Fixed and Random Effect Analysis of Multi-subject Spatial Activation Maps in Wavelet Domain

Mohammad Soleymani, *Student Member, IEEE*, G.A. Hossein-Zadeh, and Hamid Soltanian-Zadeh, *Senior Member, IEEE*

***Abstract*— A method is proposed for modeling random and fixed effects in statistical maps of multisubject fMRI data. Using this model, we separate a fixed common activation map and a random effect for each subject. The proposed model shows a good multisubject activation detection for group analysis and also illustrate that the between subject variation lies mostly in activated areas. The method was implemented and tested on both simulated and experimental functional MRI data of 9 subjects.**

I. Introduction

Functional magnetic resonance imaging (fMRI) is a noninvasive technique for detecting the activated regions of the human brain using BOLD effect and fast magnetic resonance imaging methods [1]. Group analysis of functional MRI (fMRI) determines the variation of brain activated areas among different subjects in a group and the common activated regions between different individuals in an fMRI experiment.

Variability of fMRI activation signal among different subjects is usually described by fixed and random effects [2]. Fixed effect component includes the common effect which caused by all subjects through tasks, However random effect shows the variation which was caused between sessions and different subjects.

Various methods have been used for group analysis in fMRI. The group analysis methods based on General Linear Model (GLM) framework are used extensively. In GLM based methods the following stages are applied. A statistical map is derived for each subject in the first stage and the "effect" of interest and its "standard error" is derived at each voxel. In the second stage the "effects" and "standard errors" of different subjects are combined and the final decision is made by the use of group t-test [3].

As a data-driven method, ICA(independent component analysis) was used for both single subject and multi-subject analysis[4]. Multi-subject ICA, uses the time series of all subjects, to separate spatial source. One of them is the activation source. A PCA (Principal component analysis) based, multivariate, method was applied on multisubject fMRI analysis. Applying PCA on fMRI time series creates the reduced feature space and after projecting time series on this basis a method similar to GLM can be used for group analysis [5]. Shams et al. introduced a General likelihood ratio test approach for group analysis in which linear combinations of time series of different subjects were used. Thus an adaptive weighted average of multi-subject time-series is used in a statistical framework for activation detection [6].

In our proposed method GLM is used to obtain statistical maps of individual subjects. In the second step analysis of fixed and random effect terms of these maps are separated in wavelet domain. In order to separate these effects, two dimensional wavelet transform is applied on the statistical maps. Based on a statistical method, the wavelet coefficient related to random effect is then identified. Moreover a vertical energy thresholding is used to remove the random noise from data.

Theory of the model in wavelet domain and GLM analysis are discussed in the second section. Materials which are used in this research are described in the third section and results and discussion come in the fourth section. Finally the conclusion is made in the fifth section of the paper.

II. THEORY

A. General Linear Model

In general linear model fMRI time series is modeled by some regressors related to activation pattern and other components like trends. Thus the first step in GLM is the construction of design matrix which contains the above regressors (in columns). Denote the fMRI signal in time t with x(t), and the stimulus by s(t). The simplest model is a linear system with impulse response h(t) which is convolved with input stimulus input s(t) to produce activated cerebral signal x(t).

$$x(t) = \int_0^\infty h(u)s(t-u)du \tag{1}$$

The effects from multiple stimuli are added in linear system like equation (2). In this equation $x_i(t)$ is the response regarding to i-th stimulus.

$$x_{i1}\beta_1 + \cdots + x_{ik}\beta_k \tag{2}$$

M. Soleymani is with the Control and Intelligent Processing Centre of Excellence, ECE Dept., Faculty of Eng., University of Tehran, Tehran 14395-515 Iran; (e-mail: m.soleymani@ece.ut.ac.ir).

G.A Hossein-Zadeh is with the Control and Intelligent Processing Centre of Excellence, ECE Dept., Faculty of Eng., University of Tehran, Tehran 14395-515 Iran. (Corresponding author to provide phone: +98-216-111-4178; fax: +98-218-8863-3029); (e-mail: ghzadeh@ut.ac.ir).

