Implementation of Contextual Clustering Method for Statistical Parametric Maps in Functional Magnetic Resonance Images

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Abstract: *A contextual clustering procedure for Statistical Parametric Maps is calculated from time varying three-dimensional images. The algorithm can be used for the detection of neural activations from functional Magnetic Resonance Images. Ogawa et al. (1990) have discussed about the brain magnetic resonance imaging with contrast dependent on blood oxygenation concepts. Subsequently, the processing strategies for time-course data sets in functional magnetic resonance imaging of the human brain have been analyzed by Bandettini et al. (1993). By using the voxel by voxel testing technique, the neighborhood information is utilized and this is achieved by using a Markov random field prior concept and Iterated Conditional Modes algorithm. The simulation results and human functional magnetic resonance imaging experiments using visual stimulation demonstrate that a better sensitivity is achieved with a given specifications in comparison with the voxel-by-voxel thresholding technique.*

Keywords: *Brain imaging, structural anatomy, auditory signal processing, statistical parametric mapping functional magnetic resonance images, fMRI.*

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1. Introduction

Current tomographic technologies in medical imaging enable the study of brain function by measuring hemodynamic changes related to changes in neuronal activity. The signal changes observed in functional Magnetic Resonance Imaging (fMRI) are mostly based on Blood Oxygenation Level Dependent (BOLD) methods and are usually close to the noise level. Consequently, statistical methods and signal average methods are frequently used to distinguish data signals in the noise backgrounds area. In most fMRI setups, images are acquired during alternating task (stimulus) and control (rest) conditions.

The analysis of the image series is frequently based on the computation of a statistical parametric map and statistical inferences derived from it. The voxel-by-voxel computation technique for the difference of means of intensities between control and task states is normalized by the estimated standard error. This generates a statistical map that follows the distribution in the non active area. Correlation analysis, subspace modeling, Fourier and wavelet transform methods, pseudo generalized least squares analysis using sinusoidal regression and Kolmogorov Smirnov test are examples of other approaches used to create statistical maps. The linear model is a general framework that includes the simple parametric tests. Significant active areas are found by thresholding the maps. Methods that assess statistical significance levels are based on the spatial extent of the cluster activation. In order to improve the sensitivity, thresholding technique has been developed.

Because the spatial extent must exceed a threshold, this type of method is known as Dual Parameter Thresholding (DPT) techniques. It should be noted that the fMRI time series may be temporally correlated and that the general linear model has been extended to deal with temporal correlations. Several preprocessing steps such as motion correction and temporal filtering are frequently performed before the analyzing of data. In particular, spatial filtering is frequently used to increase signal-to-noise ratio and validity of inferences are based on the theory of Gaussian fields. In addition to the above mentioned inferential data analysis approaches, several methods that emphasize the exploratory nature of the problem have been proposed. These methods include independent spatial component analysis, principal component analysis, and clustering of the time series. Ardekani *et al*. [4] have activated the detection in functional MRI using subspace modeling and maximum likelihood estimation and Bullmore have developed the statistical methods of estimation and inference for functional MRI analysis.

A single activation region typically consists of numerous voxels. Hence, it may be useful to utilize contextual information. In texture segmentation, pixel features are acquired from a pixel neighborhood. A simple example of a method that utilizes classification information from a voxel's neighborhood is the median filtering of the thresholded image. In addition, the DPT techniques and spatial filtering methods can be used which incorporate contextual information for the data analysis. An interesting option is to use the intensity value of a pixel and classification information from the pixel neighborhood in the same stage of the classification. This approach can be realized in the context of Markov Random Fields (MRF). MRFs regularize a classification by defining interactions between neighboring pixels. An MRF model is also used for the spatiotemporal analysis of fMRI data. An iterative contextual analysis method is designed which is based on MRFs. The first step in this method is to compute a statistical parametric map using well-known results from general linear models. Then, the statistical parametric map is clustered, therefore segmented into non-active and active regions. The contextual clustering algorithm is based on besag's Iterated Conditional Modes (ICM) algorithm. However, in this The ICM algorithm is modified for performing hypothesis testing by defining an artificial activation class. The null hypothesis is set such that the voxel is non-active. If the null hypothesis is rejected, then voxel is considered to be active. Simulations are used to find false positive (i.e., false activation) rates for different varying parameter values of the algorithm. This allows classification so that the probability of false values is controlled.

