Local linear estimators and a statistical framework for event related field analysis

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Abstract— **A method is described that combines linear source estimation (beamformers) with non-parametric statistical significance testing to yield vector time series estimates for brain regions of interest. These source time series are a suitable starting point for functional connectivity analysis.**

Keywords—**EMEG beamformers, non-parametric significance testing, functional connectivity analysis**

I. INTRODUCTION

One major goal of many cognitive electrophysiology experiments using electro- and magneto-encephalographic (EMEG) data is the development of a functional connectivity analysis that benefits from the millisecond resolution inherent in EMEG data. Ideally, this functional connectivity analysis should yield information about the coupling between brain regions that are responsible for the phenomena under investigation. For a number of reasons, including non-ideal detector sensitivity and specificity, as well as the inherent limitations imposed by the non-uniqueness of the bioelectromagnetic inverse problem, there are well-recognized advantages in posing this analysis problem probabilistically, and subjecting the results to statistical significance testing. In this paper, we propose a framework that combines beamformer methods ([1], [4], [9]) with nonparametric significance testing ([5], [6], [7]) to generate the source time series that may be used as the basis for functional connectivity analysis.

We assume that a paradigmatic evoked response dataset consists of continuously recorded multichannel EMEG data, including a set of labeled events (either stimuli or responses) at known times. We further assume that the desired outcome of the data analysis consists of a set of brain regions whose temporal activity has been estimated. These source time series then become the input for functional connectivity analysis. We further assume that each step of the analysis chain should be subject to significance testing.

After the data have been preprocessed (e.g., filtering and artifact suppression), the conventional analysis sequence proceeds to averaging over trials that satisfy suitable criteria, either in the time or time-frequency domains. Then peaks are identified, often by visual inspection, for source analysis. Dipole source analysis is widely used [7], but this may require considerable user intervention, and different individual fitting strategies may result in different models that fit the same data. Although linear methods have the advantage of objectivity, they do not typically result in a relatively small number of compact source regions of interest (ROIs) than can form the natural starting point for a functional connectivity analysis.

II. METHODS

In this section, we first review some source estimation methods, including some mathematical results that form the basis of beamformer theory. Then we show how non-parametric significance testing with multiple comparison correction may be used to identify compact ROIs. We then extend our beamformer discussion to estimating the time or time-frequency behavior of these ROIs. Finally, we describe briefly some methods that may be used for functional connectivity analysis from source time series data.

Source estimation methods seek to estimate properties of intracranial neuroelectric activity (location, timing, and magnitude) based on extracranial EMEG measurements and a head model such as the MRI-based finite element model. *Overdetermined global* methods seek a set of localized current sources that model the EMEG data. Spatiotemporal source modeling [7] is a typical member of this category. *Underdetermined global* methods seek an activity distribution over a set of current elements that cover the entire "source space" of the brain. Because all current elements have fixed locations, linear solution techniques apply. LORETA [7] and cortical surface current density (CSCD) estimation [1], [2] are typical examples. These methods solve a *coupled linear system*, so errors at one location require compensatory errors elsewhere.

In contrast, *local* methods optimize estimators on a per location basis, independent of estimators for other locations. Local methods find an estimator, a linear combination of EMEG channels, to estimate source activity at a location *e.g.*, linearly constrained minimum variance (LCMV) beamformers [13], [15], that are unbiased estimators of either source location or source magnitude ([3], [14]). REGAE is an alternative brain source activity local estimator for selected regions of interest [9], developed in the context of signal detection theory.

Gain matrix. Given a lead field matrix $\mathbf{L}$ and a derivation matrix $\mathbf{D}$, the gain matrix is $\mathbf{G} = \mathbf{DL}$. Each column of $\mathbf{G}$ represents a topography for a single source of unit magnitude. Given a source vector $\mathbf{q} \in \mathbb{R}^N$, the ideal measurement vector $\mathbf{v} \in \mathbb{R}^M$ for that source distribution is $\mathbf{v} = \mathbf{Gq}$. See [4] for additional details.

Beamformers. Beamformers may be classified as adaptive *vs.* non-adaptive, scalar *vs.* vector, distortionless *vs.* weight vector normalized *vs.* standardized. Scalar beamformers (BFs) apply when there is one source

Table 1. Weight vector ($\mathbf{w}^T$) formulae are shown for scalar beamformers. $\mathbf{g}_r$ is the gain vector for the r^{th} source, a column of the gain matrix, G. C is the signal space covariance. Derivations and further details may be found in [4].

