Local Linear Estimators for the Bioelectromagnetic Inverse Problem

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***Abstract*—Linear estimators have been used widely in the bioelectromagnetic inverse problem, but their properties and relationships have not been fully characterized. Here, we show that the most widely used linear estimators may be characterized by a choice of norms on signal space and on source space. These norms depend, in part, on assumptions about the signal space and source space covariances. We demonstrate that two estimator classes (standardized and weight vector normalized) yield unbiased estimators of source location for simple source models (including only the noise-free case) but biased estimators of source magnitude. In the presence of instrumental (white) noise, we show that the nonadaptive standardized estimator is a biased estimator of source location, while the adaptive weight vector normalized estimator remains unbiased. A third class (distortionless) is an unbiased estimator of source magnitude but a biased estimator of source location.**

***Index Terms*—Biomedical electromagnetic imaging, electroencephalography, magnetoencephalography.**

I. Introduction

THE bioelectromagnetic inverse problem consists of estimating the locations and magnitudes of a set of equivalent current sources that can account for measured electroencephalographic (EEG) and/or magnetoencephalographic (MEG) data (jointly EMEG).

Conventionally, the source estimation problem (recently reviewed in [1]) has been defined as a global minimization problem, that is, given a set of measurements, find a set of sources that best accounts for the measurements in their entirety. We will refer to this class of solutions as *global* solutions. The global solutions in turn, may be subdivided into *discrete* and *distributed* solutions. The discrete solutions attempt to account for the data in terms of a small number of equivalent sources, whereas the distributed sources depend on a large number of fixed sources within the brain that may be combined to obtain the desired solution. One property of global solutions is that the parts of the solution are necessarily connected. Omitting one equivalent source, for example, will generally change the position and/or magnitude of other sources. The second class of solutions (the *local* estimators) do not attempt to account for the entire measured signal but, rather, attempt to estimate the activity at points or regions of interest independently of one another. These local estimators do not depend on one another; however, their summed activity is generally not equal to the measured signal.

Several different local estimators have been proposed in the literature (e.g., [2]–[5]), more or less independently of one another. In this paper, we study the relationships between these estimators, demonstrating that they all may be viewed as members of a single family that differ in their choice of norms for two linear vector spaces that arise naturally out of the bioelectromagnetic inverse problem. We find that the linear estimators may be grouped into four classes: i) "distortionless," ii) "weight vector normalized," iii) "standardized," and iv) "hybrid." Within each of these classes, estimators may be either adaptive or nonadaptive. For a simple case of the scalar beamformer, one or two (unknown) sources, and uncorrelated noise, we find that the adaptive weight vector normalized estimators are unbiased estimators of source location but biased estimators of relative source amplitude. Conversely, the distortionless estimators are unbiased estimators of relative source amplitude but biased estimators of source location. Many of the results in this paper confirm those recently reported in [6], using a somewhat different approach.

Although we refer in this paper to the head and the brain, the results obtained are more general and can be applied to the cardiographic inverse problem as well.[1]

II. Bioelectromagnetic Forward and Inverse Problems

A. Lead Fields and the Forward Problem

If we have a known source distribution, the forward problem consists of calculating the electromagnetic field produced by that distribution as a function of space and time. The first step is to state the forward solution for a single time sample and a continuous domain. If we consider a continuous primary current source vector field $\mathbf{j}(\mathbf{r})$ within the interior volume of the head Ω (the source volume) and a scalar-valued measurement function $\nu(\mathbf{r}')$ that is continuous in spatial parameter $\mathbf{r}'$, then

$$\nu(\mathbf{r}') = \int_{\Omega} d\mathbf{r}\mathbf{L}(\mathbf{r}', \mathbf{r}) \cdot \mathbf{j}(\mathbf{r}) \tag{1}$$

is the forward solution, where the kernel $\mathbf{L}(\mathbf{r}', \mathbf{r})$ is the current density lead field, which is a vector field over Ω. The lead field

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[1]A note on notation: Matrices are indicated as boldface capitals (e.g., $\mathbf{G}$), column vectors as lowercase bold (e.g., $\mathbf{g}$), and scalars as lowercase italics (e.g., ξ). $\|\cdot\|$ indicates the L2 norm and $\cdot^T$ the transpose operator. $\mathbf{I}$ is the identity matrix, and $\mathbf{1}$ is a vector of 1's. $N(\mu, \sigma^2)$ is the univariate normal distribution with mean μ and variance σ^2, and $N(\mu, \mathbf{\Sigma})$ is the multivariate normal distribution with mean vector $\boldsymbol{\mu}$ and covariance $\mathbf{\Sigma}$.

may be calculated using one of several models [7], all of which represent the current flow within the conducting volume of the head with differing degrees of realism.

In most practical cases, when we are dealing with experimental data, the measurements are made at discrete (and nonvarying) locations and orientations; therefore, we replace $\nu(\mathbf{r}')$ with the ideal measurement vector $\mathbf{v}$. In addition, the continuous current density distribution $\mathbf{j}(\mathbf{r})$ may be replaced by a vector of current dipoles $\mathbf{q}$. Each element of $\mathbf{q}$ is a discrete current dipole that models the continuous primary source current density vector field in its neighborhood. A current dipole is specified when both its position and moment (orientation and magnitude) are given. Then, the discrete form of the forward problem is given by the matrix equation $\mathbf{v} = \mathbf{Lq}$, where $\mathbf{L}$ is the dipolar lead field matrix.

B. Gain Matrix

While magnetic field measurements may be reference-free, this is not true of the electric field, since the electric potential is only defined as a difference between two locations. For many forward solution calculations, one of these points may be infinity, but typically, the measurement is made differentially with respect to a specific reference electrode placed somewhere on or near the head. It is useful to define the measurement (or montage) matrix $\mathbf{M}$ that accounts for the reference. In the case of a single reference electrode, $\mathbf{M}$ takes the form $\mathbf{M}_{\mathrm{PhysRef}} = [\mathbf{I}, -\mathbf{1}]$. Similarly, we can define the average reference, or centering, montage as $\mathbf{M}_{\mathrm{AvgRef}} = \mathbf{I} - (1/S)\mathbf{1}\mathbf{1}^T$, where S is the number of sensors. We adopt the nomenclature that $\mathbf{M}$ maps *sensors* to *channels*. Furthermore, $\mathbf{M}$ need not be square. There may be, for example, fewer channels than sensors. Typically, there is no channel that corresponds to the reference sensor. In the case of magnetic measurements, $\mathbf{M}$ is typically the identity matrix, although many multichannel magnetometers use reference channels to cancel environmental signals, and these magnetic reference channels may be accommodated easily into our formalism.

