ip}(\omega_p) = \frac{2}{T} \sum_{t=1}^T y_i(t) \cos \omega_p t \quad (3.7)$$

$$B_{ip}(\omega_p) = \frac{2}{T} \sum_{t=1}^T y_i(t) \sin \omega_p t \quad (3.8)$$

The temporal variance of voxel time-series is calculated as

$$\sigma_i^2 = \frac{1}{T - 2p - 1} \sum_{t=1}^T \left\{ y_i(t) - \sum_p (A_{ip} \cos \omega_p t + B_{ip} \sin \omega_p t) \right\}^2 \quad (3.9)$$

The voxel time-series is then normalized as $\tilde{y}_i(t) = \frac{1}{\sigma_i}(y_i(t) - \bar{y}_i(t))$, where $\bar{y}_i(t)$ is the mean value of voxel time-series and σ_i is the standard deviation of time-series. The normalization transforms the signal to have zero mean and unit variance. This results in equal temporal variances for all the voxels. The coefficients $A_{ip}(\omega_p)$ and $B_{ip}(\omega_p)$ are recalculated with modified voxel time-series $\tilde{y}_i(t)$ at ω_p equal to stimulus frequency ($p = 1$) and also for harmonics of stimulus frequency ($p = 2, 3 \dots$). Images A_p and B_p

are then formed with the corresponding voxel coefficients A_{ip} and B_{ip} respectively for all voxels at stimulus frequency and its harmonics. These images are then smoothed using a Gaussian filter with FWHM value equivalent to twice the voxel size. The A_p and B_p images, smoothened with a Gaussian filter, are nearly Gaussian based on the central limit theorem [111], and are represented by $A_{p,s}$ and $B_{p,s}$, respectively. These images need to be corrected for spatial global variance that is evaluated by using the neighborhood periodicity images. Four images corresponding to two frequencies, one frequency each on either side of the stimulus frequency is used to compute this variance. If n is the total number of cycles of the stimulus such that $\omega_1 = 2\pi n/T$, the images of neighborhood frequency coefficients are given by

$$E_i = \frac{2}{T} \sum_{t=1}^T \tilde{y}_i(t) \cos\left(\frac{2\pi(n-1)t}{T}\right) \quad (3.10)$$

$$F_i = \frac{2}{T} \sum_{t=1}^T \tilde{y}_i(t) \sin\left(\frac{2\pi(n-1)t}{T}\right) \quad (3.11)$$

$$G_i = \frac{2}{T} \sum_{t=1}^T \tilde{y}_i(t) \cos\left(\frac{2\pi(n+1)t}{T}\right) \quad (3.12)$$

$$H_i = \frac{2}{T} \sum_{t=1}^T \tilde{y}_i(t) \sin\left(\frac{2\pi(n+1)t}{T}\right) \quad (3.13)$$

where E_i, F_i are the voxel coefficients corresponding to the discrete frequency prior to the stimulus frequency and G_i, H_i are the coefficients corresponding to the discrete frequency next to the stimulus frequency. Images E, F, G and H are then formed with the corresponding voxel coefficients E_i, F_i, G_i and H_i respectively for all voxels.

These images are also smoothed using the same FWHM value as used previously and are represented by E_s, F_s, G_s, H_s . The individual voxels of these smoothened images are represented by $E_{i,s}, F_{i,s}, G_{i,s}, H_{i,s}$, and are used to estimate the global spatial variation σ_s^2 as:

$$\sigma_s^2 = \frac{1}{4N} \sum_i [E_{i,s}^2 + F_{i,s}^2 + G_{i,s}^2 + H_{i,s}^2] \quad (3.14)$$

where N is the total number of voxels in the image. The images $A_{p,s}$ and $B_{p,s}$ are corrected with σ_s to obtain unit spatial variance. Under the null hypothesis of no activation, these images are presumed to be normally distributed. Therefore, their sum of squares distribution is a χ^2 random field with $v = 2p$ degrees of freedom, which is calculated using the individual voxel values $A_{ip,s}$ and $B_{ip,s}$ of the smoothened images as:

$$U_{i,s} = \sum_p \left(\frac{A_{ip,s}}{\sigma_s} \right)^2 + \left(\frac{B_{ip,s}}{\sigma_s} \right)^2 \quad (3.15)$$

The effective FWHM, normally higher than the nominal FWHM, which has been used for smoothing the images is calculated from a pooled variance of the derivatives of $\frac{E_s}{\sigma_s}$, $\frac{F_s}{\sigma_s}$, $\frac{G_s}{\sigma_s}$ and $\frac{H_s}{\sigma_s}$ images. These derivatives are obtained by calculating the differences at adjacent voxels [113]. The effective FWHM s_e is given by [113]:

$$s_e = \sqrt{\frac{4 \ln 2}{|\Lambda|^{1/D}}} \quad (3.16)$$

where Λ is the pooled variance and D is the image dimension. This effective FWHM value is then used to convert the χ^2 random field values $U_{i,s}$ as represented by (3.15), into the equivalent probability values of activation by

$$p(U \geq u) \approx \sum_{d=0}^D \frac{V_d}{s_e^d} \varrho_d \quad (3.17)$$

for a set value of u . In this equation V_d represents the d -dimensional size of the search region, ϱ_d being the Euler characteristic (EC) intensities. The search regions for a brain slice are given as: $V_0 = 1$, $V_1 = Perimeter/2 = \pi \mathbf{r}$ and $V_2 = Area = \pi \mathbf{r}^2$, where $\mathbf{r}$ is the approximate radius of the circle enclosing the brain voxels. For a spherical search region with radius $\mathbf{r}$, these values are given as: $V_0 = 1$, $V_1 = 4\mathbf{r}$, $V_2 = 2\pi \mathbf{r}^2$ and $V_3 = (4/3)\pi \mathbf{r}^3$ [116].

For four degrees-of-freedom (*dof*), two *dof* due to stimulus frequency and two *dof* due to the first higher harmonic, ϱ_d with $d = 0, 1, 2$ and 3 , evaluated at $p = 2$, are given as:¹

$$\varrho_0(u) = \frac{1}{4} \int_u^\infty x e^{-x/2} dx \quad (3.22)$$

$$\varrho_1(u) = \sqrt{\frac{4 \ln 2}{2\pi}} \frac{u^{3/2} e^{-u/2}}{2} \quad (3.23)$$

$$\varrho_2(u) = \frac{4 \ln 2}{2\pi} \frac{u e^{-u/2}}{2} (u - 3) \quad (3.24)$$

$$\varrho_3(u) = \left(\frac{4 \ln 2}{2\pi} \right)^{3/2} \frac{u^{1/2} e^{-u/2}}{2} (u^2 - 7u + 6) \quad (3.25)$$

3.2.4 Hartley's F -test of Significant Harmonics

For notational simplicity, the subscript indicating the voxel site is omitted in this section. Let the autocorrelation function of a mean-deducted fMRI voxel time-series $y(t)$, with initial samples corresponding to one cycle of stimulus omitted to remove the effect of temporal autocorrelation, be denoted by $r_y(t)$. This function is approximated by a linear regression of $\mathcal{P}$ harmonics of stimulus frequency, and the least square estimates of these regression coefficients are given as

¹For $2p$ degrees-of-freedom (*dof*), two *dof* due to stimulus frequency and the remaining *dof* due to the higher harmonics, ϱ_d with $d = 0, 1, 2$ and 3 are given as [116]:

$$\varrho_0(u, p) = \int_u^\infty \frac{x^{\frac{2p-2}{2}} e^{-\frac{x}{2}}}{2^{\frac{2p}{2}} \Gamma(\frac{2p}{2})} dx \quad (3.18)$$

$$\varrho_1(u, p) = \sqrt{\frac{4 \ln 2}{2\pi}} \frac{u^{\frac{2p-1}{2}} e^{-\frac{u}{2}}}{2^{\frac{2p-2}{2}} \Gamma(\frac{2p}{2})} \quad (3.19)$$

$$\varrho_2(u, p) = \frac{4 \ln 2}{2\pi} \frac{u^{\frac{2p-2}{2}} e^{-\frac{u}{2}}}{2^{\frac{2p-2}{2}} \Gamma(\frac{2p}{2})} (u - (2p - 1)) \quad (3.20)$$

$$\varrho_3(u, p) = \left(\frac{4 \ln 2}{2\pi} \right)^{3/2} \frac{u^{\frac{2p-3}{2}} e^{-\frac{u}{2}}}{2^{\frac{2p-2}{2}} \Gamma(\frac{2p}{2})} (u^2 - (4p - 1)u + (2p - 1)(2p - 2)) \quad (3.21)$$

$$\mathcal{A}_p = \frac{2}{T_s} \sum_{t=1}^{T_s} r_y(t) \cos \omega_p t, \quad \mathcal{B}_p = \frac{2}{T_s} \sum_{t=1}^{T_s} r_y(t) \sin \omega_p t \quad (3.26)$$

where $\omega_p = 2\pi(p(n-1)/T_s)$ is the p th harmonic of stimulus frequency with $\omega_{\mathcal{P}} \leq \pi$, $\mathcal{A}_p$ and $\mathcal{B}_p$ are the least square estimates of the regression coefficients and T_s is the total number of time-points in the truncated autocorrelation function. Since these coefficients are calculated from the autocorrelation function, they correspond to the squares of the amplitudes of respective frequencies, i.e., spectral density of original voxel time-series. Hence, $A_p^2 + B_p^2 = \sqrt{\mathcal{A}_p^2 + \mathcal{B}_p^2}$, where, $A_p^2 + B_p^2$ is the spectral density component of original voxel time-series at p th harmonic of stimulus frequency.

Hartley's test is based on the F -value, $F_{1\dots q}$, for a given set of $q \leq \mathcal{P}$ harmonics of the voxel i [97].

$$F_{1\dots q} = \frac{(A_1^2 + B_1^2 + A_2^2 + B_2^2 \dots + A_q^2 + B_q^2)/2q}{R^2/(T_s - 2\mathcal{P} - 1)} \quad (3.27)$$

where

$$R^2 = \sum_{r=1}^{T_s/2} [A_r^2 + B_r^2] - \sum_{p=1}^{\mathcal{P}} [A_p^2 + B_p^2] \quad (3.28)$$

where $\omega_r = 2\pi(r/T_s)$ is the r th harmonic of sampling frequency. The numerator and denominator in (3.27) have $2q$ and $(T_s - 2\mathcal{P} - 1)$ degrees of freedoms (dof), respectively.

In order to detect the number of significant harmonics, F -value based on (3.27) is calculated starting with $q = 1$, with an increasing number of harmonics, for each voxel time-series as illustrated in Algorithm 2. Because the F -values calculated with different numbers of harmonics in the numerator cannot be compared with each other directly owing to the different dof's for the numerator, they are converted into equivalent standard normal values, z values, for comparison. The z -statistic considering up to q harmonics of stimulus frequency at a voxel is denoted by $z(F_{1\dots q}, 2q, T_s - 2\mathcal{P} - 1)$. A threshold θ is defined so that a particular voxel time-series is considered for inclusion of next harmonic, i.e., $(q+1)$ th harmonic only when $z(F_{1\dots q}, 2q, T_s - 2\mathcal{P} - 1) > \theta/q$. This value of θ is related to the significance value or p -value.