2. Brain Imaging

Brain imaging basically consists of the structural anatomy, functional anatomy, auditory signal processing and the functions are explained in detail as follows.

2.1. Structural Anatomy

The basic anatomical structure of the human brain is depicted in Figure 1 It has been studied for a long time about the function of the brain in terms of crude and invasive methods. Central Nervous System (CNS) is formed by the cortex, brain stem, cerebellum and other connected subcortical areas. The brain stem and other sub cortical regions are mainly involved in lower level functions, like automation and primitive signal processing. Higher functions, such as conscious thought, are performed on the cortex is the surface of the brain. Higher functions, like memory, also rely on support from the sub cortical areas.

The surface is heavily folded to increase its area and the folds are defined as sulci and it separates the surface into small sections termed as gyri. Bigger folds that separate larger parts are called fissures, like the longitudinal fissure shown in Figure 1(a), which separates the left and right hemispheres of the brain. The division of the cortex into the four lobes, as shown in Figure 1(b), is somewhat arbitrary, but it is based on major sulci and fissures which are visible on the surface. The density of neurons, their size and shape differ between the areas. The boundaries are not always so clear in real brains and changes are seen slightly from one individual to another.

2.2. Functional Anatomy

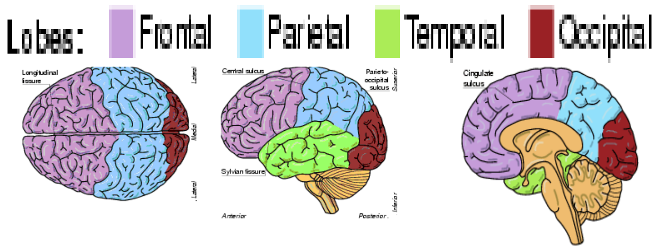
Functional anatomy mainly deals with the surface areas of the brain. The neuronal configuration is similar throughout the surface, but different inputs and outputs of the peripheral nervous system are connected to different parts of the brain. Thus, different areas of the brain are involved with different kinds of information in which different purposes are served. Table 1 provides the functional properties of the four lobes of the brain. Figure 2(a) depicts the location of some of the well known primary processing areas on the cortex. These areas are mainly connected contralaterally, which means that the areas on the left hemisphere are mainly responsible for signals from the right side of the body. The primary areas are then connected to additional areas nearby on the same hemisphere. The additional areas usually perform more complex functions based on the processing done on the primary areas. The left and right hemispheres of the brain are functionally quite symmetric in nature, but usually each task has a more dominant side. The brain is also adaptive in the sense that sometimes other areas overtake more functionally, when the dominant side suffers an injury.

2.3. Auditory Signal Processing

Audio processing may seem relatively simple compared to visual image processing. However, auditory processing is closely linked to understanding of spoken language and therefore related to higher functions, such as memory and conscious thinking. The signal processing actually begins already in the ear and in the thalamus, even before the signals reach the cortex. The early processing is used to form a tonotopic map (t-map) based on frequency on the primary auditory area. Unlike in many other sensory inputs, audio signals from both ears are used together, which makes it possible to detect the direction of the original sound by analyzing the phases of the signals. The primary auditory area responds to all kinds of sounds, but it is tightly connected with additional areas involved in more complex processing and these areas are shown in Figure 2(b).

3. Evolution of Imaging Techniques

In the past decades crude pathological methods existed for studying the brain, and functional studies were virtually impossible. Brain imaging has been developing rapidly during the last decades. Specifically in recent years, it has become also quite noninvasive, allowing theroutine imaging of living tissues. The potential future techniques used are Near InfraRed Spectroscopy (NIRS) or Diffuse Optical Imaging (DOI).