	Distortionless	*Weight-vector normalized*	*Standardized*
Non-adaptive	$\dfrac{\mathbf{g}_r^T\left(\mathbf{G}\mathbf{G}^T\right)^{-1}}{\mathbf{g}_r^T\left(\mathbf{G}\mathbf{G}^T\right)^{-1}\mathbf{g}_r}$	$\dfrac{\mathbf{g}_r^T\left(\mathbf{G}\mathbf{G}^T\right)^{-1}}{\left(\mathbf{g}_r^T\left(\mathbf{G}\mathbf{G}^T\right)^{-2}\mathbf{g}_r\right)^{1/2}}$	$\dfrac{\mathbf{g}_r^T\left(\mathbf{G}\mathbf{G}^T\right)^{-1}}{\left(\mathbf{g}_r^T\left(\mathbf{G}\mathbf{G}^T\right)^{-1}\mathbf{g}_r\right)^{1/2}}$
Adaptive	$\dfrac{\mathbf{g}_r^T\mathbf{C}^{-1}}{\mathbf{g}_r^T\mathbf{C}^{-1}\mathbf{g}_r}$	$\dfrac{\mathbf{g}_r^T\mathbf{C}^{-1}}{\left(\mathbf{g}_r^T\mathbf{C}^{-2}\mathbf{g}_r\right)^{1/2}}$	$\dfrac{\mathbf{g}_r^T\mathbf{C}^{-1}}{\left(\mathbf{g}_r^T\mathbf{C}^{-1}\mathbf{g}_r\right)^{1/2}}$

orientation per location, else they are vector BFs. Adaptive BFs utilize the signal covariance, C, while non-adaptive BFs assume the source space identity covariance. Distortionless, weight vector normalized and standardized BFs differ based on the gain constraints used in their derivation. Additional details are found in [4], [14].

Table 1 shows the functional form for scalar beamformers. These forms would be useful, for example, when the solution is constrained to a single dipole per location on a discretized model of the cortical surface. When the source space is represented as a discretized volume, with, in general, a 3-space of current sources at each location, vector beamformers must be used. In [13], Sekihara and coworkers provide equations for adaptive distortionless (equation 6 of [13]) and weight-vector normalized (equation 11 of [13]) vector beamformers. Each BF results in a different weight matrix, **W**. Each column of **W**, $\mathbf{w}_{\mathbf{r},\boldsymbol{\theta}}$, represents the linear mapping that estimates a single source magnitude indexed by location **r** and orientation θ, given the data (cf. equation (2)).

Two beamformer estimators. Beamformers may be used to estimate either source location or source time series. Formally, we can write these different estimation problems as

$$\hat{\mathbf{r}} = \arg\max_{\mathbf{r}}\left(\mathbf{w}\left(\mathbf{r},\boldsymbol{\theta}\right)_{\mathrm{WVN}}^T \mathbf{v}\mathbf{v}^T\mathbf{w}\left(\mathbf{r},\boldsymbol{\theta}\right)_{\mathrm{WVN}}\right) \quad (1)$$

$$\hat{q}_{\mathbf{r},\boldsymbol{\theta}} = \mathbf{w}\left(\mathbf{r},\boldsymbol{\theta}\right)_{\mathrm{dist}}^T\mathbf{v} \quad (2)$$

where **v** is the measurement vector and **r** is the source location. Note that the **w**'s are different, depending on the estimator. In [4] and [14], it shown that in the presence of background white noise, only adaptive weight vector normalized beamformers $\mathbf{w}\left(\mathbf{r},\boldsymbol{\theta}\right)_{\mathrm{WVN}}$ are unbiased estimators of source location (1), while only distortionless beamformers $\mathbf{w}\left(\mathbf{r},\boldsymbol{\theta}\right)_{\mathrm{dist}}$ are unbiased estimators of source magnitude (2). In addition, it is shown in [14] that adaptive beamformers have better spatial resolution than their non-adaptive counterparts. These results imply the following strategy: First use adaptive weight vector normalized beamformers to determine those locations whose activities show significant changes in activity. Then select regions for subsequent analysis, using distortionless beamformers to estimate their source time series.

Significance Testing. Randomization methods for statistical significance testing [6] are the methods of choice for many bioelectromagnetic problems ([5], [7]), since they do not require assumptions about the underlying distributions. Instead the statistical distributions are inferred from the data. For this reason, it is generally necessary to go back to single trial data when conducting within subject between condition significance tests. The prestimulus baseline data points are generally not suited for this purpose unless the temporal correlation in the prestimulus baseline is first removed. While multiple comparison corrections are necessary, we have found that global multiple comparison correction for the entire spatiotemporal source estimation problem results in apparently overly conservative results. For this reason, we propose a method for determining statistically significant source regions that decomposes the solution into its temporal and spatial domains, and tests for significance in each separately. We first apply a significance test to the signal space topographic pattern, correcting for multiple comparisons over time [5] to identify those latencies whose global signal space topographies differ between conditions. Then sources are estimated at these latencies, using a weight vector normalized beamformer to scan the set of points that span the source volume. For each latency, a source map is obtained and the statistical significance at each source location is tested, with multiple comparison correction over the source volume. The result of this process yields a set of source volume locations whose activity differs significantly between the two conditions, at least fro the specified latencies. Next, we transform these locations into ROIs for subsequent time series analysis.