Algorithm 2 Selection of significant harmonics

```

Begin
  for all voxels  $i \in \Omega$  do
     $q = 1$ 
    Compute  $F$ -value  $F_{i,1\dots q}$ 
    Compute cumulative  $z$ -statistic,  $z_i(F_{i,1\dots q}, 2q, T_s - 2\mathcal{P} - 1)$ 
    while  $z_i(F_{i,1\dots q}, 2q, T_s - 2\mathcal{P} - 1) > \frac{\theta}{q}$  do
       $q = q + 1$ 
    end while
     $\text{SPM}(z_i) = z_i(F_{i,1\dots q}, 2q, T_s - 2\mathcal{P} - 1)$ 
  end for
End
    
```

A simple threshold on $\text{SPM}\{z\}$ for detecting activated voxels is not enough as neighborhood correlations among activated voxels needs to be incorporated. The correction for contextual information is done assuming a CRF for brain activation as defined in the previous chapter.

3.2.5 Scale-space χ^2 Random Field of Higher Harmonics

In this case, the resultant A_p and B_p images formed by the voxel coefficients from (3.7) and (3.8) are spatially smoothed using a range of FWHM values, s_r , which are equally spaced on log-scale for uniform coverage of scale space. In comparison, CHH discussed earlier uses only a single level of spatial smoothing i.e. twice the voxel size thus is unable to provide information about the extent of activated regions. The smoothened A_p and B_p images are nearly Gaussian and are represented by A_{p,s_r} and B_{p,s_r} respectively. These images need to be corrected for spatial global variance and this global variance is calculated using the neighborhood periodicity images. Four images corresponding to two frequencies, one frequency each on the either side of the stimulus frequency are used to calculate this variance. As in the CHH method described earlier, voxel coefficients E_i, F_i corresponding to discrete frequency prior to the stimulus frequency and coefficients G_i, H_i corresponding to discrete frequency next to the stimulus frequency are calculated for each voxel. The images formed from these coefficients for all voxels are then smoothed using the same range of FWHM values, s_r , and are represented by $E_{s_r}, F_{s_r}, G_{s_r}, H_{s_r}$.

The global spatial variation is then estimated using the individual voxel values of these smoothened images, i.e., E_{i,s_r} , F_{i,s_r} , G_{i,s_r} , H_{i,s_r} as:

$$\sigma_{s_r}^2 = \frac{1}{4N} \sum_i [E_{i,s_r}^2 + F_{i,s_r}^2 + G_{i,s_r}^2 + H_{i,s_r}^2] \quad (3.29)$$

where N is the total number of voxels in the image. The images A_{p,s_r} and B_{p,s_r} are corrected with σ_{s_r} to obtain unit spatial variance and the final χ^2 random field with $v = 2p$ degrees of freedom is given by:

$$U_{i,s_r} = \sum_p \left(\frac{A_{ip,s_r}}{\sigma_{s_r}} \right)^2 + \left(\frac{B_{ip,s_r}}{\sigma_{s_r}} \right)^2 \quad (3.30)$$

The effective FWHM, normally higher than the nominal FWHM which has been used for smoothing the images is calculated from pooled variance of the derivatives of $\frac{E_{s_r}}{\sigma_{s_r}}$, $\frac{F_{s_r}}{\sigma_{s_r}}$, $\frac{G_{s_r}}{\sigma_{s_r}}$ and $\frac{H_{s_r}}{\sigma_{s_r}}$ images. These derivatives are obtained by calculating the differences at the adjacent voxels [59, 113]. The effective FWHM s_e is given by [113]:

$$s_{re} = \sqrt{\frac{4 \ln 2}{|\Lambda|^{1/D}}} \quad (3.31)$$

where Λ is the pooled variance and D is the image dimension. This effective FWHM value is then used to convert the χ^2 random field values U_{i,s_r} as represented by (3.30), into the equivalent probability values of activation by

$$p(U \geq u) \approx \sum_{d=0}^D \frac{V_d}{s_{1e}^d} \varrho_d \quad (3.32)$$

for a set value of u . In this equation V_d represents the d -dimensional size of the search region, ϱ_d being the EC intensities. The search regions for a brain slice are given as: $V_0 = 1$, $V_1 = Perimeter/2 = \pi \mathbf{r}$ and $V_2 = Area = \pi \mathbf{r}^2$, where $\mathbf{r}$ is the approximate radius of the circle enclosing the brain voxels [116]. For example, for four *dof*, two *dof* due to

stimulus frequency and two *dof* due to first higher harmonic, ϱ_d with $d = 0, 1$ and 2 , evaluated at $p = 2$, are given as:²

$$\varrho_0(u, \frac{s_{1e}}{s_{10e}}) = \int_u^\infty \frac{x e^{-x/2}}{4} dx + \frac{u^2 e^{-u/2}}{2} \sqrt{\frac{1}{2\pi u}} (-\ln(\frac{s_{1e}}{s_{10e}})) \quad (3.36)$$

$$\varrho_1(u, \frac{s_{1e}}{s_{10e}}) = \sqrt{\frac{4 \ln 2}{2\pi}} \left(\frac{u^{3/2} e^{-u/2}}{2} \right) \left(\frac{1 + \frac{s_{1e}}{s_{10e}}}{2} + \sqrt{\frac{1}{2\pi u}} \left(1 - \frac{s_{1e}}{s_{10e}} \right) (u - 3) \right) \quad (3.37)$$

$$\varrho_2(u, \frac{s_{1e}}{s_{10e}}) = \frac{4 \ln 2}{2\pi} \left(\frac{u e^{-u/2}}{2} \right) \left(\frac{1 + (\frac{s_{1e}}{s_{10e}})^2}{2} (u^2 - 3) + \sqrt{\frac{1}{2\pi u}} \frac{1 - (\frac{s_{1e}}{s_{10e}})^2}{2} (u^2 - 6u + 6) \right) \quad (3.38)$$

3.3 Results

3.3.1 Activation Detection Using CHH, HSH and SCH Methods

We tested our proposed methods of using higher harmonics, i.e., methods based on χ^2 random field and Hartley's F -test, on synthetic data as well as on real fMRI data obtained on a memory retrieval task. The performance of these methods are compared with the

²For $2p$ *dof*, two *dof* due to stimulus frequency and remaining *dof* due to higher harmonics, ϱ_d with $d = 0, 1$ and 2 are given as [116]:

$$\varrho_0(u, \frac{s_{1e}}{s_{10e}}, p) = \int_u^\infty \frac{x^{\frac{2p-2}{2}} e^{-\frac{x}{2}}}{2^{\frac{2p}{2}} \Gamma(\frac{2p}{2})} dx + \frac{u^{\frac{2p}{2}} e^{-\frac{u}{2}}}{2^{\frac{(2p-2)}{2}} \Gamma(\frac{2p}{2})} \sqrt{\frac{D}{4\pi u}} (-\ln(\frac{s_{1e}}{s_{10e}})) \quad (3.33)$$

$$\varrho_1(u, \frac{s_{1e}}{s_{10e}}, p) = \sqrt{\frac{4 \ln 2}{2\pi}} \left(\frac{u^{\frac{2p-1}{2}} e^{-\frac{u}{2}}}{2^{\frac{2p-2}{2}} \Gamma(\frac{2p}{2})} \right) \left(\frac{1 + \frac{s_{1e}}{s_{10e}}}{2} + \sqrt{\frac{D}{4\pi u}} \left(1 - \frac{s_{1e}}{s_{10e}} \right) (u - (2p - 1)) \right) \quad (3.34)$$

$$\begin{aligned} \varrho_2(u, \frac{s_{1e}}{s_{10e}}, p) &= \frac{4 \ln 2}{2\pi} \left(\frac{u^{\frac{2p-2}{2}} e^{-\frac{u}{2}}}{2^{\frac{2p-2}{2}} \Gamma(\frac{2p}{2})} \right) \left(\frac{1 + (\frac{s_{1e}}{s_{10e}})^2}{2} (u^2 - (2p - 1)) \right. \\ &\quad \left. + \sqrt{\frac{D}{4\pi u}} \frac{1 - (\frac{s_{1e}}{s_{10e}})^2}{2} (u^2 - (4p - 1)u + (2p - 1)(2p - 2)) \right) \end{aligned} \quad (3.35)$$

SPM approach [95]. The proposed method of using higher harmonics in χ^2 random field scale-space analysis was tested on memory retrieval task fMRI data and the results are compared with the wavelet analysis results.

3.3.1.1 Synthetic Data

Two-dimensional event-related fMRI dataset of 64×64 pixels per scan was synthetically generated, with 16 images per epoch and 2s interscan interval. A stimulus cycle contained 4s of stimulations preceded by 28s of rest time. FMRI time-series response of the activated pixels was obtained by convolving the stimulus with a hemodynamic response function $h(t)$ defined by a mixture of two gamma functions [95], as given in Eq. (2.24). Datasets were generated with canonical HRF and also with random variation of κ values, with standard deviation of 0.1κ , to simulate varying HRF conditions [2, 51], referred to as HRF with deviation. The non-activated pixels were left unchanged at zero amplitude [122]. Spatially correlated Gaussian noise was added to all the brain pixels. Temporal correlation was included using AR models at various orders: $z(t) = \sum_{k=1}^K h_k z(t-k)$. That is, by assuming AR(1) model with $h_1 = 0.4$ and AR(2) model with $\{h_1, h_2\} = \{0.4, 0.4\}$. The experiments were performed at two levels of signal-to-noise ratios, $\text{SNR} = 0.9$ and 1.2.

Figures 3.2-3.7 illustrate the result of brain activation detected on synthetic data by the proposed approaches and the SPM approach at two different SNR values: 0.9 and 1.2. The calculated area under ROC curves (full curves) is shown in Tables 3.1 and 3.3 for $\text{SNR}=1.2$. For $\text{SNR}=0.9$, results are shown in Tables 3.5 and 3.7. For some cases, we also take a closer look at ROC curves, by calculating the area under a part of ROC curves (partial curves), particularly the part with specificity in the range of 0.95 to 1.00. These values are included in Tables 3.2 and 3.4 for $\text{SNR}=1.2$. For $\text{SNR}=0.9$, results are shown in Tables 3.6 and 3.8. Since the proposed CHH method uses fixed number of harmonics for all voxels, unlike the proposed Hartley's F-test which can select the

appropriate number of harmonics for every voxel individually, we did some tests to select the appropriate number of fixed harmonics for CHH method. As shown in Figure 3.2, the optimum number of harmonics to be used for activation detection in the CHH method is the first harmonic along with the fundamental frequency. Addition of further higher harmonics does not result in an increase in the efficiency of detection of activation.