H. Soltanian-Zadeh is with the Control and Intelligent Processing Centre of Excellence, ECE Dept., Faculty of Eng., University of Tehran, Tehran 14395-515 Iran, School of Cognitive Sciences, Institute for Studies in Theoretical Physics and Mathematics, and Medical Image Analysis Laboratory, Henry Ford Health System, Detroit, MI 48202, USA (e-mail: hamids@rad.hfh.edu).

Trend is also an important part of signal which is usually modeled by a polynomial. There are also errors and noises which are modeled as ε_i, which is assumed to be a white noise. The following equation shows all effects and components together [7].

$$Y_i = \underbrace{x_{i1}\beta_1 + \cdots + x_{ik}\beta_k}_{fMRI\_response} + \underbrace{x_{ik+1}\beta_{k+1} + \cdots + x_{im}\beta_m}_{Trend} + \varepsilon_i = X_i'\beta_k + \varepsilon_i \quad (3)$$

For each bases of GLM we put a normalized column in design matrix. If we put the time series of one subject in matrix y we have $y = X\beta + \varepsilon$, in which ε is the system noise with a zero mean and normal distribution. β is a vector that shows relation between basis of signal subspaces and fMRI time series. For instance if β_1 is the corresponding coefficient of activation pattern, its value will show the relationship between time series and activation pattern. Therefore this value can be used as activation score. The least squares estimation of vector β. Can be written as:

$$\hat{\beta} = (X^T X)^{-1} X^T Y \quad (4)$$

Based on estimated β, an activation map can be constructed using t-statistics, and a contrast *c* via:

$$T_0 = \frac{c\hat{\beta}}{\sqrt{c\,\mathrm{var}(\hat{\beta})c^t}} \sim t_{dist}(N - Rank(X)) \quad (5)$$

B. *Fixed and Random Effect in Wavelet Coefficients*

Let us put the fMRI statistical maps of N_s various normalized subjects (sessions) in different slice of an $N_s \times M_1 \times M_2$ matrix **Y**. These statistical maps correspond to a specific slice among all subjects. The discrete wavelet transform of statistical maps data is achieved by:

$$D = WY \quad (6)$$

Therefore by applying a spatial wavelet transform on each of slices (activation map) a matrix D is formed, whose elements can be written as $d_{\underline{i}m}$, m={1,…,N_s}, $\underline{i}$={(1,1),…,(M_1,M_2)}.

The two dimensional wavelet transform coefficients, matrix **D,** contain the wavelet coefficients of all statistical maps, which can be written as sum of the three components.

$$\mathbf{D} = \boldsymbol{\theta} + \mathbf{R} + \mathbf{Z} \quad (7)$$

The fixed effect component **θ** is common to all subjects. The random effect component which is denoted by **R** describes the deviation of subject's activations from the common effect (inter-subject variability), where as **Z** models stochastic noise (intra subject variability). The elements of **Z** are assumed to be i.i.d each having N (0, σ^2) distribution.

If we denote s_m^2 as the sample variance of wavelet coefficients d_{im}, i= {1…, N_s } and $\bar{d}_i$ as the mean of these coefficients along different subjects, Thus it can be shown:

$$(N_s - 1)s_m^2 = \sum_{i=1}^{N_s}(d_{\underline{i}m} - \bar{d}_{\underline{i}})^2 \sim \sigma_*^2 \chi^2_{N_s-1}, \sigma_*^2 = \sigma^2 + u_m\tau_m^2 \quad (8)$$

In the above formula, u_m is one if the *i*th wavelet coefficient (d_i) contains random effect and it is zero otherwise. τ_m is the additive consequence of random effect on variance. χ_a^2 denotes chi-square distribution with *a* degrees of freedom. A good estimation for noise variance can be obtained from high frequency coefficients by following equation.

$$\hat{\sigma}^2 = N_s^{-1}\sum_{m=1}^{N_s} 0.6745^{-1} median(|\, d_{ijm}\,| : N/2 + 1 \le m \le N) \quad (9)$$

The logarithm of sample variance would approximately have a normal distribution $N(\ln(\sigma_*^2), 2(N_s - 1)^{-1})$ and if the wavelet coefficient contains random effect its mean become larger. Therefore for random effect coefficients the quantiles of $\ln(S_m^2)$ will be greater than that of $N(\ln(\sigma^2), 2(N_s - 1)^{-1})$. Thus the quantile-quantile diagram of $\ln(S_m^2)$ and $N(\ln(\sigma^2), 2(N_s - 1)^{-1})$ is used to find the wavelet coefficient with significant random effect [8]. Vertical energy thresholding was used for noise reduction. Thus the low energy coefficients were eliminated as noise parts.

