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Separation of Phase-Locked and Non-Phase-Locked Activities Using Empirical Null-Distributions Obtained from Randomized Plus/Minus Averagings of Event-Related Epochs

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Abstract – **This paper proposes a novel non-parametric statistics-based method for extracting phase-locked target source activities from non-phase-locked background activities in MEG event-related measurements. The method derives, at each pixel location and at each time point, an empirical probability distribution of non-phase-locked activities from plus/minus averagings of raw epochs. The statistical threshold that extracts the target source activities is derived based on the empirical distributions obtained at all spatio-temporal locations. Here, the multiple comparison problems are taken into account by using the maximum statistics, i.e., by using two step procedure: standardizing these empirical distributions and deriving an empirical distribution of the maximum pseudo T values. The results of numerical experiments are presented to demonstrate the method's effectiveness.**

Keywords – **MEG event-related measurements, Non-parametric statistics, Plus/minus average, Source reconstruction, Statistical significance test**

I. Introduction

Neuromagnetic imaging can visualize neural activities with a fine time resolution of milli-second order, and provide functional information about brain dynamics. One major problem here is that measured MEG signal generally contains not only magnetic fields associated with the signal sources of interest but also contains interference magnetic fields generated from non-target background source activities; such non-target source activities include brain spontaneous activities or some evoked non-phase locked activities that are not the interest of the current investigation. These non-target activities generally overlap with the target source activities in the source reconstruction, and they often make interpreting the reconstruction results difficult.

This paper proposes a novel method based on the non-parametric statistics for implementing the statistical extraction of target activities; such target activities are in principle phase-locked to the stimulus in event-related MEG/EEG measurements. This method assumes neural activities to be quasi stochastic, and forms an empirical probability distribution of non-phase-locked activities using randomized plus/minus averagings of event-related raw epochs. The method then uses this empirical distribution as the null distribution for deriving the statistical threshold; the thresholding can extract the target activities that are time-locked to the stimulus by eliminating other non-time-locked activities. In this paper, we explain the proposed statistical thresholding method with spatial filter source reconstruction [1]. This is because the formulation of the spatial filter is relatively simple and it has been successfully applied to MEG source analysis. However, the applicability of the proposed method is not limited to the spatial filter formulation and it can be used with any types of source reconstruction methods

II. Spatial filter formulation and parametric statistical significance evaluation

We define the magnetic field measured by the mth detector coil at time t as $b_m(t)$, and a column vector $\boldsymbol{b}(t) = [b_1(t), b_2(t), \ldots, b_M(t)]^T$ as a set of measured data where M is the total number of sensor coils and superscript T indicates the matrix transpose. The spatial location is represented by a three-dimensional vector $\boldsymbol{r}$: $\boldsymbol{r} = (x, y, z)$. The magnitude of the source moment is denoted $s(\boldsymbol{r}, t)$. Spatial filter techniques estimate the source current density by applying a simple linear operation to the measured data, i.e.,

$$\widehat{s}(\boldsymbol{r}, t) = \boldsymbol{w}^T(\boldsymbol{r})\boldsymbol{b}(t) = \sum_{m=1}^{M} w_m(\boldsymbol{r}) b_m(t), \qquad (1)$$

where $\widehat{s}(\boldsymbol{r}, t)$ is the estimated source magnitude. The column vector $\boldsymbol{w}(\boldsymbol{r})$ expresses a set of the filter weights, which characterizes the property of the spatial filter. Various types of spatial filter techniques have been proposed and applied to the MEG/EEG source reconstruction problems. Some of them are found in [2–5].

The evaluation of the statistical significance of the spatial filter outputs has been conventionally performed using the parametric statistics [2,5]. The basic assumption for such parametric method is that the measurement consists of deterministic signal and Gaussian noise, i.e.,

$$\boldsymbol{b}(t) = \boldsymbol{b}_I(t) + \boldsymbol{n}(t), \tag{2}$$

where $\boldsymbol{b}_I(t)$ is the signal magnetic field of interest, which is generated from brain sources that are the target of current investigation. In Eq. (2), $\boldsymbol{n}(t)$ is the noise vector and each element of $\boldsymbol{n}(t)$ is assumed to follow $\mathcal{N}(0, \sigma_0^2)$, which indicates the Gaussian distribution with zero mean and the variance of σ_0^2. These Gaussian processes represent the sensor noise that is assumed to be uncorrelated between different sensor recordings. Thus, the spatial filter outputs $\widehat{s}(\boldsymbol{r}, t)$, which are expressed as

$$\widehat{s}(\boldsymbol{r}, t) = \boldsymbol{w}^T(\boldsymbol{r})\boldsymbol{b}(t) = \boldsymbol{w}^T(\boldsymbol{r})\boldsymbol{b}_I(t) + \boldsymbol{w}^T(\boldsymbol{r})\boldsymbol{n}(t), \tag{3}$$

follows

$$\mathcal{N}(\boldsymbol{w}^T(\boldsymbol{r})\boldsymbol{b}_I(t), \sigma_0^2\|\boldsymbol{w}(\boldsymbol{r})\|^2). \tag{4}$$