As seen visually in Figure 3.3, even for the data generated using canonical HRF (SNR=1.2), the proposed approach of HSH performs better than the GLM method, for both the AR(1) and AR(2) temporally autocorrelated cases, especially in the regions of higher sensitivity and higher specificity. In the case of AR(1) data, the AUC values under the ROC curves (full curves) are 99.96 and 99.71 (Table 3.1) and AUC values for ROC curves (partial curves) are 98.99 and 94.71 (Table 3.2), for HSH method and GLM method respectively. For the case of AR(2) data, the AUC values under the ROC curves (full curves) are 99.30 and 99.60 (Table 3.1), i.e., a marginally lower value for HSH, but if we observe the AUC values for ROC curves (partial curves), which are 93.71 and 93.32 (Table 3.2), for HSH method and GLM method respectively, we find that in the region of higher sensitivity and higher specificity HSH method performs better than the GLM method. The GLM method does have an advantage in the case of datasets generated with canonical HRF because the same HRF is also assumed when the analysis is performed, whereas in the case of MSA method this advantage is missing. For this case of canonical HRF data, CHH method performance is similar to the GLM method.

In the case of data generated using an HRF with deviation (SNR=1.2), as shown in Figure 3.4, both the HSH and CHH methods perform significantly better than the GLM method, for both the AR(1) and AR(2) temporally autocorrelated cases. In the case of AR(1) data, the AUC values under the ROC curves (full curves) are 99.97, 99.66 and 99.16 (Table 3.3) and AUC values for ROC curves (partial curves) are 99.11, 92.37 and 85.67 (Table 3.4), for HSH method, CHH method and GLM method respectively. For the case of AR(2) data, the AUC values under the ROC curves (full curves) are 99.89, 99.61

Figure 3.2: Optimal number of harmonics for CHH method that uses fixed number of harmonics

Table 3.1: The AUC Values for ROC Curves (Full Curves) Comparing MSA, GLM, CHH and HSH Results: Event-related Data (SNR=1.2, Canonical HRF)

AR Model	GLM	MSA	CHH	HSH (Fundamental frequency only)	HSH (Higher harmonics)
AR(1)	99.71	99.96	99.58	99.77	99.96
AR(2)	99.60	99.54	99.35	98.36	99.30

Table 3.2: The AUC Values for ROC Curves (Partial Curves with Specificity Range: 0.95 to 1.00) Comparing MSA, GLM, CHH and HSH Results: Event-related Data (SNR=1.2, Canonical HRF)

AR Model	GLM	MSA	CHH	HSH (Fundamental frequency only)	HSH (Higher harmonics)
AR(1)	94.71	97.79	93.76	96.26	98.99
AR(2)	93.32	95.68	92.04	88.14	93.71

(a)

(b)

Figure 3.3: Comparison of proposed methods and GLM (SPM) method on detection of activation in synthetic data. Event-related experiment data with, SNR=1.2, Canonical HRF (a) AR(1) temporal autocorrelation (b) AR(2) temporal autocorrelation

Table 3.3: The AUC Values for ROC Curves (Full Curves) Comparing MSA, GLM, CHH and HSH Results: Event-related Data (SNR=1.2, HRF with Deviation)

AR Model	GLM	MSA	CHH	HSH (Fundamental frequency only)	HSH (Higher harmonics)
AR(1)	99.16	99.98	99.66	99.91	99.97
AR(2)	99.12	99.97	99.61	99.53	99.89

Table 3.4: The AUC Values for ROC Curves (Partial Curves with Specificity Range: 0.95 to 1.00) Comparing MSA, GLM, CHH and HSH Results: Event-related Data (SNR=1.2, HRF with Deviation)

AR Model	GLM	MSA	CHH	HSH (Fundamental frequency only)	HSH (Higher harmonics)
AR(1)	85.67	99.33	92.37	98.43	99.11
AR(2)	88.20	99.09	94.00	93.49	97.72

and 99.12 (Table 3.3) and AUC values for ROC curves (partial curves) are 97.72, 94.0 and 88.20 (Table 3.4), for HSH method, CHH method and GLM method respectively.

For SNR=0.9 datasets, again as seen visually in Figure 3.5, even for the data generated using canonical HRF, the proposed approach of HSH performs better than the GLM method, for AR(1) temporally autocorrelated case, especially in the regions of higher sensitivity and higher specificity. In the case of AR(1) data, the AUC values under the ROC curves (full curves) are 99.61 and 99.40 (Table 3.5) and AUC values for ROC curves (partial curves) are 94.97 and 91.57 (Table 3.6), for HSH method and GLM method respectively. For the case of AR(2) data, the AUC values under the ROC curves (full curves) are 97.95 and 99.30 (Table 3.5) and this is the only case where HSH performs marginally lower than GLM, but we must keep in view the great advantage that GLM method has in all these cases where the synthetic data is generated using canonical HRF,

(a)

(b)

Figure 3.4: Comparison of proposed methods and GLM (SPM) method on detection of activation in synthetic data. Event-related experiment data with, SNR=1.2, HRF with Deviation (a) AR(1) temporal autocorrelation (b) AR(2) temporal autocorrelation

Table 3.5: The AUC Values for ROC Curves (Full Curves) Comparing MSA, GLM, CHH and HSH Results: Event-related Data (SNR=0.9, Canonical HRF)

AR Model	GLM	MSA	CHH	HSH (Fundamental frequency only)	HSH (Higher harmonics)
AR(1)	99.40	99.72	99.07	99.06	99.61
AR(2)	99.30	98.14	98.81	95.22	97.95

Table 3.6: The AUC Values for ROC Curves (Partial Curves with Specificity Range: 0.95 to 1.00) Comparing MSA, GLM, CHH and HSH Results: Event-related Data (SNR=0.9, Canonical HRF)

AR Model	GLM	MSA	CHH	HSH (Fundamental frequency only)	HSH (Higher harmonics)
AR(1)	91.57	95.48	88.50	90.99	94.97
AR(2)	89.52	89.87	86.60	76.02	87.75

still in most of these cases HSH was able to perform better than GLM. Also as shown next, in the case of synthetic data generated using HRF with deviation, both the HSH and CHH methods perform much better than the GLM method.

In the case of data generated using an HRF with deviation (SNR=0.9), as shown in Figure 3.6, both the HSH and CHH methods perform significantly better than the GLM method, for both the AR(1) and AR(2) temporally autocorrelated cases. In the case of AR(1) data, the AUC values under the ROC curves (full curves) are 99.91, 99.57 and 98.73 (Table 3.7) and AUC values for ROC curves (partial curves) are 97.82, 90.80 and 83.71 (Table 3.8), for HSH method, CHH method and GLM method respectively. For the case of AR(2) data, the AUC values under the ROC curves (full curves) are 98.94, 99.23 and 98.07 (Table 3.7) and AUC values for ROC curves (partial curves) are 90.79, 90.94 and 78.32 (Table 3.8), for HSH method, CHH method and GLM method respectively. In

(a)

(b)

Figure 3.5: Comparison of proposed methods and GLM (SPM) method on detection of activation in synthetic data. Event-related experiment data with, SNR=0.9, Canonical HRF (a) AR(1) temporal autocorrelation (b) AR(2) temporal autocorrelation

Table 3.7: The AUC Values for ROC Curves (Full Curves) Comparing MSA, GLM, CHH and HSH Results: Event-related Data (SNR=0.9, HRF with Deviation)

AR Model	GLM	MSA	CHH	HSH (Fundamental frequency only)	HSH (Higher harmonics)
AR(1)	98.73	99.87	99.57	99.56	99.91
AR(2)	98.07	99.28	99.23	97.23	98.94

Table 3.8: The AUC Values for ROC Curves (Partial Curves with Specificity Range: 0.95 to 1.00) Comparing MSA, GLM, CHH and HSH Results: Event-related Data (SNR=0.9, HRF with Deviation)

AR Model	GLM	MSA	CHH	HSH (Fundamental frequency only)	HSH (Higher harmonics)
AR(1)	83.71	97.37	90.80	95.00	97.82
AR(2)	78.32	93.70	90.94	78.01	90.79

this case, if we look at the AUC values under the full ROC curve, CHH method performs the best.

Figure 3.7, shows the activation detection results for SNR=1.2, AR(2) dataset, for HSH method, CHH method and the GLM method. The true image is also shown for comparison. As can be observed, small areas of activation and boundaries are in general more accurately detected in HSH method, which does not involve pre-smoothing of data.

3.3.1.2 Memory Retrieval Task Data

Figure 3.8 shows the activation detected on three slices of the brain by the two proposed methods and the SPM method for the cue. Also shown in the Figure 3.9 are the activation detection results by all the three methods for the probe. In the proposed method, brain regions corresponding to the probe and cue were separated based on the difference in phase of voxel time-series. Both the proposed methods and SPM method detected

(a)

(b)

Figure 3.6: Comparison of proposed methods and GLM (SPM) method on detection of activation in synthetic data. Event-related experiment data with, SNR=0.9, HRF with Deviation (a) AR(1) temporal autocorrelation (b) AR(2) temporal autocorrelation

Figure 3.7: Illustration of detected activation on synthetic event-related data, SNR=1.2. Temporal auto-correlation AR(2) with $\{h_1, h_2\} = \{0.4, 0.4\}$, (a) HSH proposed method (b) CHH proposed method (c) GLM (SPM) results (d) the ground truth

Figure 3.8: Activation detected on three axial brain slices of a representative subject in memory retrieval task (corresponding to the cue) by (a) the SPM method, (b) the proposed HSH method, and (c) the proposed CHH method.

activation in the expected cortical areas of inferior pCS and posterior MFG following cue and in regions of posterior parietal cortex following the probe [81, 88, 89]. Inferior pre-central sulcus and posterior middle frontal gyrus are generally involved in the retrieval of information from secondary memory and also in maintaining this information for search following the presentation of the cue, hence are also activated during the probe. The activation patterns detected by the methods using higher harmonics of stimulus frequency were quite similar to those detected by the SPM method.

Since our proposed method based on Hartley's F -test is able to select the significant harmonics of stimulus frequency in each voxel time-series, shown in Figure 3.10 are the

Figure 3.9: Activation obtained on three axial brain slices of a representative subject in memory retrieval task (corresponding to the probe) by (a) the SPM method, (b) the proposed HSH method, and (c) the proposed CHH method.

Figure 3.10: HSH method results indicating the activated brain voxels that had significant higher harmonics of stimulus frequency

harmonics that were found to be significant for each one of the activated voxels. As is clear from the figure, a number of voxels from the set of activated voxels have been found to have significant higher harmonics.