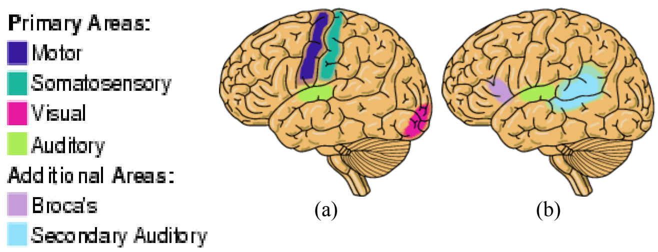


(a) (b) (c)

Figure 1. Anatomical structure of the human brain.

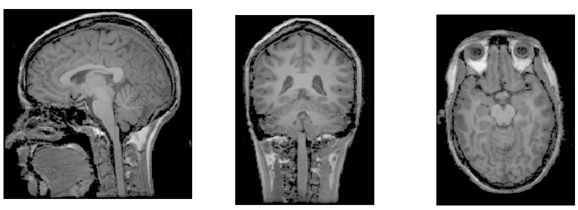
Table 1. Functional properties of the four lobes of the brain.

Lobe	Input and Output	Other Functions
Frontal	Motor	Memory and Emotions
Temporal	Auditory	Language and Structure
Parietal	Somatosensory	Association and Attention
Occipital	Visual	Pattern and Object Recognition



(a) (b)

Figure 2. Functional areas of the human brain.



(a) (b) (c)

Figure 3. Examples of structural magnetic resonance images.

It is based on the diffusion of laser-light in tissue and blood. The difficulties in using Laser based maging method includes the ability to generate high resolution images and penetrate deep into the tissues.

The images in Figure 3 shows the slices of a human head viewed from (a) sagittal, (b) frontal and (c) horizontal directions. Using standard signal processing techniques, the measurements can be turned into an image of the focused slice. The full volume is produced by scanning several adjacent slices, one after the other. The image voxels contain a kind of density measure based on the scanning parameters and the properties of the tissue. The scanning is actually very slow because of the relaxation process and adjusting the magnetic fields, requires certain amount of time. Producing high resolution images more time is consumed which is shown in Figure 3. Naturally, the quality of the images is strongly affected by homogeneities in the magnetic fields, the internal magnetic interactions and electromagnetic interference from the environment.

A study of fMRI is shown in Figure 4(a). The low resolution and the scanning parameters, optimized for BOLD, make the contrast between different tissue types which are not good. Additionally, the fast scanning and low signal-to-noise ratio of the BOLD signal make the image very noisy. Therefore, a high resolution structural MRI is often scanned separately to aid in locating the activation during analysis by super-positioning. The bright areas in the images do not necessarily correspond to the active areas. Careful analysis of the whole sequence is required to detect the activation patterns.

.a Standard Preprocessing of Images

In addition to the low signal-to-noise ratio and additive noise, which is seen in Figure **4(a)**, the fMRI measurements are contaminated with artifacts, such as head movement and physiological vascular changes. Thus, the detection and analysis of interesting phenomena is very difficult. To overcome these difficulties, the images need to be preprocessed. Figure **4(b)** is a slice after preprocessing. The level of noise is clearly reduced and the values are much more continuous. Also, the excess area outside the brain has been removed which is shown in black.

The reference time-course can be approximated using the stimulation pattern and a model of the hemodynamic response, as shown in Figure 5. The depicted pattern is a very simple case of repeated on-off type of stimulus. The stimulation time-course is then convolved with the model of the hemodynamic response which is Gaussian.

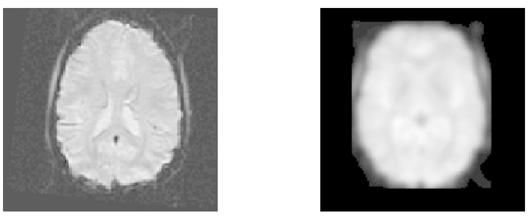
The analysis can be considered in two steps. First, the reference time-course is compared to the time-course of each voxel in the fMRI sequence statistically. This produces an image of the probability to fit the given time-course, where the voxels with the highest probabilities are considered to be active. However, the probability image is very noisy and the second step is to segment it into the active and non-active areas. The segmentation is made robust by using a statistical model for the noise, usually assumed Gaussian. The difficulty with this approach is to define a threshold for the probability of activation that produces an accurate segmentation.