Regions of Interest (ROIs). The path to ROIs begins with excursion sets. The excursion set is simply the set of points whose value exceeds a selected threshold. Given a set $X = \left\{x_1, ..., x_N\right\}$ and a mapping $p : X \to \mathbb{R}$, define the lower excursion set as $\mathcal{E}_{p(x)<p_c} = \left\{x \in X : p\left(x\right) < p_c\right\}$ [17], where p_c is some threshold, say p=0.05. The upper excursion set can be defined in the obvious way. Then if X is a discrete topological space (e.g., a discretized vector space like the source volume or a discretized manifold like the cortical surface) we can transform the excursion set into a set of ROIs. Represent the space as a graph with edges connecting nearest neighbors, where the edges are defined when the space is constructed. For example, given a discretized 2D manifold with simplicial (triangle) tiling, the point set X consists of triangle vertices. The nearest neighbor edges for each vertex consist of those triangle edges that connect each vertex to the vertices of triangles that are common to the two vertices. Call the edge set $E=\left\{e_{x_i,x_j}\right\}$, each edge labeled by it endpoints. An ROI is a simply connected subset of the excursion set $R=\left\{x_i \in X : x_i \in \mathcal{E}_{p(x)<p_c} \text{ and } e_{x_i,x_j} \in E \text{ for some } x_j \in \mathcal{E}_{p(x)<p_c}\right\}$ The ROI relation partitions the excursion set into a set of disjoint proper subsets.

Time series estimation for ROIs. Each ROI consists of a set of dipoles, with generally >1 dipole per set. In order to estimate this time series, we can use the distortionless vector beamformer. First however, we use singular value decomposition (SVD) to represent the ROI as a new set of orthogonal sources. Let $\mathbf{F}(R)$ be the gain matrix for R, such that the i^{th} column of $\mathbf{F}$ is the gain vector for $x_i \in R$, and $\mathbf{F}=\mathbf{LSR}^T$ (by SVD). Let $\mathbf{L}_{RS}$ be the (possibly truncated) matrix of left singular vectors of $\mathbf{F}$ for each of the ROIs that constitute the ROI set, consisting of N' columns. Then a distortionless vector beamformer for the ROI set is given by ([15], [13], [16])

$$\mathbf{W}_{RS}^T=\left(\mathbf{L}_{RS}^T\mathbf{C}^{-1}\mathbf{L}_{RS}\right)^{-1}\mathbf{L}_{RS}^T\mathbf{C}^{-1} \quad (3)$$

Applying $\mathbf{W}_{RS}=\left[\mathbf{w}_1 \,|\, ... \,|\, \mathbf{w}_{N'}\right]$ to the data matrix $\mathbf{V}$, yields a vector estimator of the activity for the ROI set as $\mathbf{W}^T\mathbf{V}$. It is often useful, e.g., for functional connectivity analysis to reduce this vector time series to a single scalar time series for each ROI. This may be done by summing at each time slice over the individual components, if care is taken to use a consistent orientation convention following the SVD, or by taking the r.m.s. power at each slice.

IV. Discussion

To summarize this general analytical framework:

1. Preprocess data (visual inspection, filtering, artifact correction, forward model building).
2. Determine latencies and time-frequency neighborhoods at which there are significant differences between condition and rest (or two conditions), using randomization tests with multiple comparison correction over time.
3. For those latencies or time-frequency neighborhoods whose topographies exceed significance, find those source locations (determined using a scanning (weight vector normalized) beamformer) that show significant differences between condition and rest (or between two conditions), using randomization tests with multiple comparison correction over the source volume.
4. For those source volume locations that pass both significance tests, estimate their source time series, using the LCMV local estimator method.
5. In the time and time-frequency domains, compute first-order (e.g., average, variance, entropy) and higher-order (e.g., coherence, mutual information, causality) statistics, based on the source time series.
6. Using the higher-order statistics, construct a functional connectivity model, and test hypotheses. Optionally, compare the model with additional experimental parameters (*e.g.*, reaction time).

In a companion paper [9], we describe a method based on conditional mutual information which may be used to infer casual relations between time series like those produced by the methods described here.

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