Scale-space analysis of memory retrieval data was also carried out and for this case, the data was analyzed at ten different levels of smoothing i.e. 6mm, 9mm, 10mm, 11mm, 12.2mm, 13.5mm, 14.9mm, 16.4mm, 18.2mm and 20mm using the proposed SCH method with higher harmonics. The benefit of including one higher harmonic is already shown in the case of similar CHH method, hence for SCH method also, we include one higher harmonic in analysis. The results of activation detection corresponding to the probe are as shown in Figure 3.11. The activated regions are detected more effectively with the smoothing filter size that corresponds to the activated region size. As the smoothing increases, smaller regions of activation are not detected anymore. As shown in Figure 3.12a, blob 2 is not detected anymore beyond 6mm smoothing, blob 3 beyond 9mm smoothing, blob 6 beyond 10mm, blob 1 beyond 12.2mm and blob 5 beyond 20mm. Also as seen in this figure, in the case of blob 5, its size increases as the smoothing increases from 6mm to 20mm, indicating that this blob is better detected at higher levels of smoothing as a result of its bigger size. The results of this method are compared with wavelet analysis method, as shown in Figure 3.13. We used the WSPM package, which is

(a)

Figure 3.11: Scale space analysis results on an axial brain slice of a representative subject in memory retrieval task by χ^2 random field method with various amounts of smoothing (left to right; row1: 6mm, 9mm, 10mm; row2: 11mm, 12.2mm, 13.5mm; row3: 14.9mm, 16.4mm, 18.2mm and row4: 20mm smoothing)

incorporated into the SPM package, for wavelet analysis [96]. As is clear from the figure, most of the regions detected are similar to our proposed method but the results are not as focal to the relevant cortical areas.

3.4 Discussion

Earlier frequency-domain techniques for detection of brain activation, in the case of periodic fMRI data, used only the fundamental frequency of the stimulus cycle and higher harmonics were generally discarded. In the case of block-based fMRI data, since the

(a)

(b)

Figure 3.12: Scale space analysis results (a) Detection of various blobs at different amounts of smoothing (b) Location of various blobs

(a)

Figure 3.13: Wavelet analysis results on an axial brain slice of a representative subject in memory retrieval task

fundamental frequency contains most of the energy of brain activation, higher harmonics can be ignored. In the case of event-related data, when the stimulus time forms only a small part of the experiment, the higher harmonics carry a significant part of the energy of fMRI response. In this chapter, we have presented the frequency-domain techniques for event-related data analysis, which then requires consideration of higher harmonics. We have presented two main methods of using higher harmonics. The first proposed method, i.e., CHH method, is based on χ^2 random field theory. This method uses the fundamental frequency and its first higher harmonic. The second proposed method, i.e., HSH method, is based on Hartley's test and is able to select significant harmonics in each voxel time-series. In this method, we employed a conditional random field to incorporate contextual information of brain activation. In this chapter, we have also presented yet another method, i.e., the scale-space χ^2 random field method with higher harmonics, which provides better information about the spatial extent of activation.

Our experiments with synthetic data indicate that the HSH method in general performs significantly better than the GLM method in most of the cases, whereas CHH method performs better than GLM mainly in the cases where the synthetic data is generated using an HRF with deviation. Comparing the two proposed methods with each other, we find that for almost all cases HSH method performs better than the CHH method. For real fMRI data obtained in a memory retrieval experiment, we compared the results of the two proposed methods with the GLM method, for detection of activation corresponding to both the cue and the probe. All three methods showed similar activation patterns that are task-related and acceptable visually, with HSH being comparatively more focal to cortical areas,.

We have also presented the scale-space related SCH method including the higher harmonics. We have compared the results of this proposed method with the wavelet analysis results for the memory retrieval task data. We found that the SCH method is

able to provide comparatively better information about the spatial extent of individual activations.

Chapter 4

Time-frequency and Mixed Spectrum Analysis of Resting State Data

In contrast to time-domain where the signals are represented as a function of time and frequency-domain where the signals are represented in the form of a power spectrum, time-frequency representation is able to provide the information about the variation in amplitude of individual frequency components with time.

Functional MRI data of a subject at rest can be analyzed to reveal the person's synchronized resting state brain activity pattern. One of the most important resting state networks is the default mode network consisting of a number of brain regions such as medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC)/precuneus (PCu) and bilateral inferior parietal cortex. The resting state pattern and in particular the default mode network has been found to undergo changes with the changes in the pathological condition of the brain and hence can be used as a marker for detecting the brain condition.

A number of methods have been employed to detect the default mode network including the seed-based correlation analysis, low-frequency fluctuation analysis and independent component analysis. Some of the drawbacks of these methods are that they either require a careful selection of seed region to start with or ignore the mutual information contained in low-frequency components and choosing the number of independent compo-

nents is difficult. In this chapter we intend to enhance the resting-state network detection results, in comparison to the present methods, by using the time-frequency analysis. The major advantage of the proposed time-frequency analysis technique is that it takes into account the variation in the amplitude of various frequency components along the time axis, as well as the mutual information contained in these frequency components. We also demonstrate the application of Priestley's technique, a mixed spectrum analysis technique discussed in Chapter 2 of this thesis, in detecting resting state networks.

4.1 Motivation and Contributions

Other than the task-related fMRI experiments, in which case the fMRI data is collected while the subject performs some tasks, e.g., visual, auditory, memory retrieval task, an increasingly used method of collection of fMRI data is one in which the subject is at rest and is not performing any activity. This type of data, also known as resting-state data, has been captured and analyzed by a number of researchers and some activity patterns have thus been found to occur consistently in the human brain at rest. Default mode network consisting of the brain regions such as MPFC, PCC/PCu and bilateral inferior parietal cortex is one of the main resting state networks. The default mode network of brain activity during rest was identified initially by Raichle et al. [86] in their PET studies and has since been identified in a number of fMRI studies [65, 125]. In-fact a number of studies have also found that this default network can be used as a marker for the pathological condition of the brain as the activation pattern/level of this pattern has been found to alter with a number of conditions such as AD [56], MS [13], epilepsy [121], ADHD [35, 119] and also in drug abuse cases [55].

A number of analysis techniques have been adopted to analyze the resting state fMRI data. These include mainly the seed region based technique (SBA), low-frequency amplitude techniques (ALFF and fALFF) and ICA. The seed-based analysis method has been one of the most widely used methods and it identifies brain activity pattern

correlated to a seed-region that has been pre-defined by the user [12, 30, 46]. The main challenge lies in choosing the appropriate seed-region which requires an expert knowledge of brain's functional organization and in the case of group studies, consistent choice of same seed-region proves to be much more challenging. The low frequency fluctuations ($<0.1\text{Hz}$) in resting state fMRI data were first identified by Biswal et al. [12] to be significantly correlated in the functionally connected parts of the brain. The ALFF and fALFF techniques are both based on this premise [119, 124, 125]. The main drawback in this method is that it takes into account only the sum of frequency components in the low frequency range and ignores the mutual information contained in these frequency components. The ICA technique has also been successfully used for the resting state fMRI data analysis with the spatial ICA's ability to delineate independent resting state brain networks but the main limitation remains the selection of components of interest from the complete set of independent components [32, 68]. Other techniques that have been tested on resting state fMRI data include clustering based on the affinity matrix calculated using pairs of voxels [104], clustering using the cross-correlation values between pairs of voxels in the low frequency range [25] and STFT [71].

We present a novel method based on time-frequency analysis and clustering for detection of resting state networks and in particular the default mode network [58]. Fourier transform has traditionally been used to calculate the signal spectrum but in the process of calculating the spectrum, it loses the signal time information. STFT, or spectrogram, is able to provide the time-based spectrum, but suffers from the time and frequency resolution trade-off condition. Some techniques have been developed to overcome this shortcoming of STFT. The first one of these time-frequency techniques were Wigner-Ville distribution based on the autocovariance function. This technique although overcomes the time and frequency resolution trade-off condition, it suffers from the presence of cross terms in the spectrum [24]. Various distributions in the Cohen's class aim at reducing the cross terms, while keeping the advantages of Wigner-Ville distribution [92]. The

Rihaczek-Margenau distribution of Cohen's class was found to produce the least amount of cross terms [92]. Hence, we propose to use the Rihaczek-Margenau distribution of Cohen's class to calculate the time-frequency distribution of each voxel time-series in the low frequency range and to detect the default mode network in resting state data. Additionally, we demonstrate the application of mixed spectrum analysis technique, as was discussed in Chapter 2, in detecting default mode pattern. We expect to improve resting state network detection with our proposed methods.

This chapter is organized as follows. In the models and methods section, we model the time-frequency representation and mixed spectrum representation of resting state voxel time-series. In the results section, the proposed methods are applied on synthetic data and four sets of real fMRI resting state data for default mode network detection.

4.2 Models and Methods

4.2.1 Time-Frequency Modeling of Resting State fMRI Data

Time-frequency representation of fMRI voxel time-series based on Wigner-Ville and other Cohen's distributions is carried out by the calculation of power spectrum from autocovariance function, as is used in calculation of power spectral density (psd). In the standard autocovariance function, summation is carried out over time as shown in Eq. (4.1), resulting in the autocovariance function $R_y(\tau)$ which is a function of lag/time-shift τ only. For notational simplicity, the subscript indexing the voxel is omitted in this section.

$$R_y(\tau) = \sum_{t \in \Theta} y(t)y(t + \tau) \quad (4.1)$$

The Wigner-Ville and other distributions of Cohen's class use a variation of the autocovariance function where time is still retained [24]. In this case also, the comparison of waveform with itself is carried over all lag values, but rather than integrating over time, evaluation is carried out over all valid time points. This results in so-called instantaneous autocovariance $R_y(t, \tau)$ of the fMRI data as shown in Eq. (4.2).

$$R_y(t, \tau) = y(t + \tau)y^*(t - \tau) \quad (4.2)$$

where τ is the time lag and $*$ represents the signal's complex conjugate. Both the lag and time value remain in the instantaneous autocovariance function. The Fourier transform of $R_y(t, \tau)$ is taken along the τ dimension, hence the result is a function of both time and frequency. The relationship for determining the time-frequency distribution of Cohen's class, $C_y(t, \omega)$, from the instantaneous autocovariance function is as given in Eq. (4.3) [24].

$$C_y(t, \omega) = \sum_{\tau=0}^{T-1} R_y(t, \tau)G(t, \tau)e^{-j\omega\tau}; \forall t \in \mathcal{T} \quad (4.3)$$

where function $G(t, \tau)$ is based on a two-dimensional filter (filter for the autocovariance function) and this filter is what distinguishes various distributions within the Cohen's class. The expression for filter $G(t, \tau)$ is given by the Eq. (4.4-4.5) below for both the Wigner-Ville, $WV_y(t, \omega)$, and Rihaczek-Margenau distributions of Cohen's class, $M_y(t, \omega)$.

$$G(t, \tau) = \int_{-\infty}^{\infty} g(v, \tau)e^{j\pi vt} dv \quad (4.4)$$

$$g(v, \tau) = \begin{cases} 1 & ; \text{for Wigner-Ville distribution} \\ e^{jv\tau/2} & ; \text{for Rihaczek-Margenau distribution} \end{cases} \quad (4.5)$$

The main problem with Wigner-Ville distribution is the presence of cross products in the spectrum and various Cohen's class distributions aim to reduce the amplitude of these cross products. A complex version of the original signal, also known as *analytic signal*, is generally used as it improves results during transformations in Cohen's class of distribution. As there are no negative frequencies in analytic signal, its use reduces the

amount of cross products. The approach based on Hilbert transform of signal is used to derive the analytic function [92]. The Rihaczek-Margenau distribution of Cohen's class was found to produce the least amount of cross products and is used here for calculating the spectrum of fMRI time-series and hence for further analysis [24]. The original spectrum for Rihaczek-Margenau distribution is three dimensional as it is the time-frequency distribution with amplitude of spectral components as the third dimension.