The statistical evaluation can be performed by testing the null hypothesis ($\boldsymbol{b}_I(t) = 0$) at each pixel location using Eq. (4).

III. Proposed nonparametric statistical significance evaluation

A. Data model

The signal and the noise model expressed in Eq. (2) is, in general, insufficient to express MEG measurements, and the measured data should be expressed as

$$\boldsymbol{b}(t) = \boldsymbol{b}_I(t) + \boldsymbol{b}_\xi(t) + \boldsymbol{n}(t), \tag{5}$$

where $\boldsymbol{b}_\xi(t)$ is the magnetic field generated from sources other than the signal sources of interest, such as brain spontaneous activities or some evoked activities that are not the target of current measurements. This $\boldsymbol{b}_\xi(t)$ is often referred to as the brain noise. The parametric modeling cannot efficiently take this brain noise into account, because the Gaussianity assumption does not hold for $\boldsymbol{b}_\xi(t)$.

Here, we propose a novel nonparametric method that can take such brain noise into consideration. The spatial filter outputs obtained from $\boldsymbol{b}(t)$ is expressed as

$$\widehat{s}(\boldsymbol{r}, t) = \widehat{s}_I(\boldsymbol{r}, t) + \widehat{s}_c(\boldsymbol{r}, t), \tag{6}$$

where

$$\widehat{s}_I(\boldsymbol{r}, t) = \boldsymbol{w}^T(\boldsymbol{r})\boldsymbol{b}_I(t), \tag{7}$$

$$\widehat{s}_c(\boldsymbol{r}, t) = \boldsymbol{w}^T(\boldsymbol{r})(\boldsymbol{b}_\xi(t) + \boldsymbol{n}(t)) = \boldsymbol{w}^T(\boldsymbol{r})\boldsymbol{b}_c(t). \tag{8}$$

Here, $\boldsymbol{b}_c(t) = \boldsymbol{b}_\xi(t) + \boldsymbol{n}(t)$, which represents the background non-phase-locked magnetic field plus noise. The key assumption in the proposed method is that the signal magnetic field $\boldsymbol{b}_I(t)$ and thus the estimated target activity $\widehat{s}_I(\boldsymbol{r}, t)$ are phase-locked to the stimulus, but the non-target magnetic field and the non-target activity $\widehat{s}_c(\boldsymbol{r}, t)$ are not phase-locked to the stimulus. Therefore, the background non-phase-locked magnetic field $\boldsymbol{b}_c(t)$ can be estimated by calculating the plus/minus averagings of the raw epochs. That is, when averaging raw epochs, the half number of epochs are multiplied with -1. By doing so, the phase-locked activities are averaged out but activities that are not phase-locked to the stimulus are not averaged out. This is the basis of our statistical analysis mentioned below.

B. Empirical distribution formation

In event-related measurements, the magnetic field generated from phase-locked activities is obtained by averaging raw-epoch measurements. Denoting the raw epoch measurements as $\{\boldsymbol{e}_1(t), \ldots, \boldsymbol{e}_K(t)\}$ where K is the number of raw epochs, we have $\boldsymbol{b}(t) = 1/K \sum_{j=1}^{K} \boldsymbol{e}_j(t)$. When K is very large or when $\boldsymbol{b}_c(t)$ is very small, we generally have the relationship $\boldsymbol{b}(t) \approx \boldsymbol{b}_I(t)$. However, except such extreme cases, a considerable amount of $\boldsymbol{b}_c(t)$ still exists in the averaged data $\boldsymbol{b}(t)$.