It may sometimes be the case that the data have been preprocessed by a spatial filter, e.g., a projection matrix obtained from independent components analysis. We represent the spatial filtering process by the filter matrix $\mathbf{F}$. Then, the gain matrix $\mathbf{G}$ is defined by

$$\mathbf{G} = \mathbf{FML} \tag{2}$$

and the forward solution (from dipolar sources to measurement channels) becomes $\mathbf{v} = \mathbf{Gq}$, which we use as our representation of the forward solution for a single time sample in the work we describe here.

C. Inverse Problem

We represent the forward problem abstractly as $\mathbf{Q} \xrightarrow{\mathbf{G}} \mathbf{V}$, where $\mathbf{Q} = \mathbb{R}^N$ is the N-dimensional real vector space of sources (the source space, consisting of N sources), and $\mathbf{V} = \mathbb{R}^M$ is the M-dimensional real vector space of measurements (the measurement, or signal, space, consisting of M channels). Then, the inverse problem consists of finding a mapping $\mathbf{V} \xrightarrow{\mathbf{G}^{\oplus}} \mathbf{Q}$ from signals to sources. Since $N \gg M$, this problem is ill-posed, and solutions must be based on models that reduce the dimension of the solution space.

III. Linear Estimators

A. Linear Estimator Algebra

We have introduced the two principal vector spaces $\mathbf{Q}$ and $\mathbf{V}$, which are the source space and signal (or measurement) space, respectively. To solve the linear estimation problem, we need to add additional structure, i.e., a metric or norm. A conventional way to represent this is through the use of dual spaces $\mathbf{Q}^*$ and $\mathbf{V}^*$ [8]. Then, $\mathbf{Q} \xrightarrow{\boldsymbol{\Theta}_{\mathbf{Q}}} \mathbf{Q}^*$ and $\mathbf{V} \xrightarrow{\boldsymbol{\Theta}_{\mathbf{V}}} \mathbf{V}^*$, where $\boldsymbol{\Theta}_{\mathbf{Q}}$ and $\boldsymbol{\Theta}_{\mathbf{V}}$ are symmetric, positive definite matrices. Since $\mathbf{V}^* \xrightarrow{\mathbf{G}^T} \mathbf{Q}^*$, we can write linear inverse solutions as

$$\mathbf{V} \xrightarrow{\boldsymbol{\Theta}_{\mathbf{V}}} \mathbf{V}^* \xrightarrow{\mathbf{G}^T} \mathbf{Q}^* \xrightarrow{\boldsymbol{\Theta}_{\mathbf{Q}}^{-1}} \mathbf{Q} \tag{3}$$

or $\mathbf{G}^{\oplus} = \boldsymbol{\Theta}_Q^{-1}\mathbf{G}^T\boldsymbol{\Theta}_V$. Given $\mathbf{G}$, the problem is solved once we know (or choose) suitable metrics on $\mathbf{Q}$ and $\mathbf{V}$. If we want the inverse estimator to be a pseudoinverse (i.e., $\mathbf{G}\mathbf{G}^{\oplus} = \mathbf{I}$), then once we choose $\boldsymbol{\Theta}_{\mathbf{Q}}$, $\boldsymbol{\Theta}_{\mathbf{V}}$ is constrained by the requirement that $\mathbf{G}\mathbf{G}^{\oplus} = \mathbf{I}$. If we choose $\boldsymbol{\Theta}_{\mathbf{Q}} = \mathbf{I}$, we find that $\boldsymbol{\Theta}_{\mathbf{V}} = (\mathbf{G}\mathbf{G}^T)^{-1}$, and then, $\mathbf{G}^{\oplus} = \mathbf{G}^T(\mathbf{G}\mathbf{G}^T)^{-1}$ is the well-known minimum norm solution, which accounts for the data exactly. Of course, we can choose some other form for $\boldsymbol{\Theta}_{\mathbf{Q}}$ (such as a Sobolev norm [9], of which Loreta [10] is an example) or a lead field normalized metric [11]. We refer to such metrics as "B-norms" in Table III.

If we relax the constraint that $\mathbf{G}\mathbf{G}^{\oplus} = \mathbf{I}$, then we are free to choose not only $\boldsymbol{\Theta}_{\mathbf{Q}}$ but $\boldsymbol{\Theta}_{\mathbf{V}}$ as well. This path leads us to local estimators. While we are relatively free in making these choices, not all admissible metrics will lead to useful estimators. In this paper, we will derive several useful metrics as the solution to a set of constrained minimization problems, where the constraints have explicit physical and statistical significance. The signal and source space norms ($\boldsymbol{\Theta}_V$ and $\boldsymbol{\Theta}_Q$, respectively) that we derive, as well as their associated linear estimators, are summarized in Table III.

Note that from the minimum norm solution, we can get an estimate for a single scalar source at the target location $\mathbf{r}_0$ as

$$\mathbf{w}_{\mathbf{r}_0}^T = \mathbf{g}_{\mathbf{r}_0}^T(\mathbf{G}\mathbf{G}^T)^{-1} \tag{4}$$

where $\mathbf{g}_{\mathbf{r}_0}$ is the column of $\mathbf{G}$ corresponding to the source located at $\mathbf{r}_0$. The weight vector $\mathbf{w}_{\mathbf{r}_0}^T$ in (4) is an example of a local estimator. For an arbitrary set of weight vectors, we can define the scan matrix $\mathbf{W}$ as

$$\mathbf{W} \triangleq [\mathbf{w}_0, \ldots, \mathbf{w}_{N-1}]^T. \tag{5}$$

In this paper, we will also refer to the scan matrix as a weight matrix $\mathbf{W}^T$, where each row is a weight vector $\mathbf{w}_{\mathbf{r}_0}^T$ that maps a measurement vector into a source space magnitude. This notation is consistent with that frequently used in the beamformer literature. If $\mathbf{G}\mathbf{W}^T = \mathbf{I}$, then $\mathbf{W}^T$ is a pseudoinverse of $\mathbf{G}$, $\mathbf{G}^+$.

