Establishing and validating a new source analysis method using phase*

Chirumamilla VC, Gonzalez-Escamilla G, Kumar S, Longfei X, Groppa S, Muthuraman M.

Abstract— **Electroencephalogram (EEG) measures the brain oscillatory activity non-invasively. The localization of deep brain generators of the electric fields is essential for understanding neuronal function in healthy humans and for damasking specific regions that cause abnormal activity in patients with neurological disorders. The aim of this study was to test whether the phase estimation from scalp data can be reliably used to identify the number of dipoles in source analyses. The steps performed included: i) modeling different phasic oscillatory signals using auto-regressive processes at a particular frequency, ii) simulation of two different noises, namely white and colored noise, having different signal-to-noise ratios, iii) simulation of dipoles at different areas in the brain and iv) estimation of the number of dipoles by calculating the phase differences of the simulated signals. Moreover we applied this method of source analysis on real data from temporal lobe epilepsy (TLE) patients. The analytical framework was successful in identifying the sources and their orientations in the simulated data and identified the epileptogenic area in the studied patients which was confirmed by pathological studies after TLE surgery.**

I. INTRODUCTION

EEG (Electroencephalogram) is one of the most widely used neuroimaging techniques to study brain functional networks at sub-millisecond time scale. EEG source localization has been an integral part of neuroimaging studies for the last two decades. Source analysis methods can be divided into two types: 1) dipole analysis and 2) current density reconstruction. In dipole analysis, there has been several algorithms based on equivalent current dipole [1], one of them being the MUSIC algorithm [2]. Two of the current density reconstruction methods are minimum norm [3] and low resolution brain electromagnetic tomography (LORETA) [4]. In the beamformer approach there are namely linearly constrained minimum variance (LCMV) [5], dynamic imaging of coherent sources (DICS) [6], and synthetic aperture magnetometry (SAM) [7]. Other approaches include spatiotemporal mapping [8], Kalman filter [9], and Bayesian [10]. However, before utilizing any of these approaches, the forward problem must be solved. The solution is based on either spherical head models (single sphere [11] and concentric spheres [12]) or realistic head models (boundary element method (BEM) [13] and finite element method (FEM) [14]). After developing any new method, the best way to test its robustness is to apply the simulation to a dataset in which the results are already known. In the present study, phase source analysis was tested with different noises and different numbers of dipoles, as well as different dipole orientations and locations. In the end the method was applied to epilepsy patients in whom the sources are more focal and validated with the outcome of epilepsy surgery.

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VC Chirumamilla, GG Escamilla, S Groppa, and M Muthuraman: Department of Neurology, Johannes Gutenberg University, Mainz, Germany. venkatachaitanya409@gmail.com, gabriellbk@gmail.com, mmuthura@uni-mainz.de, segroppa@uni-mainz.de.

S Kumar: Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany. saurabhsay@gmail.com.

X Longfei: Institute for Digital Signal Processing and System Theory, Faculty of Engineering, Christian Albrechts University Kiel, 24143 Germany. xionglongfei@hotmail.com,

II. METHODS

A. EEG data acquisition and spectral analysis

In this study, EEG data from ten female patients (mean age ± SD: 39 ± 13.89 years) with temporal lobe epilepsy were analyzed. EEG was recorded with the international 10-20 system. Depending on the patient, 40-60 electrodes were placed on the scalp to record ictal epileptic activity. In each patient, a 10 second segment with a sampling rate of 200 Hz of EEG was selected after seizure onset. The Welch's periodogram was used for computing the power spectral density (PSD) estimate of the dynamic and stochastic seizure EEG time signal. The PSD was estimated for one second windows and average over the entire 10 second segment which in turn gave a frequency resolution of 1 Hz. In epilepsy patients, the phase source analysis method was implemented based on a single seizure peak frequency from the spectral analysis of the 10 second data segment.