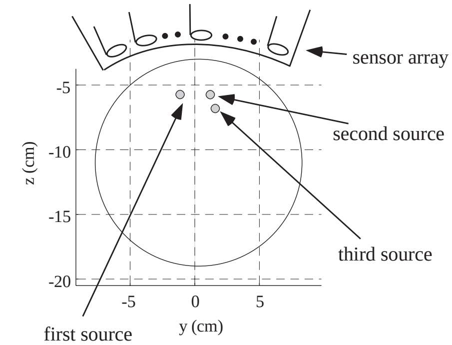
Such non-phase-locked magnetic field existing in the averaged data, $\boldsymbol{b}_c(t)$, can be estimated from

$$\boldsymbol{b}_c(t) = 1/K \sum_{j=1}^{K} \epsilon_j \boldsymbol{e}_j(t), \tag{9}$$

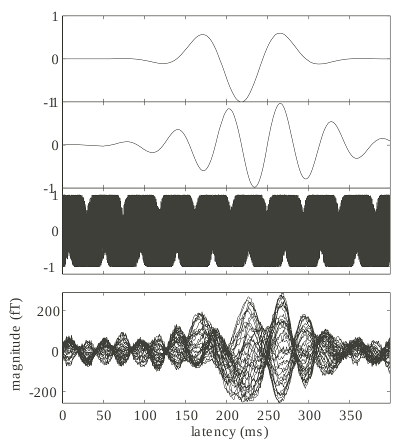
where the coefficients $\epsilon_1, \ldots, \epsilon_K$ have a value of either -1 or 1. We assign -1 or 1 to $\epsilon_1, \ldots, \epsilon_K$ by drawing -1 or 1 randomly from K/2 number of -1 and K/2 number of 1 without replacements. As a result, a half of $\epsilon_1, \ldots, \epsilon_K$ have a value of -1 and the other half have a value of 1. Here, there are a number of ways to assign -1 or 1 to $\epsilon_1, \ldots, \epsilon_K$ (the number is equal to $K!/(\frac{K}{2}!)^2$.) and we can obtain many different $\boldsymbol{b}_c(t)$. We denote one of such $\boldsymbol{b}_c(t)$ as $\boldsymbol{b}_c^\beta(t)$, which is expressed as

$$\boldsymbol{b}_c^\beta(t) = 1/K \sum_{j=1}^{K} \epsilon_j^* \boldsymbol{e}_j(t), \tag{10}$$

where $\epsilon_1^*, \ldots, \epsilon_K^*$ is one realization of the -1 or 1 assignment. In Eq. (10), β is a index for many different -1 or 1 assignments and $\beta = 1, \ldots, K_B$ where K_B indicates the total number of different assignments. We next calculate $\widehat{s}_c^\beta(\boldsymbol{r}, t)$ by applying the spatial filter to $\boldsymbol{b}_c^\beta(t)$, i.e., $\widehat{s}_c^\beta(\boldsymbol{r}, t) = \boldsymbol{w}^T(\boldsymbol{r})\boldsymbol{b}_c^\beta(t)$. We then calculate $\widehat{F}(x)$, which is the empirical distribution of $\widehat{s}_c^\beta(\boldsymbol{r}, t)$, such that $\widehat{F}(x) = \sharp\{\widehat{s}_c^\beta(\boldsymbol{r}, t) \leq x\}/K_B$ where $\sharp\{\widehat{s}_c^\beta(\boldsymbol{r}, t) \leq x\}$ indicates the number of $\widehat{s}_c^\beta(\boldsymbol{r}, t)$ which are less than or equal to x. This procedure is repeated and the empirical distribution is calculated at all pixel locations and at all time points. To explicitly show that $\widehat{F}(x)$ is obtained at each spatial location $\boldsymbol{r}$ and each time point t, $\widehat{F}(x)$ is rewritten as $\widehat{F}(x|\boldsymbol{r},t)$ in the following explanation.



(a)



(b)

Figure 1: (a)The coordinate system and source-sensor configuration used in the numerical experiments. The large circle indicates the projection of the sphere used for the forward calculation. (b)Time courses assigned to the three sources and simulated event-related recordings. the initial phase of the third source's time course is randomly fluctuated between 0 and $3\pi/2$. The third panel from the top shows all such time courses.