B. Resolution Kernel

Formally, the resolution kernel $R(\mathbf{r}_0, \mathbf{r})$ may be defined implicitly ([12], [13]) as

$$\hat{j}(\mathbf{r}_0) = \int_\Omega d\mathbf{r} R(\mathbf{r}_0, \mathbf{r})\mathbf{j}(\mathbf{r}) \quad (6)$$

where $\hat{j}(\mathbf{r}_0)$ is the estimated source current density at target location $\mathbf{r}_0$ for source distribution $\mathbf{j}(\mathbf{r})$. In the discrete case, given the true source distribution $\mathbf{q}$, the estimated source distribution obtained by application of the scan matrix $\mathbf{W}^T$ will be given by

$$\hat{\mathbf{q}} = \mathbf{W}^T\mathbf{G}\mathbf{q}. \quad (7)$$

Then, we can represent the resolution kernel for all target locations and a given scan matrix $\mathbf{W}^T$ as the $N \times N$ matrix $\mathbf{K}$ given by

$$\mathbf{K} = \mathbf{W}^T\mathbf{G} \quad (8)$$

where (7) is the discrete version of (6). In words, the resolution kernel has the effect of projecting the source space up to the measurement space and then back down into the source space again.

Consider two different views of the physical interpretation of the resolution kernel, each obtained by selecting a single location for analysis. First, assume that the true source distribution is given by a unit source at location $\mathbf{r}_0$. Then, (7) leads to the interpretation of the resolution kernel as a point spread function, measuring how much the inverse estimate for a point source is "blurred" by the scan matrix. For such a unit point source, we may rewrite (7) as

$$\hat{\mathbf{q}} = \mathbf{W}^T\mathbf{g}_{\mathbf{r}_0} \quad (9)$$

where $\mathbf{g}_{\mathbf{r}_0}$ is the lead field (column) vector for location $\mathbf{r}_0$.

Now, consider an alternative view. Choose a target location $\mathbf{r}_0$, and successively place sources of unit strength at each source space location; this can be represented by the $N \times N$ identity matrix.

Symbolically, we can write $\hat{\mathbf{q}}^T = \mathbf{w}_{\mathbf{r}_0}^T\mathbf{G}\mathbf{I}$, which measures the extent to which sources at all locations project through the estimator for the target location. We may also consider a random distribution of sources across the entire source space, where each source is independent and identically distributed as $q \sim N(0, 1)$. Then, the source space covariance is the identity matrix $\mathbf{I}$. We can ask how much of this uniform activity will be projected onto a target location $\mathbf{r}_0$. Since there is only a single target location, we may consider only the row from $\mathbf{W}^T$ that projects onto the target location $\mathbf{w}_{\mathbf{r}_0}^T$ and obtain from (7) the estimated power $\hat{q}_{\mathbf{r}_0}^2 = \mathbf{w}_{\mathbf{r}_0}^T\mathbf{G}\mathbf{I}\mathbf{G}^T\mathbf{w}_{\mathbf{r}_0}$.

We view $\mathbf{w}_{\mathbf{r}_0}^T\mathbf{G}$ as an interference function, measuring the interference that the scan matrix imposes on our estimate, given an identity source space covariance. This expression plays a central role in our derivation of local estimators, and we will refer to it as the resolution kernel at $\mathbf{r}_0$, or

$$\mathbf{k}_{\mathbf{r}_0}^T = \mathbf{w}_{\mathbf{r}_0}^T\mathbf{G}. \quad (10)$$

For the minimum norm inverse, $\mathbf{K}$ is symmetric, so the rows and columns of $\mathbf{K}$ are identical, and thus, (9) and (10) lead to the same distribution (i.e., the point spread function and the interference function are identical in the minimum norm case). However, the resolution kernel in the more general case is not necessarily symmetric; therefore, the point spread and interference functions generally will not be the same.

C. Nonadaptive Scalar Estimators

Our approach is to derive a family of local estimators by finding a set of estimators that minimize the norm of the resolution kernel at $\mathbf{r}_0$, subject to one or more constraints, or, from (10)

$$\min \|\mathbf{k}_{\mathbf{r}_0}\|^2. \quad (11)$$

The constraints, which will be described below, avoid the trivial solution $\|\mathbf{k}_{\mathbf{r}_0}\|^2 = 0$ and assure that $\mathbf{w}_{\mathbf{r}_0}$ is actually a useful estimator. Therefore, the problem posed is to find the local estimator $\mathbf{w}_{\mathbf{r}_0}$ that is the solution to (11), subject to one or more constraints.

1) Distortionless Estimators: From (10), we can rewrite the squared norm in (11) as

$$\|\mathbf{k}\|^2 = \mathbf{w}^T\mathbf{G}\mathbf{G}^T\mathbf{w}. \quad (12)$$

Then, for target location $\mathbf{r}_0$, the problem described in (11) becomes

$$\mathbf{w}_{\mathbf{r}_0} = \underset{\mathbf{w}}{\operatorname{argmin}}(\mathbf{w}^T\mathbf{G}\mathbf{G}^T\mathbf{w}). \quad (13)$$

A natural (but not unique) constraint is obtained by requiring that

$$\mathbf{w}^T\mathbf{g}_{\mathbf{r}_0} = 1 \quad (14)$$

where $\mathbf{g}_{\mathbf{r}_0}$ is the lead field (column vector) for location $\mathbf{r}_0$. In words, (14) means that the solution must have unit gain for a source located at $\mathbf{r}_0$, or, given a measurement distribution corresponding to a point source, the desired solution $\mathbf{w}$ will return an unbiased magnitude estimate for that source. It has therefore been referred to as a "distortionless" beamformer [5].