The time-frequency representation $M_y(t, \omega)$ from Eq. (4.3) is modified by keeping only the frequency components in the range of 0.01Hz-0.1Hz. This is the frequency range that has been found to be related the resting state network [12, 119, 125]. The time-frequency distribution matrix is then transformed into a vector by concatenating individual frequency components starting with the lowest frequency component. If m is the number of frequency components that lie in the range of 0.01Hz-0.1Hz, then the total length of this time-frequency vector becomes $m \times T$. This time-frequency vector is then used for detection of patterns by cluster analysis, as shown in Algorithm 3.

Algorithm 3 Time-frequency Analysis of Resting State Data

```

begin
  for voxels  $i \in \Omega$  do
     $y(t) = y_i(t)$ 
    Compute  $R_y(t, \tau)$  values for  $y(t)$ 
    Compute  $C_y(t, \omega)$ 
    Select frequency components in range of 0.01Hz-0.1Hz
  end for
  Perform cluster analysis
end

```

4.2.2 Mixed Spectrum Modeling of Resting State fMRI Data

In the mixed spectrum model, discussed in Chapter 2, the continuous spectrum part of the mixed spectrum was seen as a result of temporal autocorrelations. Our premise is that we should be able to detect resting state networks by analyzing the temporal autocorrelation values, instead of the frequency components. The default mode network

has low frequency oscillations in the range of 0.01Hz-0.08Hz, likely to be related to temporal autocorrelations [103]. In the case of task-related data's mixed spectrum analysis with Priestley's method, as presented a earlier chapter of this thesis, the autocovariance function of voxel time-series was truncated in the front, up to a truncation point τ_1 , to remove the temporal autocorrelation effect from discrete spectrum. In the case of resting state data, this initial part of autocovariance function is the one that we use now for detecting the resting state patterns. In the first step, autocovariance values at unity lag are thresholded to get the resting state patterns. Thereafter, we find the default mode network by selecting a subset of these voxels that have similar autocorrelation pattern up to a truncation point, as shown in Algorithm 4.

Algorithm 4 Mixed Spectrum Analysis of Resting State Data

```

begin
  for voxels  $i \in \Omega$  do
     $y(t) = y_i(t)$ 
    Compute  $R_y(\tau)$  values for  $y(t)$ 
  end for
  Threshold  $R_y(1)$  to find resting state pattern
  Select voxels with similar  $R_y(\tau)$  to get default mode network
end

```

4.3 Results

The proposed time-frequency distribution method and mixed spectrum analysis with Priestley's method for resting state network analysis were tested on synthetic data and four real fMRI resting state datasets. For clustering in time-frequency method, k -means clustering algorithm was employed. The results of these methods were compared with a widely used fALFF method [94]. The resting state datasets have been obtained from NITRC database [28].

4.3.1 Synthetic Data

Unlike the task related fMRI data, where the signal in the activated voxels has been well studied and known as the convolution of HRF with the stimulus signal, in the case of

Table 4.1: The Sensitivity and Specificity Values for Synthetic Data (SNR=1.2)

Method	False Positive	False Negative	True Positive	True Negative	Sensitivity	Specificity
fALFF	189	7	287	3613	97.62	95.03
MSA	190	17	277	3612	94.22	95.00
Time-Frequency	23	3	291	3779	98.98	99.40

resting state data, the actual signal in the resting state networks is not very well known. Hence, in order to construct our resting state synthetic data, we took one of the time-series from the default mode network of an actual resting state dataset and another time-series from outside the resting state network. These time-series were then used to construct the synthetic resting state network as shown in Figure 4.1a, where the networked regions are shown in black. Gaussian random noise was then generated and added to these time-series. We have tested our methods on two different SNR values, i.e., 1.2 and 1.6. For the proposed time-frequency analysis method, time-frequency distribution of each time-series was calculated and time-frequency vector formed, followed by k -means cluster analysis for $k=2$. The results of the two proposed methods and the standard fALFF method are as shown in Figures 4.1b-g. As is evident from the tables (Tables 4.1-4.2), for both the synthetic datasets our proposed time-frequency analysis method, with a sensitivity value of 98.98 and specificity value of 99.40 for SNR=1.2 and corresponding values of 100.0 and 99.97 for SNR=1.6, outperforms the fALFF method, which has sensitivity and specificity values of 97.62 and 95.03 for SNR=1.2 and corresponding values of 98.64 and 98.5 for SNR=1.6. Our second proposed method based on mixed spectrum analysis with Priestley's method performs similar to the standard fALFF method.

4.3.2 Resting State fMRI Data

In this resting state fMRI dataset, 16 brain slices of brain has been captured with TR=1s for 248 time-points. The pre-processing of data included realignment of data for removal

Figure 4.1: Synthetic data results: (a) True image; (b) fALFF method (c) Proposed MSA method (d) Proposed time-frequency method for SNR=1.2; (e) fALFF method (f) Proposed MSA method (g) Proposed time-frequency method for SNR=1.6

Table 4.2: The Sensitivity and Specificity Values for Synthetic Data (SNR=1.6)

Method	False Positive	False Negative	True Positive	True Negative	Sensitivity	Specificity
fALFF	57	4	290	3745	98.64	98.50
MSA	57	1	293	3745	99.66	98.50
Time-Frequency	1	0	294	3801	100.0	99.97

of movement related artifacts. Subject data with movement values less than 1mm translation motion and 1degree rotation motion were used for further analysis. Individual subject datasets were also normalized with the EPI template, available in SPM5 package [95], for group comparison of resting state patterns.

The time-frequency distribution of each voxel time-series for all the subjects was calculated followed by the time-frequency vector as described in the previous section. This time-frequency vector was then used for cluster analysis. We tested both the k -means and hierarchical clustering methods and the results of both the methods were quite similar. The dendrogram from hierarchical clustering also identified clusters in the range of 3 to 5 for these subjects. The average results of four subjects are shown in Figures 4.2a, 4.2b and 4.2c for values of $k=3,4$ and 5 respectively. These four subjects, with no significant differences, were chosen because during the pre-processing of their resting-state fMRI datasets they were found to have head movement related parameters within the acceptable limits. Datasets with unacceptable head movement related parameters were not used. Also, we wanted to test the efficacy and performance of our proposed method on more than one dataset. Figure 4.4 shows $k=3$ results for a representative subject in 3D. Figure 4.2e shows the results from the fALFF method for comparison. The average of fALFF results were taken after thresholding each individual subject results with $z>1.5$. Also shown in Figures 4.3,4.5-4.7, are the individual results of four subjects with values of $k=2,3$ and 4. These figures show the complete sets of clusters detected for a given value of k as well as the default mode cluster separately as identified from these set of clusters. As can be observed, clustering with three clusters i.e. $k = 3$ results is most efficient in detecting the default mode network. Observing the Figure 4.2a-c, which shows the averaged results of four subjects with $k=3,4$ and 5 respectively, it may appear that number of regions detected in default mode network are decreasing with the increase in k value, but if we observe the individual subject results in Figure 4.3, we see that the regions detected for all k values are nearly same. The

only effect being that as the value of k increases, the k -means algorithm tries to form more clusters, resulting in some of the voxels from a particular cluster be redistributed to form additional clusters. This is more pronounced in the subject with results shown in Figure 4.5, where, as the value of k increases, the voxels from initially detected cluster regions reduces. There is thus no direct relationship between the increase in k value and the corresponding decrease in the number of regions detected in default-mode network. Also shown in these figures are the fALFF results for each subject for comparison with the proposed method.

We also applied the Priestley's technique on time-series of the resting brain to identify the voxels having significant autocorrelation, as stated earlier. Threshold level for autocorrelation values was estimated by fitting the histogram of brain voxel autocorrelation values with a Gaussian curve and then by calculating a significance level greater than 0.95. Figures 4.3h, 4.5h-4.7h, show the patterns of such voxels obtained on the four sets of resting brain data thresholded at the shown autocorrelation values. Thereafter, we detect the default mode network by finding a subset of these voxels that have similar autocorrelation pattern. Results are as shown in Figures 4.3i, 4.5i-4.7i. The average result of four subjects is shown in Figure 4.2d.

4.4 Discussion

The earlier methods of detecting resting state networks in resting state fMRI data were mainly based on seed-based correlation analysis, low-frequency fluctuation analysis and ICA. Some of the drawbacks of these methods are they either require a careful selection of seed region to start with or ignore the mutual information contained in low-frequency components and choosing the number of independent components is difficult. Our proposed method based on time-frequency analysis technique has an advantage it takes into account the variation in the amplitude of various frequency components along the time axis, as well as the mutual information contained in these frequency components. Also

Figure 4.2: Average resting state pattern results for four subjects (a)-(c) Time-frequency vector based clustering results with k-means clustering (a) $k=3$ (b) $k=4$ (c) $k=5$ (d) MSA method based result (e) zfALFF method results with $z>1.5$

there is no need to choose a seed region or to make a selection of components. We also presented a mixed spectrum analysis method which uses temporal autocorrelation values, instead of frequency components, to detect the default mode network.

Based on the test on synthetic data and four sets of resting state datasets, we find that our proposed time-frequency analysis method is able to better detect default-mode network than the standard method that uses sum of low-frequency component amplitudes. Our mixed spectrum method based results were similar to fALFF method results for synthetic data and visually slightly better for actual fMRI resting state data, but then not as good as time-frequency analysis results.