C. Statistical thresholding with multiple comparisons

The proposed method uses the maximum statistics to incorporate the multiple comparison problems; the use of the maximum statistics has been studied in [6]. To utilize the maximum statistics, we first standardize the empirical distribution $\widehat{F}(x|\boldsymbol{r},t)$ by calculating $T_\beta(\boldsymbol{r},t)$ such that

$$T_\beta(\boldsymbol{r},t) = \frac{\widehat{s}_c^\beta(\boldsymbol{r},t) - \langle \widehat{s}_c^\beta(\boldsymbol{r},t)\rangle_\beta}{\widehat{\sigma}(\boldsymbol{r},t)}. \quad (11)$$

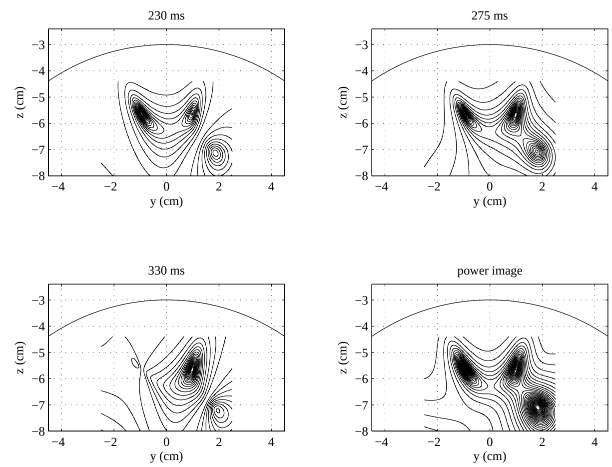


Figure 2: Source reconstruction results at 230 ms(upper left), 275 ms(upper right), and 330 ms(bottom left). The bottom-right results show the power reconstruction, $\sqrt{\langle \widehat{s}(\boldsymbol{r},t)^2\rangle}$, where $\langle\cdot\rangle$ indicates the average over 0 and 400 ms.

Here,

$$\widehat{\sigma}^2(\boldsymbol{r},t) = \langle \widehat{s}_c^\beta(\boldsymbol{r},t)^2\rangle_\beta - \langle \widehat{s}_c^\beta(\boldsymbol{r},t)\rangle_\beta^2,$$

and $\langle\cdot\rangle_\beta$ indicates the average with respect to the index β.

We calculate $T_{max}(\boldsymbol{r},t)$, which is the maximum $T_\beta(\boldsymbol{r},t)$ value. The maximum T_β value at the ith pixel location and jth time point is denoted T_{max}^{ij} where $i = 1,\ldots,K_N$ and $j = 1,\ldots,K_t$ and K_N and K_t, respectively, indicate the total number of pixels and time points. We next obtain the empirical distribution of T_{max}^{ij}, $\widehat{H}(x)$, such that $\widehat{H}(x) = \sharp\{T_{max}^{ij} \le x\}/(K_N K_t)$ where $\sharp\{T_{max}^{ij} \le x\}$ is the number of T_{max}^{ij} values which are less than or equal to x. We can obtain the threshold for the $(1-\alpha)$ significance level, T^{th}, such that $T^{th} = \widehat{H}^{-1}(1-\alpha)$. The inverse of this empirical distribution can be calculated by first sorting T_{max}^{ij} in the increasing order

$$T_{max}^{(1)} \le T_{max}^{(2)} \le \cdots \le T_{max}^{(K_N K_t)}, \quad (12)$$

and choose $T_{max}^{(p)}$ as T^{th} where $p = [(1-\alpha)K_N K_t]$ and $[\cdot]$ indicates the maximum integer that does not exceed the value in the parenthesis. We finally obtain the statistical threshold $\Sigma(\boldsymbol{r},t)$ by converting the value of T^{th} into the value of source activities, i.e.,

$$\Sigma(\boldsymbol{r},t) = T^{th}\widehat{\sigma}(\boldsymbol{r},t) + \langle \widehat{s}_c^\beta(\boldsymbol{r},t)\rangle_\beta. \quad (13)$$

We evaluate the statistical significance of the spatial filter outputs by comparing the outputs $|\widehat{s}(\boldsymbol{r},t)|$ with $\Sigma(\boldsymbol{r},t)$, and when $|\widehat{s}(\boldsymbol{r},t)| \ge \Sigma(\boldsymbol{r},t)$, the outputs $\widehat{s}(\boldsymbol{r},t)$ is considered to be statistically significant.

IV. Numerical experiments

We conducted numerical experiments to show the effectiveness of the proposed statistical thresholding. We use a sensor alignment of the 37-sensor array from Magnes^{TM} (4D Neuroimaging Inc., San Diego) neuromagnetometer. Three signal sources were assumed to exist on a single plane ($x = 0$ cm). The source-sensor configuration and the coordinate system are illustrated in Fig. 1(a). The simulated magnetic field were calculated for 400 ms post stimulus time window with 1 ms sample. Three time courses shown in Fig. 1(b) were assigned to the three sources. Here, the initial phase of the third source time course is randomly fluctuated between 0 and $3\pi/2$. The first and the second sources are considered as the signal sources of interest and the third source represents the stimulus-evoked non-phase-locked activity. We set the third source intensity 3 times greater than the intensities of the first and the second sources. (The intensities of the first and the second sources were set equal.) Spontaneous MEG measured using the same sensor array was added to the calculated signal-magnetic field to create a simulated raw-epoch data. Four hundred raw-epochs were generated, and averaged to create the final simulated event-related recordings. The resultant simulated recordings are also shown in Fig. 1(b).