Now, the minimization problem may be stated as

$$\mathbf{w}_{\mathbf{r}_0} = \underset{\mathbf{w}}{\operatorname{argmin}}(\mathbf{w}^T\mathbf{G}\mathbf{G}^T\mathbf{w}) \text{ s.t. } \mathbf{w}^T\mathbf{g}_{\mathbf{r}_0} = 1. \quad (15)$$

The solution to (15) may be obtained using variational methods combined with the use of a Lagrange multiplier [4], [14]. The Lagrange functional associated with (15) is given by

$$L(\mathbf{w}, \lambda) = \mathbf{w}^T\mathbf{G}\mathbf{G}^T\mathbf{w} + 2\lambda\left(\mathbf{w}^T\mathbf{g}_{\mathbf{r}_0} - 1\right) \quad (16)$$

and the solution is found at

$$\left.\frac{\partial L(\mathbf{w}, \lambda)}{\partial \mathbf{w}}\right|_{\mathbf{w}=\mathbf{w}_{\mathbf{r}_0}} = 0 \quad (17)$$

to be

$$\mathbf{w}_{\mathbf{r}_0} = \frac{(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}}{\mathbf{g}_{\mathbf{r}_0}^T(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}}. \quad (18)$$

Finally, the estimated source magnitude at $\mathbf{r}_0$ is given by $\hat{q}_{\mathbf{r}_0} = \mathbf{w}_{\mathbf{r}_0}^T \mathbf{v}$. Note that the physical units for the weight vector given by (18) are Ampere-meters per Volt (or Tesla) (AmV^{-1} or AmT^{-1}), yielding a dipole magnitude estimate in appropriate physical units.

Consider the interpretation of (18) in terms of signal and source space norms. First, rewrite (18) as $\mathbf{w}_{\mathbf{r}_0}^T = \left(\mathbf{g}_{\mathbf{r}_0}^T (\mathbf{G}\mathbf{G}^T)^{-1} \mathbf{g}_{\mathbf{r}_0}\right)^{-1} \mathbf{g}_{\mathbf{r}_0}^T (\mathbf{G}\mathbf{G}^T)^{-1}$. Note that for some measurement vector $\mathbf{v}$, $\mathbf{g}_{\mathbf{r}_0}(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{v}$ is a scalar, and this implies that $(\mathbf{G}\mathbf{G}^T)^{-1}$ is a signal space norm, since it is symmetric and positive definite by construction. Therefore, $\mathbf{\Theta}_V = (\mathbf{G}\mathbf{G}^T)^{-1} : \mathbf{V} \rightarrow \mathbf{V}^*$, and $\mathbf{G}^T(\mathbf{G}\mathbf{G}^T)^{-1} : \mathbf{V} \rightarrow \mathbf{Q}^*$ [see (3)]. Then, if the source space norm $\mathbf{\Theta}_Q$ is given by the diagonal matrix whose nonzero entries are $\mathbf{g}_{\mathbf{r}}^T(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}}$, the complete scan matrix may be written as $\mathbf{W}^T = \mathbf{\Theta}_Q^{-1}\mathbf{G}^T\mathbf{\Theta}_V$. These norms may vary, depending on the estimator. Table III summarizes the signal and source space norms associated with the linear estimators that we derive in this paper.

Let us note briefly two alternative formulations to the problem given by (11)–(15). First, we might wish to find the solution that makes $\mathbf{k}_{\mathbf{r}_0}$, which is the resolution kernel, as close as possible to a δ function. To do this, we would solve for $\operatorname{argmin}_{\mathbf{w}} \|\mathbf{k}_{\mathbf{r}_0} - \delta_{\mathbf{r}_0}\|$, where $\delta_{\mathbf{r}_0}$ is an N-dimensional vector of 0's, except for a 1 at $\mathbf{r}_0$. It can be shown [9] that this results in a minimum norm solution, unless a constraint like (14) is applied. Second, in the derivation of (18), we have ignored any spatial properties of the interference, which might make the resolution kernel more closely approximate a δ function. If we wish to include spatial information, a natural way to do this is to modify (12) by the incorporation of a diagonal matrix $\mathbf{D}$, such that $d_{ii} = \|\mathbf{r}_0 - \mathbf{r}_i\|^2$. Then, (13) becomes

$$\mathbf{w}_{\mathbf{r}_0} = \underset{\mathbf{w}}{\operatorname{argmin}}(\mathbf{w}^T\mathbf{G}\mathbf{D}\mathbf{G}^T\mathbf{w}) \tag{19}$$

and the derivation proceeds accordingly, although some care needs to be taken at $\mathbf{r}_0$. This route leads to a solution essentially equivalent to that described in [15]. The principal results we report in this paper obtain whether or not we include $\mathbf{D}$.

2) Weight Vector Normalized Estimator: What we have obtained with (18) is, by construction, an unbiased estimator of the *dipole magnitude* at any location [due to constraint (14)]. However, simulations [6] and theory (see the Appendix and [6]) demonstrate that when (18) is used to scan for the maximum current, it will provide a biased estimate of the *dipole location*. This is discussed in greater detail below (Section III-G).