Figure 4.3: Resting state pattern results for Subject 1 (a)-(f) Time-frequency vector based clustering results with (a) complete set of clusters using k-means clustering with $k=3$ (b) cluster corresponding to default mode cluster for $k=3$ (c) complete set of clusters using k-means clustering with $k=4$ (d) cluster corresponding to default mode cluster for $k=4$ (e) complete set of clusters using k-means clustering with $k=5$ (f) cluster corresponding to default mode cluster for $k=5$ (g) fALFF results (h)-(i) MSA method results with (h) voxels having significant temporal autocorrelation (ac) values (i) the connectivity pattern of voxels obtained based on cross-correlation (cc) values

Figure 4.4: Time-frequency vector based k-means clustering results ($k=3$) for Subject 1 in 3D

Figure 4.5: Resting state pattern results for Subject 2 (a)-(f) Time-frequency vector based clustering results with (a) complete set of clusters using k-means clustering with $k=3$ (b) cluster corresponding to default mode cluster for $k=3$ (c) complete set of clusters using k-means clustering with $k=4$ (d) cluster corresponding to default mode cluster for $k=4$ (e) complete set of clusters using k-means clustering with $k=5$ (f) cluster corresponding to default mode cluster for $k=5$ (g) fALFF results (h)-(i) MSA method results with (h) voxels having significant temporal autocorrelation (ac) values (i) the connectivity pattern of voxels obtained based on cross-correlation (cc) values

Figure 4.6: Resting state pattern results for Subject 3 (a)-(f) Time-frequency vector based clustering results with (a) complete set of clusters using k-means clustering with $k=3$ (b) cluster corresponding to default mode cluster for $k=3$ (c) complete set of clusters using k-means clustering with $k=4$ (d) cluster corresponding to default mode cluster for $k=4$ (e) complete set of clusters using k-means clustering with $k=5$ (f) cluster corresponding to default mode cluster for $k=5$ (g) fALFF results (h)-(i) MSA method results with (h) voxels having significant temporal autocorrelation (ac) values (i) the connectivity pattern of voxels obtained based on cross-correlation (cc) values

Figure 4.7: Resting state pattern results for Subject 4 (a)-(f) Time-frequency vector based clustering results with (a) complete set of clusters using k-means clustering with $k=3$ (b) cluster corresponding to default mode cluster for $k=3$ (c) complete set of clusters using k-means clustering with $k=4$ (d) cluster corresponding to default mode cluster for $k=4$ (e) complete set of clusters using k-means clustering with $k=5$ (f) cluster corresponding to default mode cluster for $k=5$ (g) fALFF results (h)-(i) MSA method results with (h) voxels having significant temporal autocorrelation (ac) values (i) the connectivity pattern of voxels obtained based on cross-correlation (cc) values

Chapter 5

Conclusion

Functional MRI technique is one of the most important neuroimaging techniques because of its non-invasive nature. Analysis of the acquired fMRI data is complex because the brain functionality is measured indirectly in the form of BOLD signal and also because of the presence of a number of artifacts and noise components in image data. In this thesis, we have proposed and tested frequency-domain and time-frequency domain statistical analysis techniques to handle temporal autocorrelation, and, to detect brain activation and resting state brain networks. Specifically, (i) we have proposed a mixed spectrum analysis method, for more effective removal of temporal autocorrelation effect in voxel time-series in a model-free manner while detecting activation, for detecting resting-state networks from a new perspective and also to simplify detection of physiological signals in fMRI data; (ii) introduced two frequency-domain approaches of using higher harmonics of stimulus frequency to enhance activation detection in periodic event-related data. One of these methods can selectively include higher harmonics. Second method is also extended to scale-space domain to provide enhanced information on spatial extent of activation, and (iii) proposed a novel time-frequency domain technique to detect default-mode networks in resting state fMRI data.

In Chapter 2, we presented the mixed spectrum analysis of fMRI data. The proposed MSA method was tested on a number of synthetic datasets generated with various temporal autocorrelation structures and values to simulate the varying temporal auto-

correlation structure across various brain regions and persons. Performing the sensitivity and specificity analysis using ROC curves, we found that our proposed model-free method of handling temporal autocorrelation in voxel time-series is better, with lower error rates, at handling varying temporal autocorrelation structures as compared to the fixed models. In the experiments on real fMRI memory-retrieval task dataset and visual task dataset, activations detected were more focal to the relevant cortical regions as compared to the GLM method. Applying Priestley's MSA principle, we were also able to accurately detect default mode networks in our experiments on four sets of resting-state datasets. Default mode network consists of anatomically separated regions such as precuneus, medial frontal and inferior parietal and temporal regions, that show high level of functional connectivity during resting state [103]. This is a new approach as it uses temporal autocorrelation values instead of low frequency amplitudes or seed-region time-series as are normally used. The MSA method was also tested on two sets of fMRI datasets, to detect the physiological signal related frequency components. Results were compared with the normally used spatial ICA based technique and detected frequency components were found to be similar. In comparison to sICA, the proposed method is easier to apply as it does not require accurate pre-identification of anatomical brain regions. The CRF principle, earlier applied to incorporate spatial correlation of activations, was also applied for regularization of AR(1) values in model-based pre-whitening case. Based on our tests on synthetic data, using box-plots to plot deviations of AR(1) values from actual values and also based on test on a fMRI dataset, CRF method was found to be more effective in reducing the deviations than the normally used smoothing filter based regularization. This method can easily be extended for models other than AR(1) model.

In Chapter 3, we presented two methods of enhancing activation detection in event-related data using higher harmonics of stimulus signal. HSH method uses selective inclusion of higher harmonics, whereas CHH uses fixed number of harmonics for each voxel time-series. Our experiments with synthetic data showed that, in the cases where HRF

used for generating data was deviated from canonical HRF, both the proposed HSH and CHH methods performed better than the GLM method, with lower error rates as calculated from ROC curves. For the case of synthetic data generated with canonical HRF, HSH method performed better than the GLM method mainly in the region of higher sensitivity and higher specificity, whereas CHH results were mostly similar to GLM results. For real fMRI data obtained in a memory retrieval experiment, HSH results were comparatively more focal and localized to the cortical areas. In this chapter, we have also extended a scale-space method based on χ^2 random field, to include higher harmonics of stimulus frequency in its analysis. Comparing the results of this method with the wavelet analysis method, for the memory retrieval task data, we found that it provides more detailed information about the spatial extent of each activated region.

In Chapter 4, we presented a novel method based on Cohen’s class of distribution for time-frequency analysis of the fMRI data. This method uses time-frequency distribution of low-frequency components. Based on the tests on synthetic data and four sets of resting state datasets, we found that our proposed method is able to better alienate default-mode network than the standard method that uses sum of low-frequency component amplitudes. Also the proposed method is less tedious than the other commonly used seed-based time-series analysis method as there is no need to select seed regions.

5.1 Future Work

The analysis of default mode network in human brain is an important approach towards understanding the functionality of human brain and in turn the human behavior. At the same time, behavioral study of humans is the key foundation in development of virtual agents that can interact in a natural manner. Hence we realize that we can merge the two fields by using this knowledge about the functionality of default mode network in developing better virtual agents or virtual patients. We have done some initial research

on this aspect, although challenging it is likely to result in significant improvement in development of virtual agents and virtual patients.

Another possibility of future work is in expanding the CRF model to perform spatio-temporal analysis. Presently, we have applied the CRF model only for spatial correlation of activation. In terms of state transitions probabilities along the time-series, these can be learned from the stimulus signal.

Priestley's method can also be improved to see if it can differentiate between the harmonics generated by temporal autocorrelation effect and those generated by the periodic phenomenon. In the present case, we were able to show that there are no harmonics generated by the temporal autocorrelation effect in the case of fMRI data based on our tests on the fMRI resting state and task related datasets.

Our proposed Hartley's F-test based method is able to detect appropriate number of harmonics in the periodic signal; hence it can be applied for a number of other spectrum based applications in fields other than fMRI.

References

- [1] P. Agnihotri, R. Fazel-Rezai, and N. Kaabouch. Comparative analysis of various brain imaging techniques. In *Engineering in Medicine and Biology Society (EMBC), 2010 Annual International Conference of the IEEE*, pages 3029–3032, 2010.
- [2] G. K. Aguirre, E. Zarahn, and M. D’Esposito. The variability of human, BOLD hemodynamic responses. *NeuroImage*, 8(4):360–369, 1998.
- [3] M. Artis, J. G. Clavel, M. Hoffmann, and D. Nachane. Harmonic regression models: a comparative review with applications. Technical Report No. 333, 2007.
- [4] P. A. Bandettini, A. Jesmanowicz, E. C. Wong, and J. S. Hyde. Processing strategies for time-course data sets in functional MRI of human brain. *Magnetic Resonance in Medicine*, 30:161–173, 1993.
- [5] J. Baudewig, P. Dechent, K. D. Merboldt, and J. Frahm. Thresholding in correlation analyses of magnetic resonance functional neuroimaging. *Magnetic Resonance Imaging*, 21(10):1121–1130, 2003.
- [6] R. Baumgartner, L. Ryner, W. Richter, R. Summers, M. Jarmasz, and R. Somorjai. Comparison of two exploratory data analysis methods for fMRI: fuzzy clustering vs. principal component analysis. *Magnetic Resonance Imaging*, 18(1):89–94, 2000.
- [7] R. Baumgartner, C. Windischberger, and E. Moser. Quantification in functional magnetic resonance imaging: fuzzy clustering vs. correlation analysis. *Magnetic Resonance Imaging*, 16(2):115–125, 1998.

- [8] C. F. Beckmann and S. M. Smith. Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Transactions on Medical Imaging*, 23(2):137–152, 2004.
- [9] R. J. Bhansali. A mixed spectrum analysis of the Lynx data. *Journal of the Royal Statistical Society, Series A*, 142(2):199–209, 1979.
- [10] B. Biswal, A. E. DeYoe, and J. S. Hyde. Reduction of physiological fluctuations in fMRI using digital filters. *Magnetic Resonance in Medicine*, 35(1):107–113, 1996.
- [11] B. Biswal and J. L. Ulmer. Blind source separation of multiple signal sources of fMRI data sets using independent component analysis. *Journal of Computer Assisted Tomography*, 23(2):265–271, 1999.
- [12] B. Biswal, F. Z. Yetkin, V. M. Haughton, and J. S. Hyde. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, 34(4):537–541, 1995.
- [13] S. Bonavita, A. Gallo, R. Sacco, M. D. Corte, A. Bisecco, R. Docimo, L. Lavorgna, D. Corbo, A. D. Costanzo, F. Tortora, M. Cirillo, F. Esposito, and G. Tedeschi. Distributed changes in default-mode resting-state connectivity in multiple sclerosis. *Multiple Sclerosis*, 17(4):411–422, 2011.
- [14] S. T. Bow. *Pattern recognition and image preprocessing*. Marcel Dekker, NY, 2002.
- [15] F. D. Bowman. Spatio-temporal modeling of localized brain activity. *Biostatistics*, 6(4):558–575, 2005.
- [16] E. Bullmore, M. Brammer, S. C. Williams, S. Rabe-Hesketh, N. Janot, A. David, J. Mellers, R. Howard, and P. Sham. Statistical methods of estimation and inference for functional MR image analysis. *Magnetic Resonance in Medicine*, 35(2):261–277, 1996.

- [17] V. D. Calhoun, T. Adali, L. K. Hansen, J. Larsen, and J. J. Pekar. ICA of functional MRI data: an overview. In *Proceedings of the 4th International Symposium on Independent Component Analysis and Blind Signal Separation*, pages 281–288, 2003.
- [18] C. Chatfield. *The analysis of time series: an introduction*. Texts in statistical science. Chapman & Hall/CRC, 2004.
- [19] H. Chen, D. Yao, W. Chen, and L. Chen. Delay correlation subspace decomposition algorithm and its application in fMRI. *IEEE Transactions on Medical Imaging*, 24(12):1647–1651, 2005.
- [20] S. Chen, C. A. Bouman, and M. J. Lowe. Clustered components analysis for functional MRI. *IEEE Transactions on Medical Imaging*, 23(1):85–98, 2004.
- [21] K. H. Chuang and J. H. Chen. IMPACT: Image-based physiological artifacts estimation and correction technique for functional MRI. *Magnetic Resonance in Medicine*, 46:344–353, 2001.
- [22] K. H. Chuang, M. J. Chiu, C. C. Lin, and J. H. Chen. Model-free functional MRI analysis using Kohonen clustering neural network and fuzzy C-means. *IEEE Transactions on Medical Imaging*, 18(12):1117–1128, 1999.
- [23] A. Cichocki and S. Amari. *Adaptive blind signal and image processing*. Wiley, 2002.
- [24] L. Cohen. *Time-Frequency Analysis*. Prentice Hall, Englewood Cliffs, NJ, 1995.
- [25] D. Cordes, V. Haughton, J. D. Carew, K. Arfanakis, and K. Maravilla. Hierarchical clustering to measure connectivity in fMRI resting-state data. *Magnetic Resonance Imaging*, 20(4):305–317, 2002.
- [26] M. S. Dagli, J. E. Ingelholm, and J. V. Haxby. Localization of cardiac-induced signal change in fMRI. *NeuroImage*, 9(4):407–415, 1999.