After the spatial activation patterns have been formed, the true activation time-course of each area is formed by taking the mean sequence of all the voxels in the area. Again, if the segmentation is poor then it is due to an incorrect threshold value and the time-courses are not generated accurately.

4. Statistical Parametric Mapping

Kwong [8] have implemented the fRMI with echo planar imaging. Friston *et al*. [5] have made a report on Statistical parametric maps in functional imaging under general linear approach. The use of temporal correlation coefficients for magnetic resonance mapping of functional brain activation under individualized thresholds and spatial response delineation was analyzed by Kkleinschmidt *et al.* [7].

Characterizing a regionally specific effect rests on estimation and inference. Inferences in neuroimaging may be about differences expressed when comparing one group of subjects to another or within subjects. Changes are noted over a sequence of observations. They may pertain to structural differences in voxel-based morphometry or Neuro physiological indices of brain functions.



(a) A scanned slice without processing

(b) After the standard preprocessing has been applied. The images do not show a direct measure of activation.

Figure 4. Sample of functional magnetic resonance image..

.i Realignment

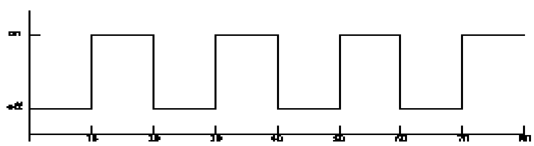
Kuppusamy *et al*. [9] have used the statistical assessment of cross correlation, variance methods and analyzed the importance of electro-cardiogram gating in functional magnetic resonance imaging. Brammer used the concept of multidimensional wavelet analysis of functional magnetic resonance images and a new statistical approach was introduced for detecting the significant activation in functional MRI by Marchini *et al*. [10] Kannan *et al*. [11] has analysed the genetic code by the implementation of artificial Neural Network with Hidden Markov Model.

But in this paper changes in signal intensity over time from any one voxel, can arise from head motion and this represents a serious confound, particularly in fMRI studies. Despite restraints on head movement, co-operative subjects still show displacements upto several millimeters. Realignment involves (1) estimating the 6 parameters of an affine “rigid-body” transformation that minimizes the [sum of squared] differences between each successive scan and a reference scan (usually the first or the average of all scans in the time series) and (2) applying the transformation by re-sampling the data using tri-linear interpolation. Estimation of the affine transformation is usually effected with a first order approximation of the Taylor expansion in which the effect of movement on signal intensity using the spatial derivatives of the images are observed. This leads to a simple iterative least square solution that corresponds to a Gauss-Newton search. For most imaging modalities this procedure is sufficient to realign scans. However, in fMRI, even after perfect realignment, movement-related signals can still persist. This calls for a further step in which the data are adjusted for residual movement-related effects.

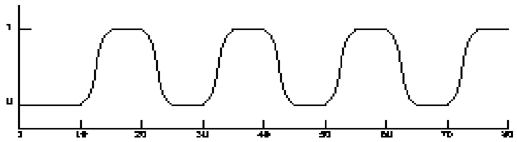
The Bayesian alternative to classical inference with SPMs rests on conditional inferences about an effect if the data is given as opposed to classical inferences about the data in which the effect is zero. Bayesian inferences about spatially extended effects use Posterior Probability Maps (PPMs). Although less commonly used than SPMs, PPMs are potentially very useful because they do not have to contend with the multiple comparisons problem induced by classical inference. The coloring is based on a smooth gradient for a range of smoothly interpolated values, which makes stronger activation and in brighter (hotter) colors. The color gradient can be seen in Figure 6(b), which shows the histogram of the activation volume.

As the active regions are sparsely distributed the volume is noisy. Therefore, the main lobe of the histogram can be considered as noise or the inactive region. The volume is always shown so that the tail of the histogram with the most energy or mass which is considered to be the positive extreme.