B. Realistic head models

The head model was estimated separately for each individual subject based on 3T structural magnetic resonance imaging (MRI) data, which was obtained before epilepsy surgery. Boundary element method (BEM) was used to solve Poisson's equation in a head model [11]. It uses three realistic layers extracted from the subject's MRI data, namely the scalp, skull and brain, as well as the source space, that is, the cortical surface. In the BEM model, the conductivity is assumed to be isotropic for each of the layers specified above. The conductivity values used for the scalp,

skull, and brain were 1, 0.0125, and 1 S/m, respectively. The maximum possible number (n = 22) of different dipole orientations was simulated. Each vertex of the cortical surface is considered a dipole. The lead-field matrix was estimated for each subject separately which contains the geometric information about the dipole locations (x, y, z), orientations (θ, ϕ), and magnitudes as well as the volume conductor properties of the three layers.

C. Auto-regressive process and phase difference

The auto-regressive (AR) process is a random process that models the current value as the sum of previous values. In the second order AR process (AR2) the current value is the sum of two previous values and present noise. It can be mathematically described as:

$$y_t = a_1 y(t-1) + a_2 y(t-2) + \eta_t \quad (1)$$

where y_t is the current value, a_1 and a_2 are the AR2 coefficients and η_t is the current white noise term. The AR2 coefficients are estimated as follows:

$$a_1 = 2\cos\left(\frac{2\pi}{T}\right)\exp\left(\frac{-1}{\tau}\right) \quad (2)$$

$$a_2 = -\exp\left(\frac{-2}{\tau}\right) \quad (3)$$

where τ is the relaxation time and T is the oscillation period. The main motivation for choosing second order model was that it provides more control over the estimated parameters (eg., phase) than higher order AR processes. Additionally, in this paper [12] the authors have shown with second order AR processes the phase estimation for narrow band frequency spectrum is optimal than higher order AR processes. In our case the phase estimation was based on a single peak frequency and not on a broad band frequency spectrum. The AR2 model was generated with a sampling frequency of 1000 Hz for 10 seconds of data. An ideal band pass filter was imposed to have a specific frequency of 10 Hz. All simulations were done on 97 EEG electrodes following the 10-20 layout system.

The phase difference between two signals, p and q, can be estimated by taking the argument of the cross spectrum between the signals at a particular frequency as given below:

$$\hat{\varphi}(\omega) = \left|\arg\left(\hat{S}_{pq}(\omega)\right)\right| \quad (4)$$

where ω is the frequency to be analyzed, $\hat{S}_{pq}(\omega)$ is the cross spectrum and $\hat{\phi}(\omega)$ is the phase difference.

D. Inverse solution using beamformer spatial filter

Phase can be estimated at any location in the brain using a linear transformation, i.e. spatial filter, which can relate the underlying neural activity to the electromagnetic field measured at the brain surface. The neural activity can be modeled as a current dipole or sum of current dipoles. Let us consider a to be an X by 1 vector containing electric potentials recorded using X electrodes. The potential due to a single dipole with location vector l is given as

$$a = H(l).d(l) \quad (5)$$

where $H(l)$ denotes the transfer function with matrix size X by 3 and $d(l)$ denotes the dipole moment along x, y, z directions. If a measured is due to N number of dipoles at different locations $l_j = 1,2,...N$ and noise n, then a can be given by

$$a = \sum_{j=1}^{N} H(l_j).d(l_j) + n \quad (6)$$

The spatial filter is designed from a covariance matrix of data a. The dipole moment in terms of mean and covariance $C(l_j)$ is obtained by assuming that noise is zero mean and that the covariance matrix L and moments related to the different dipoles are uncorrelated. The covariance matrix $C(a)$ of measured potentials can be given as

$$C(a) = \sum_{j=1}^{N} H(l_j).C(l_j).H^T(l_j) + L \quad (7)$$

For a narrow band volume element L_0 centered at location l_0 given by an X by 3 matrix $X(l_0)$ can be defined for a spatial filter

$$z = X^T(l_0).a \quad (8)$$

where z is filter output. In order to design an optimal filter, the approach is to extract the $X(l_0)$ that minimizes the variance and also satisfies the linear constraint for a narrowband filter which alludes to the name linearly constrained minimum variance spatial filter (LCMV). The LCMV method includes design of spatial filters that pass the signal from particular locations, while attenuating the signal from other locations in the brain.