- [27] B. R. Daniel and G. H. Raymond. Multivariate statistical analysis in fMRI. *IEEE Engineering in Medicine and Biology magazine*, 25(2):60–64, 2006.
- [28] NITRC Database. NITRC Website (<http://www.nitrc.org>), 2011.
- [29] X. Descombes, F. Kruggel, and D. Y. von Cramon. fMRI signal restoration using a spatio-temporal Markov random field preserving transitions. *NeuroImage*, 8(4):340–349, 1998.
- [30] A. Di Martino, A. Scheres, D. S. Margulies, A. M. Kelly, L. Q. Uddin, Z. Shehzad, B. Biswal, J. R. Walters, F. X. Castellanos, and M. P. Milham. Functional connectivity of human striatum: a resting state fMRI study. *Cerebral Cortex*, 18(12):2735–2747, 2008.
- [31] A. Eklund, M. Andersson, C. Josephson, M. Johansson, and H. Knutsson. Does parametric fMRI analysis with SPM yield valid results? - An empirical study of 1484 rest datasets. *Neuroimage*, 61:565–578, 2012.
- [32] F. Esposito, A. Aragri, I. Pesaresi, S. Cirillo, G. Tedeschi, E. Marciano, R. Goebel, and F. Di Salle. Independent component model of the default-mode brain function: combining individual-level and population-level analyses in resting-state fMRI. *Magnetic Resonance Imaging*, 26(7):905–913, 2008.
- [33] F. Esposito, E. Formisano, E. Seifritz, R. Goebel, R. Morrone, G. Tedeschi, and F. Di Salle. Spatial independent component analysis of functional MRI time-series: to what extent do results depend on the algorithm used? *Human Brain Mapping*, 16(3):146–157, 2002.
- [34] M. J. Fadili, S. Ruan, D. Bloyet, and B. Mazoyer. A multistep unsupervised fuzzy clustering analysis of fMRI time series. *Human Brain Mapping*, 10(4):160–178, 2000.

- [35] C. Fassbender, H. Zhang, W. M. Buzy, C. R. Cortes, D. Mizuiri, L. Beckett, and J. B. Schweitzer. A lack of default network suppression is linked to increased distractibility in ADHD. *Brain Research*, 1273:114–128, 2009.
- [36] H. Fischer and J. Hennig. Neural network-based analysis of MR time series. *Magnetic Resonance in Medicine*, 41(1):124–131, 1999.
- [37] R.S.J. Frackowiak, K.J. Friston, C. Frith, R. Dolan, C.J. Price, S. Zeki, J. Ashburner, and W.D. Penny. *Human Brain Function*. Elsevier Academic Press, 2nd edition, 2004.
- [38] L. R. Frank, R. B. Buxton, and E. C. Wong. Estimation of respiration-induced noise fluctuations from undersampled multislice fMRI data. *Magnetic Resonance in Medicine*, 45:635–644, 2001.
- [39] K. J. Friston, A. P. Holmes, K. J. Worsley, J. B. Poline, C. Frith, and R. S. J. Frackowiak. Statistical parametric maps in functional imaging: a general linear approach. *Human Brain Mapping*, 2:189–210, 1995.
- [40] K. J. Friston, P. Jezzard, and R. Turner. Analysis of Functional MRI Time-Series. *Human Brain Mapping*, 1:153–171, 1994.
- [41] K. J. Friston, O. Josephs, E. Zarahn, A. P. Holmes, S. Rouquette, and J. Poline. To smooth or not to smooth? Bias and efficiency in fMRI time-series analysis. *NeuroImage*, 12(2):196–208, 2000.
- [42] T. Gautama and M. M. Van Hulle. Optimal spatial regularisation of autocorrelation estimates in fMRI analysis. *Neuroimage*, 23:1203–1216, 2004.
- [43] K. A. Gedif. *Detecting brain activations in functional magnetic resonance imaging (fMRI) experiments with a maximum cross-correlation statistic*. Southern Methodist University, 2008.

- [44] D. Gembris, J. G. Taylor, S. Schor, W. Frings, D. Suter, and S. Posse. Functional magnetic resonance imaging in real time (FIRE): sliding-window correlation analysis and reference-vector optimization. *Magnetic Resonance in Medicine*, 43(2):259–268, 2000.
- [45] G. H. Glover, T. Q. Li, and D. Ress. Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. *Magnetic Resonance in Medicine*, 44(1):162–167, 2000.
- [46] A. M. Golestani and B. G. Goodyear. Regions of interest for resting-state fMRI analysis determined by inter-voxel cross-correlation. *NeuroImage*, 56(1):246–251, 2011.
- [47] C. Gossel, D. P. Auer, and L. Fahrmeir. Bayesian spatiotemporal inference in functional magnetic resonance imaging. *Biometrics*, 57(2):554–562, 2001.
- [48] C. Goutte, P. Toft, E. Rostrup, F. Nielsen, and L. K. Hansen. On clustering fMRI time series. *NeuroImage*, 9(3):298–310, 1999.
- [49] M. A. Gray, L. Minati, N. A. Harrison, P. J. Gianaros, V. Napadow, and H. D. Critchley. Physiological recordings: basic concepts and implementation during functional magnetic resonance imaging. *NeuroImage*, 47(3):1105–1115, 2009.
- [50] J. M. Hammersley and P. Clifford. Markov field on finite graphs and lattices. 1971.
- [51] L. Hernandez, D. Badre, D. Noll, and J. Jonides. Temporal sensitivity of event-related fMRI. *NeuroImage*, 17(2):1018–1026, 2002.
- [52] X. Hu, T. H. Le, T. Parrish, and P. Erhard. Retrospective estimation and correction of physiological fluctuation in functional MRI. *Magnetic Resonance in Medicine*, 34:201–212, 1995.

- [53] S.A. Huettel, A.W. Song, and G. McCarthy. *Functional magnetic resonance imaging*. Sinauer Associates Inc, USA, 2004.
- [54] A. Hyvarinen and E. Oja. Independent component analysis: algorithms and applications. *Neural Networks*, 13(4-5):411–430, 2000.
- [55] G. H. Jiang, Y. W. Qiu, X. L. Zhang, L. J. Han, X. F. Lv, L. M. Li, C. L. Lin, F. Z. Zhuo, S. Y. Hu, and J. Z. Tian. Amplitude low-frequency oscillation abnormalities in the heroin users: a resting state fMRI study. *NeuroImage*, 57(1):149–154, 2011.
- [56] W. Koch, S. Teipel, S. Mueller, J. Benninghoff, M. Wagner, A. L. Bokde, H. Hampel, U. Coates, M. Reiser, and T. Meindl. Diagnostic power of default mode network resting state fMRI in the detection of Alzheimer’s disease. *Neurobiology of Aging*, 33(3):466–478, 2012.
- [57] A. Kumar and J. C. Rajapakse. Power spectral based detection of brain activation. *Neural Computing and Applications*, 16(6):551–557, 2007.
- [58] A. Kumar and J. C. Rajapakse. Time-frequency method based activation detection in functional MRI time-series. In *Lecture Notes in Bioinformatics*, 4774, pages 368–377, 2007.
- [59] A. Kumar and J. C. Rajapakse. Scale-space analysis of event-related fMRI data using higher harmonics. In *IEEE Conference Publications, Defense Science Research Conference*, pages 1–4, 2011.
- [60] J. Lafferty, A. McCallum, and F. Pereira. Conditional random fields: probabilistic models for segmenting and labeling sequence data. In *Proceedings of the Eighteenth International Conference on Machine Learning, ICML ’01*, pages 282–289, 2001.

- [61] N. Lange and S. Zeger. Non-linear Fourier time series analysis for human brain mapping by functional magnetic resonance imaging. *Appl. Statist.*, 46(1):1–29, 1997.
- [62] B. Lenoski, L. C. Baxter, L. J. Karam, J. Maisog, and J. Debbins. On the performance of autocorrelation estimation algorithms for fMRI analysis. *IEEE Journal of Selected Topics in Signal Processing*, 2(6):828–838, 2008.
- [63] M. A. Lindquist. The statistical analysis of fMRI data. *Statistical Science*, 23(4):439–464, 2008.
- [64] J. J. Locascio, P. J. Jennings, C. I. Moore, and S. Corkin. Time series analysis in the time domain and resampling methods for studies of functional magnetic resonance brain imaging. *Human Brain Mapping*, 5(3):168–193, 1997.
- [65] X. Y. Long, X. N. Zuo, V. Kiviniemi, Y. Yang, Q. H. Zou, C. Z. Zhu, T. Z. Jiang, H. Yang, Q. Y. Gong, L. Wang, K. C. Li, S. Xie, and Y. F. Zang. Default mode network as revealed with multiple methods for resting-state functional MRI analysis. *Journal of Neuroscience Methods*, 171(2):349–355, 2008.
- [66] W. Lu and J. C. Rajapakse. Approach and applications of constrained ICA. *IEEE Transactions on Neural Networks*, 16(1):203–212, 2005.
- [67] T. E. Lund, K. H. Madsen, K. Sidaros, W. L. Luo, and T. E. Nichols. Non-white noise in fMRI: Does modelling have an impact? *Neuroimage*, 29:54–66, 2006.
- [68] L. Ma, B. Wang, X. Chen, and J. Xiong. Detecting functional connectivity in the resting brain: a comparison between ICA and CCA. *Magnetic Resonance Imaging*, 25(1):47–56, 2007.
- [69] J. L. Marchini and Ripley B. D. A new statistical approach to detecting significant activation in functional MRI. *NeuroImage*, 12(4):366–380, 2000.