This effectively fixes the sign ambiguity of ICA. However, there are cases where the histogram is almost symmetric in nature and all the energy is in the main lobe. From this, it is understood that there is no significant focal activation in the volume.

(a)  An

ideal stimulation time-course comprising of rest and activation periods



(b) The corresponding ideal reference time-course with The hemodynamic response. In reality the detected time-course varies significantly

Figure 5. Illustration of an ideal stimulus.

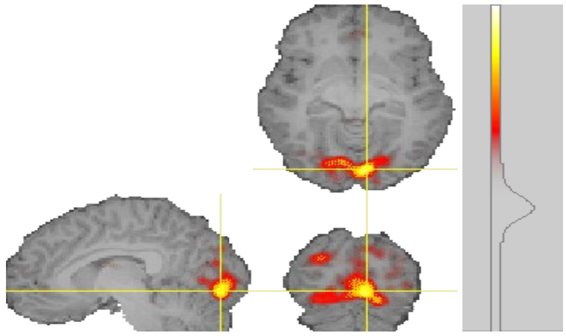


Figure 6. First partial view of the interactive user interface.

Figure 6 reflects the fact that the volumes from three orthogonal directions with the cross-hairs pinpointing the current location and the histogram of the activation volume. The structural volume is drawn using grayscale values and the amount of activation with color gradient, where brighter (hotter) colors means stronger activation. The gradient used for coloring the activation pattern is fitted to the range from the main lobe to the more powerful extreme. The lower end of the gradient is fully transparent and the higher end is fully opaque. As mentioned, the color also changes smoothly from darker (colder) to brighter (hotter) values. It is very easy to see that a strongly activated area is located at the back of the brain on the right side, most probably related to processing visual information. It is also possible to calculate and show the variability from the volume, but calculating the volumetric distribution is very time consuming. Still, the volume may allow easier interpretation of certain kind of variability, as shown in one of the results from the experiments in Figure 9.

The left disk of Figure 7 shows the spread of the Euclidean distances between the members of the group and the right disk between the distances to all other groups, with the black circles marking the mean values of those distances.

5.1. Complete User Interface

Multi-modal information is brought together to allow the interactive human interpretation. The complete user interface, for a single component is shown in Figure 8, which combines the parts shown in Figures 6, 7 and 6 The interface includes some numerical properties of the component shown above and below the time-course. Also, a possible reference time-course is shown as a two colour pattern beneath the activation time-course. The bands depict the on-off nature of the stimulus.

The numerical information is related to the grouping and the histogram of the activation pattern. The number of estimates in the group and the normalized rank of the component are on the top. The ratio of energy between the upper and lower tail of the histogram, related to skewness and the amount of energy in the main lobe of the histogram are on the bottom.

Additionally, the user interface offers helpful interactive tools, which make it very user friendly. The functional overlay can be toggled on or off to reveal the structure underneath. The activation pattern can also be viewed without the structural template. The component does not contain clear or focal activations. The current location can be centered on the strongest activation automatically. All the interactive tools are focused on making the interpretation fast and easy.

.a Volume Acquisition

During the four repetitions of speech and resting periods 10 full head volumes were acquired in each condition with a scanning interval of approximately 3 seconds, resulting in a total of 80 volumes. It is common that under a hypothesis driven experiment the scanning is focused only on a few slices of the brain, which have been classified as interesting beforehand. Sometimes this is beneficial, since it could allow faster scanning or increased resolution, but as ICA is a purely data-driven method then it would be rather impossible to define the interesting regions of the brain beforehand. And again, such scanning would limit the data too much to fully characterize unexpected phenomena.

.a Volume Preparation

Before data analysis, the volumes were processed in the usual way fMRI data is processed by using the traditional analysis method. This was done with the SPM toolbox and resulted, for each of the 14 subjects, in 80 volumes with a resolution of 95 X 79 X 69 voxels. Additionally, the volumes were masked with a cortical mask to remove uninteresting voxels outside the brain. This effectively lowered the amount of data to half, still leaving an intimidating 80 X 254484 observation matrix per subject.