III. MATERIALS AND METHODS

A. *Simulation data*

Functional MRI data were simulated for nine subjects. Each subject is data contains one slice of 64×64 pixels in 252 time point. Each time series is composed of Gaussian white noise and simulated BOLD signal with a contrast randomly selected from a normal distribution with mean 2% and standard deviation 0.37%. 16 different activated regions

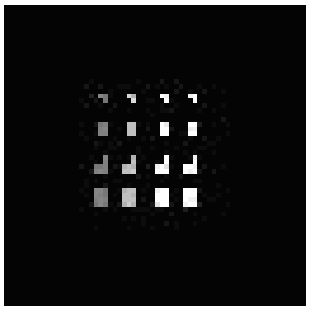

Fig. 1. The activated regions where activation was added on simulation data with random contrasts.

are shown in figure 1 defined for data. Hemodynamic response is modeled with a Gamma function with variable parameters among active voxels.

B. *Experimental data*

A set of sensory-motor fMRI data is analyzed in this research which is provided by fMRI data center (http://www.fmridc.org) [9]. The functional data acquired during an event related fMRI experiment in a 1.5 T scanner. During the experiments, 128 T2*-weighted volume images were acquired using asymmetric spin echo pulse sequence. Each volume image consisted of 16 slices and each slice was

composed of 64×64 pixels. A set of anatomical images was also acquired from each subject, which consists of 128 sagittal slices with 256×256 pixels. Nine young non-demented subjects were selected from these data. Their functional images were motion corrected using the AFNI software package (Medical College of Wisconsin, Milwaukee, WI) [10]. Then their anatomical images were transferred to the standard space of Talairach and Tournoux and the resulted transform is used for spatial normalization of functional images in the AFNI software package. The anatomical images were used to localize the active regions in the AFNI software. For each volume of functional data, the sub sampling process produced a volume image with 54×64×50 voxels and voxel size of 3×3×3 mm.

Drifts and the mean component were removed from time series of each voxel using high pass filter [5].

C. Methods

The method which was used in this paper includes three steps. first, statistical maps of analogous slices of different

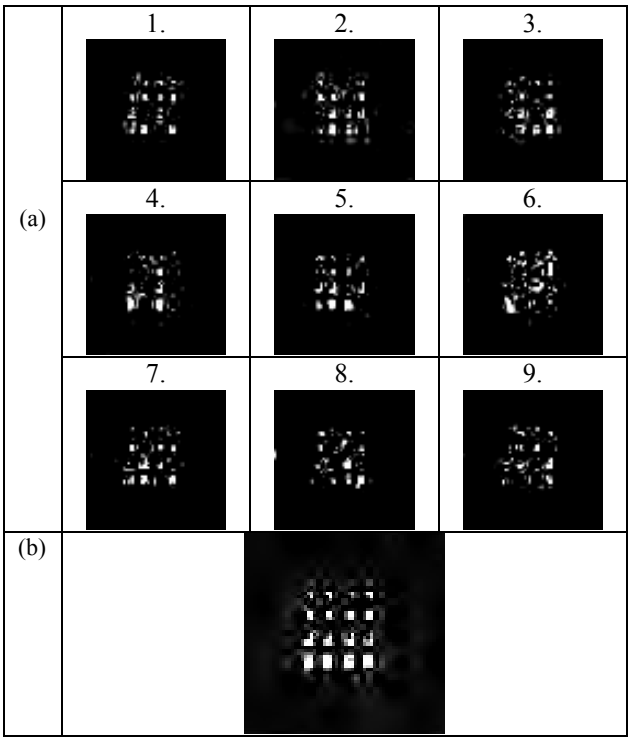

Fig. 2. Random effect and fixed effect components obtained from T-map simulation data. (a) Random effects of 9 subjects. (b) fixed effect component.