The physical explanation for the failure of (18) to identify where the correct location lies is the nonlinear dependence of the lead field on depth. In order to overcome this bias, we need to add an additional constraint that will overcome the depth dependence of the lead field. As proposed in [5] (see also [16]), we will constrain the solution for uniform weight vector magnitude as

$$\mathbf{w}^T\mathbf{w} = 1. \tag{20}$$

The constraint $\mathbf{w}^T\mathbf{w} = 1$ assures that the weight vector magnitude will be the same at all locations. Then, to find the solution to this constrained minimization problem, we follow [5] by adding a new (pseudo)constraint $\mathbf{w}^T\mathbf{g} = \xi$

$$\mathbf{w}_{\mathbf{r}_0} = \underset{\mathbf{w}}{\operatorname{argmin}}(\mathbf{w}^T\mathbf{G}\mathbf{G}^T\mathbf{w}) \text{ s.t. } \mathbf{w}^T\mathbf{g} = \xi \text{ and } \mathbf{w}_\xi^T\mathbf{w}_\xi = 1. \tag{21}$$

What (21) means in words is that we first find a one-parameter family of solutions to the constrained minimization problem $\mathbf{w}_\xi$. All of these solutions "point" in the same direction in measurement space, but their norm (equivalently, gain) is undefined. Then, we use the second constraint $\mathbf{w}_\xi^T\mathbf{w}_\xi = 1$ to single out a specific length that satisfies the condition. We can solve this in two steps. First, solve the variational problem

$$\mathbf{w}_{\mathbf{r}_0,\xi} = \underset{\mathbf{w}}{\operatorname{argmin}}(\mathbf{w}^T\mathbf{G}\mathbf{G}^T\mathbf{w}) \text{ s.t. } \mathbf{w}^T\mathbf{g} = \xi. \tag{22}$$

The solution to (22) is obtained by steps essentially similar to (16) and (17), and we obtain

$$\mathbf{w}_{\mathbf{r}_0,\xi} = \xi \frac{(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}}{\mathbf{g}_{\mathbf{r}_0}^T(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}}. \tag{23}$$

To determine the value of ξ, combine (20) and (23) to obtain

$$\begin{aligned} 1 &= \mathbf{w}_{\mathbf{r}_0,\xi}^T\mathbf{w}_{\mathbf{r}_0,\xi} \\ &= \xi^2 \left[\frac{(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}}{\mathbf{g}_{\mathbf{r}_0}^T(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}}\right]^T \left[\frac{(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}}{\mathbf{g}_{\mathbf{r}_0}^T(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}}\right]. \end{aligned} \tag{24}$$

After some rearrangement, we obtain

$$\xi = \frac{\mathbf{g}_{\mathbf{r}_0}^T(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}}{\left[\mathbf{g}_{\mathbf{r}_0}^T(\mathbf{G}\mathbf{G}^T)^{-2}\mathbf{g}_{\mathbf{r}_0}\right]^{1/2}}. \tag{25}$$

Then, taking (23) and (25) and simplifying, we get

$$\mathbf{w}_{\mathbf{r}_0} = \frac{(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}}{[\mathbf{g}_{\mathbf{r}_0}^T(\mathbf{G}\mathbf{G}^T)^{-2}\mathbf{g}_{\mathbf{r}_0}]^{1/2}} \tag{26}$$

and the estimated dipole magnitude given by $\hat{q}_{\mathbf{r}_0} = \mathbf{w}_{\mathbf{r}_0}^T\mathbf{v}$. Note that the weight vector given by (26) is dimensionless; therefore, the resulting dipole magnitude estimate is presented in measurement units (Volts or Tesla). This is consequence of the weight vector magnitude normalization. As we show in the Appendix, the weight vector obtained from (26) yields a biased estimator of source location.

3) Standardized Estimator: Notice that constraints (15) or (21) introduced a new norm into the estimator problem when demanding that $\mathbf{w}_\xi^T\mathbf{w}_\xi = 1$, or equivalently, $\mathbf{w}_\xi^T\mathbf{I}\mathbf{w}_\xi = 1$. It is, of course, possible to choose some other metric on the space of weight vectors. One natural choice is the matrix $\mathbf{G}\mathbf{G}^T$, which constrains the expected value of the interference from brain sources at all locations to be uniform, i.e., given a uniform (maximum entropy) source space covariance. Then, the relevant minimization problem becomes

$$\underset{\mathbf{w}}{\operatorname{argmin}}(\mathbf{w}^T\mathbf{G}\mathbf{G}^T\mathbf{w}) \text{ s.t. } \mathbf{w}^T\mathbf{g} = \xi \text{ and } \mathbf{w}_\xi^T\mathbf{G}\mathbf{G}^T\mathbf{w}_\xi = 1. \tag{27}$$

Following steps equivalent to (22) and (23), and combining with the constraint $\mathbf{w}_\xi^T\mathbf{G}\mathbf{G}^T\mathbf{w}_\xi = 1$, we obtain

$$\xi = \left[\mathbf{g}_{\mathbf{r}_0}^T(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}\right]^{1/2}. \tag{28}$$

Then, substituting (28) into (23), we obtain the desired weight vector as

$$\mathbf{w}_{\mathbf{r}_0} = \frac{(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}}{\left[\mathbf{g}_{\mathbf{r}_0}^T(\mathbf{G}\mathbf{G}^T)^{-1}\mathbf{g}_{\mathbf{r}_0}\right]^{1/2}}. \tag{29}$$

The units for the weight vector in (29) are AmV^{-1} or AmT^{-1}, and therefore, this estimator, like the distortionless estimator, yields dipole magnitude estimates in physical units (Am). In [17], Pascual-Marqui obtained a local estimator, which he calls "standardized" Loreta, or sLoreta. The power output of the estimator obtained from (29) is exactly equivalent to that obtained using sLoreta. However, scanning estimators derived from (29), including sLoreta, are biased estimators of source location in the presence of uncorrelated noise, as we show in the Appendix.

The estimators that we describe in this section have been called nonadaptive [6] since their functional form depends only on the forward solution and not on the data.

D. Adaptive Scalar Estimators

If $\mathbf{q}(t)$ is a multivariate random process with covariance $\mathbf{R_Q}$, and $\mathbf{G}$ is a linear mapping $\mathbf{Q} \xrightarrow{G} \mathbf{V}$, then (see [24]), the signal space covariance of $\mathbf{v}(t)$ in the absence of instrumental and environmental noise is $\mathbf{R_v} = \mathbf{G}\mathbf{R_Q}\mathbf{G}^T$. This is the bridge from the estimators that we have just derived to minimum variance beamformers typically used in signal processing applications, including bioelectromagnetic applications (e.g., [4], [5], [15], [17], and [18]). If we assume that $\mathbf{R_Q}$ is unit variance and uncorrelated (e.g.., the identity matrix), then $\mathbf{R_v} = \mathbf{G}\mathbf{G}^T$. Of course, we can estimate $\mathbf{R_v}$ directly from the data, assuming that the underlying random process is stationary. Using the estimated $\mathbf{R_v}$ in place of the theoretical $\mathbf{R_v}$, the form of the weight vector equations we have derived remains unchanged, but all instances of $\mathbf{G}\mathbf{G}^T$ are replaced with $\mathbf{R_v}$. This is shown in Table III, where we represent either $\mathbf{G}\mathbf{G}^T$ or $\mathbf{R_v}$ as the matrix $\mathbf{\Gamma}$. We call $\mathbf{\Gamma} = \mathbf{G}\mathbf{G}^T$ nonadaptive and $\mathbf{\Gamma} = \mathbf{R_v}$ adaptive [6].