6. Results: Individual Experiments

The observation matrix of each subject was then analyzed with the method. The FastICA algorithm was run 100 times using a bootstrapping of 20% and PCA whitening to the 30 strongest principal components in each run. FastICA was used in symmetric mode with nonlinearity concepts estimating 15 independent components in each run. This resulted in 1500 independent component estimates per subject, which were then clustered with correlation threshold 0.8 and power 8.

7. Conclusions

The utilization of contextual information was studied for the analysis of fMRI data. The results presented here demonstrate that the context-free thresholding is more sensitive to random noise than the contextual analysis. Better sensitivity was achieved with contextual clustering. The results show that the spatial autocorrelations present in a typical fMRI study in which the effect is small particularly for family-wise tests. The main conceptual difference between the method of Descombes and the method presented here is that the former performs data restoration and analysis for the original spatio-temporal fMRI data while the latter clusters a standard statistical parametric map. In addition, Simulated Annealing (SA) optimization algorithm was used to find the global maximum of the objective function.

A strong point of ICM is the exclusive dependence on local image characteristics. For fMRI data, the ICM algorithm converged in ten cycles. The small number of cycles assures that a deviating data distribution either due to activation or art-fact at one location does not increase the false positive probability or reduce the power. The results indicate that the power of the developed contextual algorithm is superior to that of conventional voxel-by-voxel thresholding of a statistical parametric map. A method for analyzing the consistency of independent components was presented and its usefulness was tested in a real fMRI study. The method works well with real fMRI data indeed, makes interpreting the results easier and more reliable.

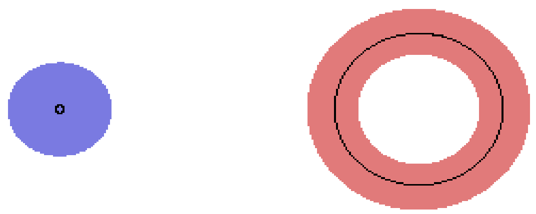


Figure 7. Third partial view of the interface, showing the discrimination power of the group.

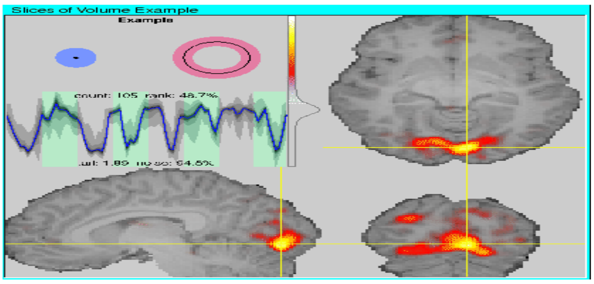


Figure 8. The complete view of the interactive user interface, showing all the information related to a single component.

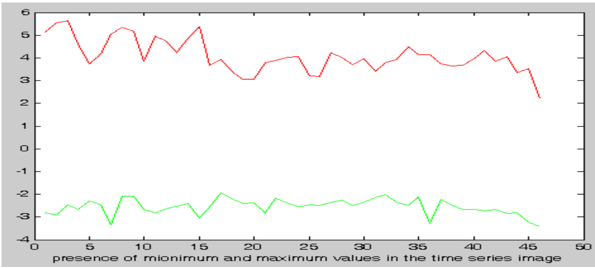


Figure 9. Minimum and maximum values in the time series image.

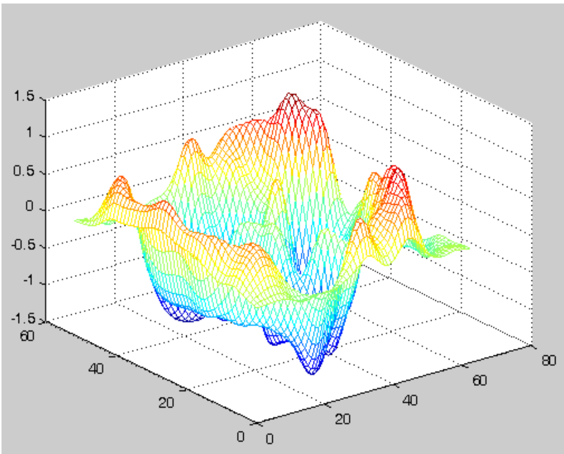


Figure 10. Filtered image –Frame 13.