subjects are obtained. Statistical maps are made by a *t* statistic, which is defined as:

$$T = c\hat{\beta} / S \qquad (9)$$

T is the value of the effect of interest divided by S which denotes the estimated standard deviation of noise on the specified time series. Fixed effect component of statistical maps is derived by averaging the wavelet coefficient of all subjects in group and noise reduction by vertical energy thresholding. Random effect of subjects individually

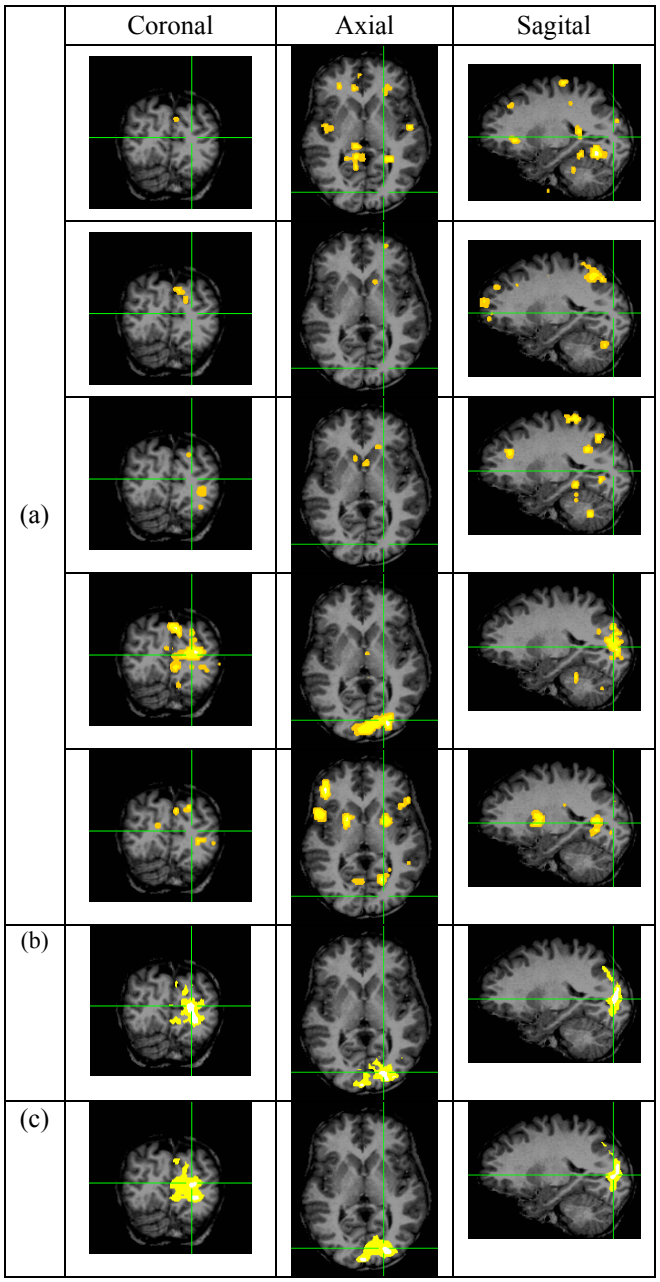

Fig. 3. Random effect and fixed effect components obtained from T-map on experimental data which is shown in anatomical images with false alarm rate 0.005 on talairach standard atlas. (a) Random effects on 4 different subjects. (b) the results of averaging statistical maps. (c)Fixed effect of 9 subjects

obtained after applying the separation algorithm.

IV. RESULTS AND DICUSSION

The algorithm is applied to simulated and experimental data and results are achieved. Statistical maps are found using statistical parametric mapping software, SPM2 (http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). These maps include normalized T values. Then fixed and random effect components in wavelet domain are separated via the method of section I.A. The results of simulation data (Fig 2) show that random effects manifest themselves around

activated regions. This is due to the variability of activation amplitude (BOLD effect) among different subject. In fact the random spatial random effect of each subject demonstrates the deviation of subjects from common effect. ROC curves of fixed effect and averaging statistical maps that are shown in figure 2. The ROC curves show the effect of noise reduction in proposed model on noisy simulated data.