The eigenspace-projected adaptive spatial filter [4] was applied to these averaged recordings. The whole data between 0 to 400 ms was used for calculating the covariance matrix and the weight vector of the spatial filter was obtained with this covariance matrix. The filter was first applied to the simulated recordings in Fig. 1(b). The results of the source reconstruction are shown in Fig. 2. Here, the reconstruction contains the three sources, including the third source that is not phase-locked to the stimulus. Then, total 100 of $\boldsymbol{b}_c^{\beta}(t)$ were calculated using the proposed procedure, and the same spatial filter was applied to $\boldsymbol{b}_c^{\beta}(t)$ to create $\widehat{s}_c^{\beta}(\boldsymbol{r}, t)$. An empirical null distribution was obtained using $\widehat{s}_c^{\beta}(\boldsymbol{r}, t)$ ($\beta = 1, \ldots, 100$), and derive the threshold for each pixel and each time point using Eq. (13). The thresholded reconstruction results are shown in Fig. 3. Here when $|\widehat{s}(\boldsymbol{r}, t)| < \Sigma(\boldsymbol{r}, t)$, $\widehat{s}(\boldsymbol{r}, t)$ was set to zero. The results show that the third source is removed, verifying the effectiveness of the proposed method for thresholding out the non-phase-locked activity, even when it is stimulus evoked.

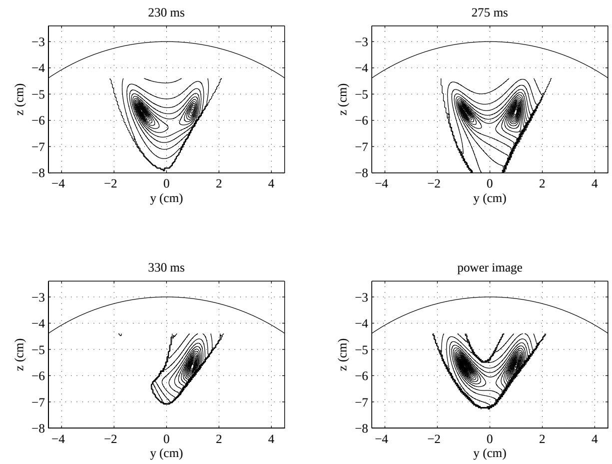


Figure 3: Results of the proposed statistical thresholding applied to the reconstruction results in Fig. 2.

References

[**1**] K. Sekihara and S. S. Nagarajan, "Neuromagnetic source reconstruction and inverse modeling," in *Modeling and Imaging of Bioelectric Activity - Principles and Applications*, pp.213–250. Kluwer Academic/Plenum Publishers, 2004.

[**2**] S. E. Robinson and J. Vrba, "Functional neuroimaging by synthetic aperture magnetometry (SAM)," in *Recent Advances in Biomagnetism*, Sendai, pp., 302–305, Tohoku University Press.

[**3**] B. D. van Veen, W. van Drongelen, M. Yuchtman, and A. Suzuki, "Localization of brain electrical activity via linearly constrained minimum variance spatial filtering," *IEEE Trans. Biomed. Eng.*, vol. 44, pp. 867–880, 1997.

[**4**] K. Sekihara, S. S. Nagarajan, D. Poeppel, A. Marantz, and Y. Miyashita, "Application of an MEG eigenspace beamformer to reconstructing spatio-temporal activities of neural sources," *Human Brain Mapping*, vol. 15, pp. 199–215, 2002.

[**5**] A. M. Dale, A. K. Liu, B. R. Fischl, R. L. Buckner, J. W. Belliveau, J. D. Lewine, and E. Halgren, "Dynamic statistical parametric mapping: Combining fMRI and MEG for high-resolution imaging of cortical activity," *Neuron*, vol. 26, pp. 55–67, 2000.

[**6**] D. Pantazis, T. E. Nichols, S. Baillet, and R. M. Leahy, "Spatiotemporal localization of significant activation in MEG using permutation tests," in *Conference Report for the Information Processing in Medical Imaging 2003*, Ambleside, UK, pp., 99–999.