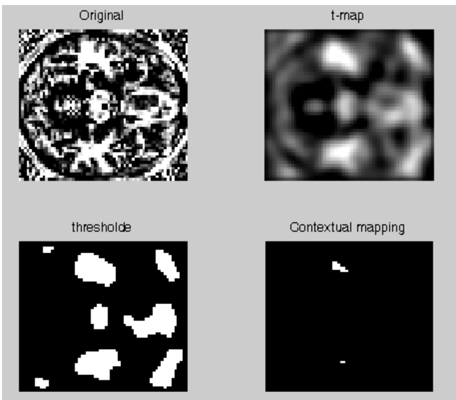


Figure 11. Frame 13.

References

[1] Ardekani B., Kershaw J., Kashikura K., and Kanno I., "Activation Detection in Functional MRI Using Subspace Modeling and Maximum

Likelihood Estimation," *IEEE Transactions on Medical Images*, vol. 18, no. 2, pp. 101-114, 1996.

[2] Bandettini P., Jesmanowicz A., Wong E., and Hyde J., "Processing Strategies or Time-Course Data Sets in Functional MRI of the Human Brain," *Magnetic Resonance in Medicine*, vol. 30, no. 2, pp. 161-173, 2003.

[3] Brammer M., (1998) "Multidimensional Wavelet Analysis of Functional Magnetic Resonance Images," *Human Brain Mapping*, vol. 6, no. 5, pp. 378-382, 1998.

[4] Bullmore E., Brammer M., Williams S., Rabe-Hesketh S., Janot N., David A., Mellers J., Howard R., and Sham P., "Statistical Methods of Estimation and Inference for Functional MR Image Analysis," *Magnetic Resonance in Medicine*, vol. 35, no. 1, pp. 261-277, 1996.

[5] Friston K., Holmes A., Worsley K., Poline J., Frith C., and Frackowiak R., "Statistical Parametric Maps in Functional Imaging: A General Linear Approach," *Human Brain Mapping*, vol. 2, no. 4, pp. 189-210,1995.

[6] Ogawa S., Lee T., Kay A., and Tank D., "Brain Magnetic Resonance Imaging with Contrast Dependent on Blood Oxygenation," *Proceedings of the National Academy of Sciences.* vol. 87, no. 4, pp. 9868-9872, 1990.

[7] Kkleinschmidt A., Requardt M., Merboldt K., and Frahm J., "On The Use of Temporal Correlation Coefficients for Magnetic Resonance Mapping of Functional Brain Activation: Individualized Thresholds and Spatial Response Delineation," *International Journal Imaging Systems and Technology*, vol. 6, no. 10, pp. 238-244, 1995.

[8] Kwong K., "Functional Magnetic Resonance Imaging with Echo Planar Imaging", *Magnetic Resonance in Medicine*, vol. 11, no. 2 , pp. 1-20, 1995.

[9] Kuppusamy K., Lin W., and Haacke E., "Statistical Assesment of Crosscorrelation and Variance Methods and the Importance of Electro-Cardiogram Gating in Functional Magnetic Resonance Imaging," *Magnetic Resonance in Medicine*, vol. 15, no. 2 , pp. 169-181, 1997.

[10] Marchini J. and Ripley B., "A New Statistical Approach to De tecting Significant Activation in Functional MRI," *NeuroImage*, vol. 12, no. 4, pp. 366-380, 2000.

[11] Senthamarai K. and Vijayalakshmi C., "Implementation of Artificial Neural Network With Hidden Markov Model for Analyzing the Genetic Code," *Journal of Engineering and Applied Sciences*, vol. 2, no. 1, pp. 17-29, 2007.

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