- [70] A. Meyer-Baese, A. Wismueller, and O. Lange. Comparison of two exploratory data analysis methods for fMRI: unsupervised clustering versus independent component analysis. *IEEE Transactions on Information Technology in Biomedicine*, 8(3):387–398, 2004.
- [71] A. Mezer, Y. Yovel, O. Pasternak, T. Gorfine, and Y. Assaf. Cluster analysis of resting-state fMRI time series. *NeuroImage*, 45(4):1117–1125, 2009.
- [72] M. Misaki and S. Miyauchi. Application of artificial neural network to fMRI regression analysis. *NeuroImage*, 29(2):396–408, 2006.
- [73] P. P. Mitra and B. Pesaran. Analysis of dynamic brain imaging data. *Biophysical Journal*, 76(2):691–708, 1999.
- [74] C. H. Moritz, B. P. Rogers, and M. E. Meyerand. Power spectrum ranked independent component analysis of a periodic fMRI complex motor paradigm. *Human Brain Mapping*, 18(2):111–122, 2003.
- [75] K. Muller, G. Lohmann, S. Zysset, and D. Y. Cramon. Wavelet statistics of functional MRI data and the general linear model. *Journal of Magnetic Resonance Imaging*, 17(1):20–30, 2003.
- [76] S. C. Ngan and X. Hu. Analysis of functional magnetic resonance imaging data using self-organizing mapping with spatial connectivity. *Magnetic Resonance in Medicine*, 41(5):939–946, 1999.
- [77] S. C. Ngan, X. Hu, L. H. Tan, and P. L. Khong. Improvement of spectral density-based activation detection of event-related fMRI data. *Magnetic Resonance Imaging*, 27(7):879–894, 2009.
- [78] W. Ou, W. M. III Wells, and P. Golland. Combining spatial priors and anatomical information for fMRI detection. *Medical Image Analysis*, 14(3):318–331, 2010.

- [79] W. Penny and K. Friston. Mixtures of general linear models for functional neuroimaging. *IEEE Transactions on Medical Imaging*, 22(4):504–514, 2003.
- [80] V. Perlberg, P. Bellec, J. L. Anton, M. Pelegrini-Issac, J. Doyon, and H. Benali. CORSICA: correction of structured noise in fMRI by automatic identification of ICA components. *Magnetic Resonance Imaging*, 25(1):35–46, 2007.
- [81] S. Pollmann, S. Zysset, C. J. Wiggins, and D. Y. Von Cramon. Dissociation of memory retrieval and search processes: an event-related fMRI study. *Microscopy Research and Technique*, 51(1):29–38, 2000.
- [82] M. B. Priestley. Analysis of stationary processes with mixed spectra-II. *Journal of the Royal Statistical Society. Series B*, 24(2):511–529, 1962.
- [83] M. B. Priestley. The analysis of stationary processes with mixed spectra-I. *Journal of the Royal Statistical Society. Series B*, 24(1):215–233, 1962.
- [84] M. B. Priestley. *Spectral analysis and time series*. Academic Press, London, 1981.
- [85] P. L. Purdon and R. M. Weisskoff. Effect of temporal autocorrelation due to physiological noise and stimulus paradigm on voxel-level false-positive rates in fMRI. *Human Brain Mapping*, 6(4):239–249, 1998.
- [86] M. E. Raichle, A. M. MacLeod, A. Z. Snyder, W. J. Powers, D. A. Gusnard, and G. L. Shulman. A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, 98(2):676–682, 2001.
- [87] J. C. Rajapakse, F. Kruggel, J. M. Maisog, and D. Y. von Cramon. Modeling hemodynamic response for analysis of functional MRI time-series. *Human Brain Mapping*, 6(4):283–300, 1998.

- [88] J. C. Rajapakse, F. Kruggel, S. Zysset, and D. Y. von Cramon. Neuronal and hemodynamic events from fMRI time-series. *Journal of Advanced Computational Intelligence*, 2(6):185–194, 1998.
- [89] J. C. Rajapakse and J. Piyaratna. Bayesian approach to segmentation of statistical parametric maps. *IEEE Transactions on Biomedical Engineering*, 48(10):1186–1194, 2001.
- [90] J. C. Rajapakse, C. L. Tan, X. Zheng, S. Mukhopadhyay, and K. Yang. Exploratory analysis of brain connectivity with ICA. *IEEE Engineering in Medicine and Biology Magazine*, 25(2):102–111, 2006.
- [91] U. E. Ruttimann, M. Unser, R. R. Rawlings, D. Rio, N. F. Ramsey, V. S. Mattay, D. W. Hommer, J. A. Frank, and D. R. Weinberger. Statistical analysis of functional MRI data in the wavelet domain. *IEEE Transactions in Medical Imaging*, 17:142–154, 1998.
- [92] J. L. Semmlow. *Biosignal and biomedical image processing*. Marcel Dekker Inc., USA, 2004.
- [93] FMRLAB Software. Swartz Centre for Computational Neuroscience Website (<http://sccn.ucsd.edu/fmrlab/>), June 2008-2012.
- [94] Rest Software. Forum of Resting State fMRI Website (<http://restfmri.net/forum/REST>), June 2009-2012.
- [95] SPM Software. Wellcome Department of Imaging Neuroscience, 2004. Statistical Parametric Mapping Website (<http://www.fil.ion.ucl.ac.uk/spm/>), June 2004-2012.
- [96] WSPM Software. Wavelet-based SPM Website (<http://miplab.epfl.ch/wspm/>), June 2011-2012.

- [97] T. Subba Rao, M. B. Priestley, and O. Lessi. *Applications of time-series analysis in astronomy and meteorology*. Chapman & Hall, Great Britain, 1997.
- [98] P. Suetens. *Fundamentals of medical imaging*. Cambridge University Press, U.K., 2009.
- [99] B. Thirion and O. Faugeras. Dynamical components analysis of fMRI data through kernel PCA. *NeuroImage*, 20(1):34–49, 2003.
- [100] C. G. Thomas, R. A. Harshman, and R. S. Menon. Noise reduction in BOLD-based fMRI using component analysis. *NeuroImage*, 17(3):1521–1537, 2002.
- [101] M. Unser and A. Aldroubi. A review of wavelets in biomedical applications. *Proceedings of the IEEE*, 84(4):626–638, 1996.
- [102] D. Van De Ville, T. Blu, and M. Unser. Surfing the brain: an overview of wavelet-based techniques for fMRI data analysis. *IEEE Engineering in Medicine and Biology Magazine*, 25(2):65–78, 2006.
- [103] M. P. van den Heuvel and H. E. Hulshoff Pol. Exploring the brain network: a review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology*, 20(8):519–534, 2010.
- [104] A. Venkataraman, Koene R. A. Van Dijk, R. L. Buckner, and P. Golland. Exploring functional connectivity in fMRI via clustering. In *Proceedings of the 2009 IEEE International Conference on Acoustics, Speech and Signal Processing, ICASSP '09*, pages 441–444, 2009.
- [105] M. Voultzidou, S. Dodel, and J. M. Herrmann. Neural networks approach to clustering of activity in fMRI data. *IEEE Transactions on Medical Imaging*, 24(8):987–996, 2005.

- [106] S. Wang, L. Luo, X. Liang, Z. Gui, and C. Chen. Estimation and removal of physiological noise from undersampled multi-slice fMRI data in image space. *International Conference of the IEEE Engineering in Medicine and Biology Society*, 2:1371–1373, 2005.
- [107] Y. Wang and J. C. Rajapakse. Contextual modeling of functional MR images with conditional random fields. *IEEE Transactions on Medical Imaging*, 25(6):804–812, 2006.
- [108] W. A. Woodward and H. L. Gray. A comparison of autoregressive and harmonic component models for the lynx data. *Journal of the Royal Statistical Society Series A (General)*, 146(1):71–73, 1983.
- [109] M. W. Woolrich, M. Jenkinson, J. M. Brady, and S. M. Smith. Fully bayesian spatio-temporal modeling of fMRI data. *IEEE Transactions on Medical Imaging*, 23(2):213–231, 2004.
- [110] M. W. Woolrich, B. D. Ripley, M. Brady, and S. M. Smith. Temporal autocorrelation in univariate linear modeling of fMRI data. *NeuroImage*, 14(6):1370–1386, 2001.
- [111] K. J. Worsley. Testing for signals with unknown location and scale in a χ^2 random field, with an application to fMRI. *Advances in Applied Probability*, 33(4):773–793, 2001.
- [112] K. J. Worsley. Spatial smoothing of autocorrelations to control the degrees of freedom in fMRI analysis. *NeuroImage*, 26(2):635–641, 2005.
- [113] K. J. Worsley, A. C. Evans, S. Marrett, and P. Neelin. A three dimensional statistical analysis for CBF activation studies in human brain. *Journal of Cerebral Blood Flow and Metabolism*, 12:900–918, 1992.

- [114] K. J. Worsley and K. J. Friston. Analysis of fMRI time-series revisited—again. *NeuroImage*, 2(3):173–181, 1995.
- [115] K. J. Worsley, C. H. Liao, J. Aston, V. Petre, G. H. Duncan, F. Morales, and A. C. Evans. A general statistical analysis for fMRI data. *NeuroImage*, 15(1):1–15, 2002.
- [116] K. J. Worsley, S. Marrett, P. Neelin, A. C. Vandal, K. J. Friston, and Evans A. C. A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping*, 4:58–73, 1996.
- [117] K. J. Worsley, M. Wolforth, and A. C. Evans. Scale space searches for a periodic signal in fMRI data with spatially varying hemodynamic response. In *Proceedings of BrainMap’95 Conference*, 1997.
- [118] F. Xu, A. V. Zibonele, and H. Lu. Wavelet decomposition analysis for ultra-high temporal resolution fMRI time-series. *IEEE workshop on Engineering in Medicine and Biology*, pages 86–89, 2007.
- [119] Y. F. Zang, Y. He, C. Z. Zhu, Q. J. Cao, M. Q. Sui, M. Liang, L. X. Tian, T. Z. Jiang, and Y. F. Wang. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain and Development*, 29(2):83–91, 2007.
- [120] E. Zarahn, G. K. Aguirre, and M. D’Esposito. Empirical analyses of BOLD fMRI statistics. I. Spatially unsmoothed data collected under null-hypothesis conditions. *NeuroImage*, 5(3):179–197, 1997.
- [121] Z. Zhang, G. Lu, Y. Zhong, Q. Tan, W. Liao, Z. Wang, Z. Wang, K. Li, H. Chen, and Y. Liu. Altered spontaneous neuronal activity of the default-mode network in mesial temporal lobe epilepsy. *Brain Research*, 1323:152–160, 2010.

- [122] J. Zhou and J. C. Rajapakse. Fuzzy approach to incorporate hemodynamic variability and contextual information for detection of brain activation. *Neurocomputing*, 71(16-18):3184–3192, 2008.
- [123] K. H. Zou, A. J. O’Malley, and L. Mauri. Receiver-operating characteristic analysis for evaluating diagnostic tests and predictive models. *Circulation*, 115(5):654–657, 2007.
- [124] Q. H. Zou, C. Z. Zhu, Y. Yang, X. N. Zuo, X. Y. Long, Q. J. Cao, Y. F. Wang, and Y. F. Zang. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *Journal of Neuroscience Methods*, 172(1):137–141, 2008.
- [125] X. N. Zuo, A. Di Martino, C. Kelly, Z. E. Shehzad, D. G. Gee, D. F. Klein, F. X. Castellanos, B. B. Biswal, and M. P. Milham. The oscillating brain complex and reliable. *NeuroImage*, 49(2):1432–1445, 2010.