In general, the adaptive solution will have better resolution than the nonadaptive solution [6], but the accuracy of the solution will depend critically on a suitable (i.e., data-based) estimate of the signal space covariance matrix and the accuracy of the forward model. Since the background (or noise) covariance is generally different from the signal covariance, using the noise covariance generally will give an incorrect estimate of the source location and magnitude.

Table I shows that within each class (nonadaptive or adaptive), the local estimators that we have derived differ by a scale factor, i.e.., a scalar field over the source space. The entries in the table may be calculated by observing that within the adaptive or nonadaptive classes, the estimators differ only in the source space metric. What this means is that once the source space covariance is chosen (either $\mathbf{I}$ or implicitly from $\mathbf{R_v}$), the subclasses (distortionless, weight vector normalized, or standardized) are all represented by vector fields that are directionally equivalent (that is, at any location, the three weight vectors all point in the same direction), and these vectors differ only in magnitude.

TABLE I

EACH CELL IN THE TABLE INDICATES THE SCALAR FIELD EQUATION OVER THE SOURCE VOLUME $\mathbf{\Omega}$ THAT MAY BE USED TO MAP THE ESTIMATOR INDICATED BY THE jTH COLUMN TO THE ESTIMATOR INDICATED BY THE iTH ROW, WHEN ESTIMATORS ARE OF THE SAME TYPE (EITHER NONADAPTIVE OR ADAPTIVE). TO CHANGE BETWEEN NONADAPTIVE AND ADAPTIVE, $\mathbf{\Gamma}$ (AS DEFINED IN TABLE III) SHOULD BE SUBSTITUTED AS INDICATED, EQUIVALENT TO A TENSOR FIELD OVER $\mathbf{\Omega}$

	Distortionless	*Weight vector normalized*	*Standardized*
Distortionless	1	$\dfrac{(\mathbf{g}_r^T\mathbf{\Gamma}^{-2}\mathbf{g}_r)^{1/2}}{\mathbf{g}_r^T\mathbf{\Gamma}^{-1}\mathbf{g}_r}$	$\dfrac{1}{(\mathbf{g}_r^T\mathbf{\Gamma}^{-1}\mathbf{g}_r)^{1/2}}$
Weight vector normalized	$\dfrac{\mathbf{g}_r^T\mathbf{\Gamma}^{-1}\mathbf{g}_r}{(\mathbf{g}_r^T\mathbf{\Gamma}^{-2}\mathbf{g}_r)^{1/2}}$	1	$\dfrac{(\mathbf{g}_r^T\mathbf{\Gamma}^{-1}\mathbf{g}_r)^{1/2}}{(\mathbf{g}_r^T\mathbf{\Gamma}^{-2}\mathbf{g}_r)^{1/2}}$
Standardized	$(\mathbf{g}_r^T\mathbf{\Gamma}^{-1}\mathbf{g}_r)^{1/2}$	$\dfrac{(\mathbf{g}_r^T\mathbf{\Gamma}^{-2}\mathbf{g}_r)^{1/2}}{(\mathbf{g}_r^T\mathbf{\Gamma}^{-1}\mathbf{g}_r)^{1/2}}$	1

E. Hybrid Estimators

All of the linear estimators that we have described so far are obtained as the solution to a minimization problem, subject to specified constraints. However, several estimators described in the literature (e.g., [4], [18], and [19]) do not fall neatly into this constrained optimization framework, although they are encompassed by the linear estimator model described in Section III-A. We refer to these as "hybrid" since the numerator and denominator metrics $\mathbf{\Gamma}^{-1}$ are not the same. These hybrid estimators begin as one of the location-biased estimators that we have described in Sections III-C and D. For example, [4] and [18] begin with a minimum variance distortionless beamformer, whereas [19] begins with a lead field normalized minimum norm estimator. Then, the hybrid methods add a second normalization (equivalent to imposing a new norm on source space) to more-or-less successfully compensate for the location bias in the initial estimator. This may be done by using the instrumental noise covariance projected back to the source space by the initial estimator matrix, yielding a new source space metric. In this paper, we do not study the properties of these hybrid estimators in further detail.

F. Vector Estimators

The scalar estimators described in Tables I and II assume that we seek to estimate the dipole magnitude at a target location, given a fixed orientation. This would be the case, for

TABLE II
COMPARISON OF THE LINEAR ESTIMATOR CLASSES THAT WE DERIVE WITH THOSE REPORTED IN THE LITERATURE FOR USE WITH THE BIOELECTROMAGNETIC INVERSE PROBLEM. WE ANALYZE SCALAR ESTIMATORS IN THIS PAPER, BUT PRACTICAL APPLICATIONS TYPICALLY USE VECTOR ESTIMATORS. THEREFORE, NOT ALL PROPERTIES OF THESE VECTOR ESTIMATORS MAY BE ACCOUNTED FOR BY THE CLASSIFICATION SYSTEM WE PROPOSE. FOR EXAMPLE, SAM [18] IS AN ORIENTATION-ADAPTIVE VECTOR BEAMFORMER, AND THE ORIENTATION ADAPTATION ALGORITHM HAS NO CLEAR SCALAR COUNTERPART

Class	*Relatives*
Non-adaptive distortionless	WROP [15]
Non-adaptive weight vector normalized	
Non-adaptive standardized	sLoreta [17]
Adaptive distortionless	Distortionless LCMV [4], [5], [6]
Adaptive weight vector normalized	Borgiotti-Kaplan [5]
Adaptive standardized	
Hybrid	Neural activity index [4]; SAM [18]; DSPM [19]

example, when scanning with a cortically constrained source model, where the dipoles are constructed to be oriented normal to the cortical surface. Often, the dipole orientations are not known *a priori*, and there is a three-space of current dipoles at each location. The solution to this problem involves the application of vector estimators. Such estimators, clearly of considerable practical importance, are described by a number of authors (including [4], [5], [15], [17], and [18]), and we refer the interested reader to these sources. Vector estimators may be understood according to the same methods used to develop Table III, and their detailed discussion here would not add any new conceptual information to the questions that we address here.