III. Results

A. Simulation and epilepsy patients

The dipole simulation was carried out for 22 different orientations as depicted in Figure 1A. The simulations were repeated for two different noises, namely white and colored noise, each with 10 different signal-to-noise ratio factors ranging from 0.1 to 1.0. Each of these simulations was repeated for 100 realizations and 10×2 pairs of dipoles, one in each hemisphere. The phase difference was calculated between each channel and all other remaining channels using Eq.4 which gives a phase difference matrix of size 97 by 97 that contains both positive and negative values for simulated

SNR	White Noise (Euclidean distance (mm))		Colored Noise (Euclidean distance (mm))	
	Mean	Std	Mean	Std
0.1	10	5	11	5
0.2	10	3	10	4
0.3	9	4	9	3
0.4	9	3	9	3
0.5	8	2	7	3
0.6	6	2	6	3
0.7	5	2	5	3
0.8	4	2	4	2
0.9	2	1	2	1
1.0	2	1	2	1

Table 1. Euclidean distance between simulated MNI coordinates for white and colored noise with 10 different signal-to-noise ratio (SNR) factors ranging from 0.1 to 1.0.

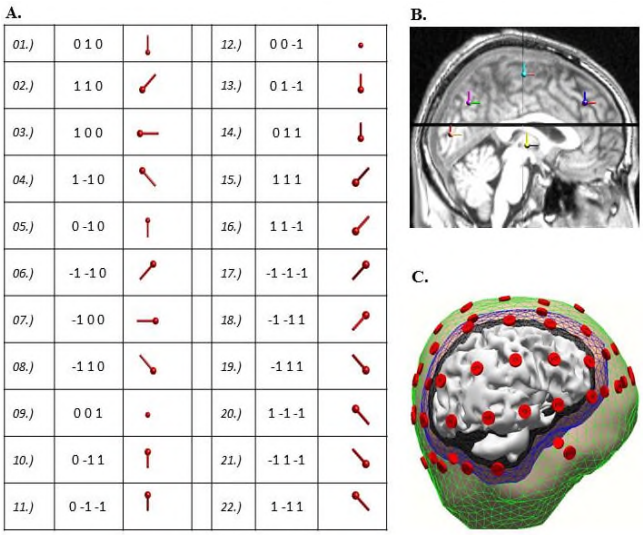

Figure 1. (A) Coordinates (x, y, z) of 22 simulated orientations with the dipole depicted in red. (B) Sum of five simulated dipole locations separately with two different orientations is shown in the slice (sagittal plane). (C) Head model showing the different layers: brain, cerebrospinal fluid, skull and skin. The red dots represent channel locations.

data. We tested the significance of the source location results by measuring the Euclidean distance (ED) between the simulated MNI co-ordinates and the actual estimated co-ordinates and those estimations are summarized in Table 1.

No significant difference was found between white or colored noise ($p = 0.25$). In Figure 1B, the simulation results of five different dipole locations with two different orientations are shown on a right sagittal slice. Figure 1C shows a depiction of the computed head model of a representative patient with the four different layers (from inside to outside: brain, cerebrospinal fluid, skull and skin) and the channel locations used (red dots).

B. Validation using epilepsy patients data

We implemented the phase source analysis method on real EEG data collected from temporal lobe epilepsy patients and localized the brain sources of the epileptic activity of each subject. All the sources obtained are shown in a single axial