The method is also applied to experimental data random effect and fixed effect components of 9 subjects are obtained. Another simple group analysis using GLM, which is the average of statistical maps result, are shown beside wavelet fixed effect results in figure 3 (for better observation on overlay activations and random effects are thresholded on experimental data). These results are shown on anatomical data which was obtained during the experiment. Regions where activations are detected include occipital cortex, precentral gyrus, cerebellum, inferior frontal gyrus, thalamus, mid temporal gyrus. AFNI software is used to overlay functional activations on anatomical data in talairach atlas. The detected points as random effect components can show regions which have variation in activation or become active in minority of subjects. The experimental results show that the fixed effect of statistical maps makes smooth activated regions.

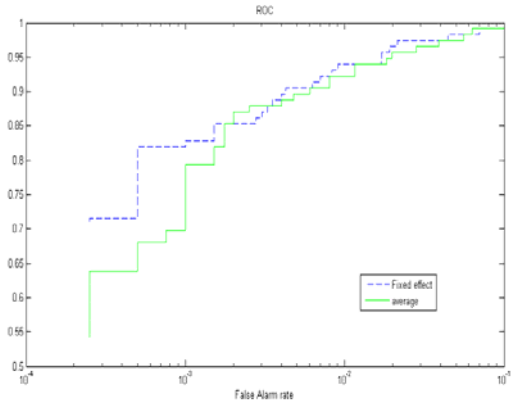

Fig 4. ROC curves, False alarm rate vs. Sensitivity.

V. CONCLUSION

In order to model the variability of fMRI statistical maps and to separate the random effects (inter subject variability) from stochastic noise, we proposed a model in wavelet domain. Proposed model is capable of modelling the variation of activation regions among different subjects. The model was fit to simulated and experimental fMRI data, and illustrations of fixed and random effect parts are presented. Based on this model, a complete multi-subject study of fMRI data is carrying on, in which the estimated random and fixed effect parts will be used for activation detection.

The proposed method in this paper gives us good results on common effect with an extra option to have between subject variations for all subjects individually.

REFERENCES

[1] G.A. Hossein-Zadeh, H. Soltanian-Zadeh, and B. A. Ardekani, "Multiresolution fMRI Activation Detection Using Translation Invariant Wavelet Transform and Statistical Analysis Based on Resampling", *IEEE Transactions on medical imaging*, vol. 22, no. 3, pp. 302-314, 2003.

[2] K.J Friston, A.P Holmes, K.J Worsley, J.P Poline, C.D Frith, and R.S.J Frackowiak, "Statistical Parametric Maps in Functional Imaging: AGenral Linear Approach", *Human Brain Mapping*, vol. 2, pp. 189-210, 1995.

[3] D.G Leibovici, and S. Smith, "Comparing groups of subjects in fMRI studies: a review of GLM approach, fMRI technical report TR00DL1, 2000.

[4] V.D Calhoun, T Adail, G.D Pearlson and J.J. Pekar, "A Method for Making Group Inferences from Functional MRI Data Using Independent Component Analysis", *Human Brain Mapping*, vol. 14, pp. 140-151, 2001.

[5] H. Benali, J Mattout, M. Plegrini-Issacc, F. Meusburger, O. Derpierre, F. Kherif, J.B. Poline, and Y. Burnod, Hierarchical multivariate group analysis for functional MRI data, IEEE *Science Symposium and Medical Imaging Conference*, 2004.

[6] S.M Shams, G.A Hossein-Zadeh, and H Soltanian-Zadeh, "Activation detection in multi-subject studies of fMRI using GLRT", *IEEE Nuclear Science Symposium and Medical Imaging Conference*, 2004.

[7] J. Worsley, H. Liao, J. Aston, V. Petre, H. Duncan, F. Morales, and C. Evans, "A General Statistical Analysis for fMRI data", *NeuroImage*, vol. 15, pp. 1-15, 2002.

[8] U. Jung, and J.C. Lu, "A Wavelet-Based Random-Effect Model for Multiple sets of Complicated Functional Sata", Technical Report, Georgia-Tech University, 2004.

[9] RL. Buckner, AZ. Snyder, AL Sanders, ME. Raichle, and JC. Morris, "Functional Brain Imaging of Young Nondemented and Demented Older Adults", *Journal of Cognitive Neuroscience*, vol 2, No 12, pp 24-34.

[10] R.W. Cox and J. S. Hyde, "Software tools for analysis and visualization of fMRI data," *NMR Biomed*., vol. 10, pp. 171-178, 1997.