In Table II, we classify several previously reported vector estimators in terms of the descriptions used in this paper.

G. Estimation Bias

A statistical estimator is unbiased if the expected value of the estimated parameter is the value of the physical quantity to be estimated: symbolically $E(\hat{x}) = x$ for some parameter x. In this work, we consider two different estimators, both obtained from the same set of weight vectors. The dipole magnitude estimator (or beamformer) is given by

$$\hat{q} = \mathbf{w}^T \mathbf{v} \tag{30}$$

and the location (or scanning) estimator is given by

$$\hat{\mathbf{r}} = \arg\max_{\mathbf{r}} \left(\mathbf{w}_{\mathbf{r}}^T \mathbf{v} \mathbf{v}^T \mathbf{w}_{\mathbf{r}} \right). \tag{31}$$

For the estimators given by (30) and (31), we now consider three different conditions for determining estimator bias.

1) Source Space Localization Estimation for a Single Dipolar Source: Often, estimators are used in the scanning mode to estimate the location of one or more sources in the brain. This may be done iteratively or through use of the scan matrix (5). If the true source location is $\mathbf{r}_0$, then the scan is unbiased iff $E(\hat{\mathbf{r}}) = \mathbf{r}_0$. In the Appendix, we show that in the presence of additive white noise, this condition is met only by the adaptive weight vector normalized estimators. However, as we also show in the Appendix, the nonadaptive standardized estimator (sLoreta) is unbiased only in the absence of noise. This is consistent with the simulations reported in [17], where correct location is reported for the nonadaptive standardized beamformer (sLoreta) but only in the noise-free case. These conclusions are also consistent with the results reported in [6].

2) Source Magnitude Estimation for a Pair of Uncorrelated Sources: The other common use of weight vectors is to estimate a source time series, given a location. In the case of a pair of uncorrelated sources, the distortionless estimators will correctly estimate the time series for each of a pair of sources, or $E(\hat{q}(t)) = q(t)$. This is imposed by the constraint that $\mathbf{w}_{\mathbf{r}_0}^T \mathbf{g}_{\mathbf{r}_0} = 1$ [see (14)] for both the nonadaptive and the adaptive distortionless estimators. In the adaptive case, however, the condition will only be met if the sources are uncorrelated (see Section III-G3 below). However, both the standardized and the weight vector normalized estimators will be biased estimators of relative source magnitude. This may be seen by considering two sources at different locations of unit magnitude. Then, for the standardized beamformer [from (29)]

$$\frac{E(\hat{q}_0)}{E(\hat{q}_1)} = \frac{\left(\mathbf{g}_{\mathbf{r}_0}^T \mathbf{\Gamma}^{-1} \mathbf{g}_{\mathbf{r}_0} E(q_0)\right)^{1/2}}{\left(\mathbf{g}_{\mathbf{r}_1}^T \mathbf{\Gamma}^{-1} \mathbf{g}_{\mathbf{r}_1} E(q_1)\right)^{1/2}} \neq \frac{E(q_0)}{E(q_1)} \text{ in general} \tag{32}$$

since the $\mathbf{\Gamma}^{-1}$ norms of $\mathbf{g}_{\mathbf{r}_0}$ and $\mathbf{g}_{\mathbf{r}_1}$ are not generally equal. A similar analysis applies to all but the distortionless estimators. This bias has an effect on the scanning beamformer since deeper sources will appear smaller than shallower sources of the same magnitude when the scanner output is viewed as a map.

3) Source Magnitude Estimation for a Pair of Correlated Sources: It is known (e.g., [4]) that sources whose time series are highly correlated in time will be mislocalized by minimum variance estimators. This may be understood by considering the signal space covariance structure. When two sources are completely correlated, the rank of the covariance will be reduced since the signals are always represented by a single vector direction in measurement space. Because the nonadaptive estimators do not use the estimated signal space covariance, they will not exhibit this problem. This correlation bias has different implications for electric and magnetic measurements. In the electrical case, a single tangential dipole may appear quite similar in its signal space projection to a pair of completely correlated radial dipoles, and linear estimators often have practical problems distinguishing between these two possibilities. If we assume that real sources are generally only partially correlated, the correlation bias imposed by the minimum variance estimators may actually be of benefit in identifying these tangential sources. The problem of distinguishing between radial and tangential sources arises to a much more limited extent with magnetic measurements since magnetic measurements have little or no signal derived from radial sources.