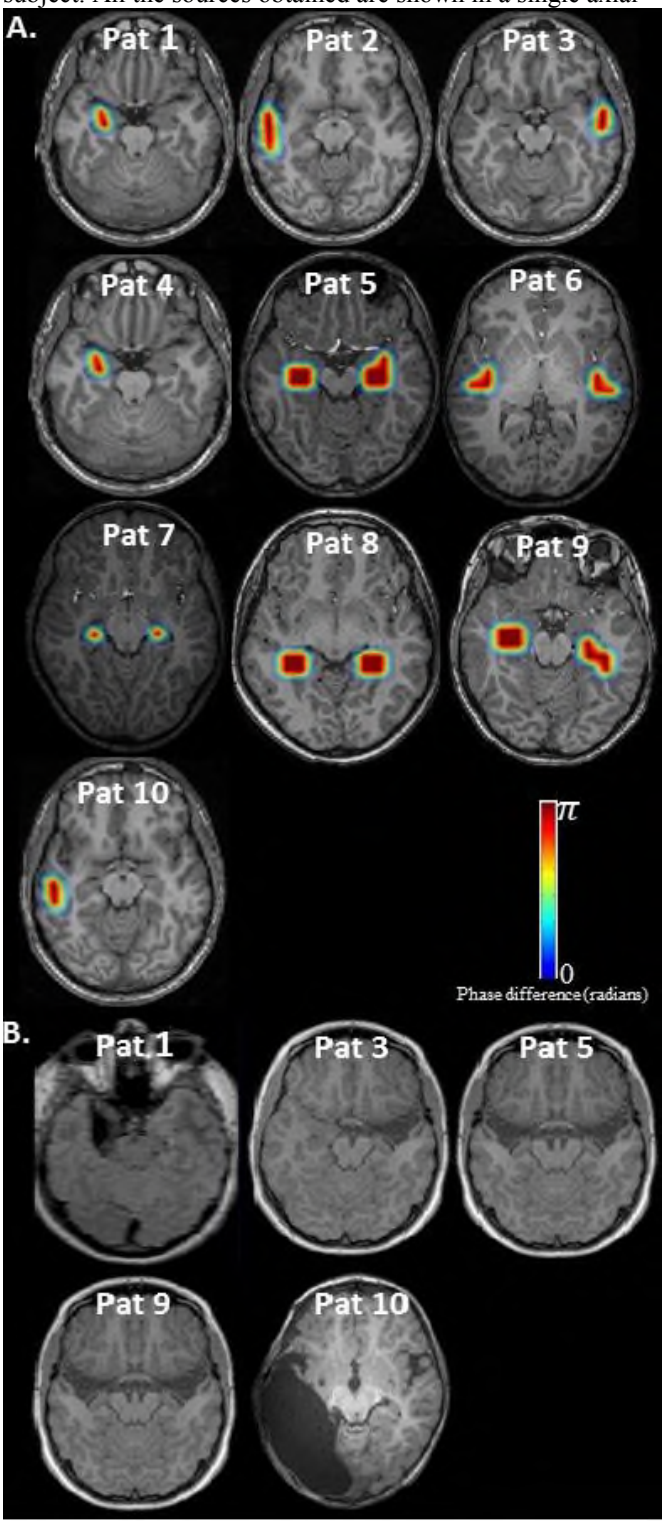

Figure 2. (A) The sources identified in ten patients by the phase source analysis method are shown individually on a single axial slice. (B) The part of the brain that was removed by surgery in five patients.

slice for each patient separately in Figure 2A. The post-operative MRI images were taken with 1.5 T and are only available for five patients namely pat 1, pat 3, pat 5, pat 9 and pat 10. The Figure 2B shows in an axial slice the part of the brain that was removed by surgery in five patients.

IV. Discussion and conclusion

Several previous studies have used source localization methods to reveal the underlying functional network architecture in healthy subjects and also in clinical populations. In our previous study, we identified neural networks in epilepsy patients using dynamic imaging of coherent sources (DICS) that used maximum power as a reference for computation of neural coupling [13]. Now, we have implemented the source analysis technique for the first time using phase. We tested this method by simulation of different dipole locations and orientations in the brain assuring the spatial accuracy of the method. The robustness of the method was also tested with two different noises and with 10 different levels of signal-to-noise ratio. Applying the proposed method to actual epilepsy patient's EEG data, we could successfully localize the correct sources concordant with the epilepsy surgical procedure. This shows that source phase-localization analysis on EEG data could become an integrated tool in the epilepsy pre-surgical procedure.

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