TABLE III

LINEAR ESTIMATORS CONSIDERED IN THIS PAPER MAY BE GLOBAL OR LOCAL, AND THE LOCAL ESTIMATORS MAY BE NONADAPTIVE ($\boldsymbol{\Gamma} = \mathbf{G}\mathbf{G}^T$) OR ADAPTIVE ($\boldsymbol{\Gamma} = \mathbf{R}$). EACH WEIGHT VECTOR CLASS MAY BE SEEN TO CONSTITUTE A VECTOR FIELD OVER THE SOURCE VOLUME $\boldsymbol{\Omega}$. $\mathbf{G}$ IS THE GAIN MATRIX, AND $\mathbf{R}$ IS THE ESTIMATED SIGNAL SPACE COVARIANCE. IN ADDITION, LOCAL ESTIMATORS MAY BE DISTORTIONLESS, WEIGHT VECTOR NORMALIZED, OR STANDARDIZED. EACH VALID COMBINATION LEADS TO A DIFFERENT WEIGHT VECTOR DEFINING EQUATION OR, EQUIVALENTLY, THE CHOICE OF SIGNAL SPACE AND SOURCE SPACE METRICS. THE NOTATION "diag $[\mathbf{g}_\mathbf{r}^T \boldsymbol{\Gamma}^{-1} \mathbf{g}_\mathbf{r}]$" STANDS FOR A DIAGONAL MATRIX WHOSE rTH DIAGONAL ELEMENT IS $\mathbf{g}_\mathbf{r}^T \boldsymbol{\Gamma}^{-1} \mathbf{g}_\mathbf{r}$, ETC. TWO CHECKMARKS IN THE CELLS OF THE LAST TWO COLUMNS SHOW THE ESTIMATORS DERIVED FROM THESE WEIGHT VECTORS ARE UNBIASED WITH RESPECT TO LOCATION AND RELATIVE MAGNITUDE, RESPECTIVELY, IN THE PRESENCE OF NOISE, WHILE ONE CHECKMARK INDICATES THAT THE ESTIMATOR IS ONLY UNBIASED IN THE NOISE-FREE CASE (DESCRIBED IN SECTION III-G)

Method Type	*Class*		*Weight vector (w^T)*	*Γ*	$\mathbf{V} \xrightarrow{\Theta_V} \mathbf{V}$	$\mathbf{Q} \xrightarrow{\Theta_Q} \mathbf{Q}^*$	*Location unbiased*	*Relative magnitude unbiased*
Global (pseudo-inverse)	*Minimum L2-norm*		$\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1}$	$\mathbf{G}\mathbf{G}^T$	$(\mathbf{G}\mathbf{G}^T)^{-1}$	$\mathbf{I}$		
	Minimum B-norm		$\mathbf{b}_r^{-1}\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1}$	$\mathbf{G}\mathbf{B}^{-1}\mathbf{G}^T$	$(\mathbf{G}\mathbf{B}^{-1}\mathbf{G}^T)^{-1}$	$\mathbf{B}$		
Local	*Non-adaptive*	*Distortionless*	$\frac{\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1}}{\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1} \mathbf{g}_r}$	$\mathbf{G}\mathbf{G}^T$	$(\mathbf{G}\mathbf{G}^T)^{-1}$	$\mathrm{diag}[\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1} \mathbf{g}_r]$		✓✓
		weight vector normalized	$\frac{\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1}}{(\mathbf{g}_r^T \boldsymbol{\Gamma}^{-2} \mathbf{g}_r)^{1/2}}$	$\mathbf{G}\mathbf{G}^T$	$(\mathbf{G}\mathbf{G}^T)^{-1}$	$\mathrm{diag}[(\mathbf{g}_r^T \boldsymbol{\Gamma}^{-2} \mathbf{g}_r)^{1/2}]$		
		Standardized	$\frac{\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1}}{(\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1} \mathbf{g}_r)^{1/2}}$	$\mathbf{G}\mathbf{G}^T$	$(\mathbf{G}\mathbf{G}^T)^{-1}$	$\mathrm{diag}[(\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1} \mathbf{g}_r)^{1/2}]$	✓	
	Adaptive	*Distortionless*	$\frac{\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1}}{\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1} \mathbf{g}_r}$	$\mathbf{R}$	$\mathbf{R}^{-1}$	$\mathrm{diag}[\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1} \mathbf{g}_r]$		✓✓
		weight vector normalized	$\frac{\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1}}{(\mathbf{g}_r^T \boldsymbol{\Gamma}^{-2} \mathbf{g}_r)^{1/2}}$	$\mathbf{R}$	$\mathbf{R}^{-1}$	$\mathrm{diag}[(\mathbf{g}_r^T \boldsymbol{\Gamma}^{-2} \mathbf{g}_r)^{1/2}]$	✓✓	
		Standardized	$\frac{\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1}}{(\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1} \mathbf{g}_r)^{1/2}}$	$\mathbf{R}$	$\mathbf{R}^{-1}$	$\mathrm{diag}[(\mathbf{g}_r^T \boldsymbol{\Gamma}^{-1} \mathbf{g}_r)^{1/2}]$		

IV. DISCUSSION

We have shown that linear estimators used for bioelectromagnetic source estimation may be classified by the metrics that they impose on source space and signal space. Using this framework, we can make rigorous inferences regarding estimation bias by studying the extrema of the resolution kernels by deriving functional forms for the resolution kernel derivatives in the presence of uncorrelated noise. These results confirm those reported in [6], where the resolution kernel functions themselves were investigated, rather than their derivatives. Although we do not report studies of spatial resolution in this work, in [6], it is shown that that the spatial resolution of sLoreta is broader than that of the adaptive minimum variance beamformer.

As a general rule, the signal space metric is the principal determinant of the spatial resolution, and the source space metric is the principal determinant of estimator bias. These observations lead to some practical guidelines for the selection of linear estimators. When the signal space covariance can be estimated accurately, which in turn depends critically on the assumption of stationarity, adaptive estimators will yield better spatial resolution than nonadaptive estimators. In addition, only the adaptive weight vector normalized estimator can be used as an unbiased estimator of source location in the presence of uncorrelated noise. However, if an unbiased comparison is required between source magnitudes at different locations, then distortionless estimators should be used.

The use of weight vector normalized scanning estimators is limited, however, by its magnitude ratio estimation bias, which will lead deeper sources to appear weaker when using these estimators. We consider briefly two methods to overcome this problem. The first uses a recursively applied local estimator algorithm and is based on methods described originally in [20]; it also shares some common features with the RAP MUSIC algorithm [21]. In this approach, we first apply a scanning estimator to identify a source location peak. We can then construct a new constrained scanning beamformer that has zero gain at the previously identified target location. Successive applications of these increasingly constrained scanning estimators, until some stopping criterion is satisfied, will yield a set of sources that can account for the observed data.

The second approach to the multiple source problem that we consider is randomization testing [22]. This approach is applicable to event-related datasets, where multiple samples are available. Randomization tests have the added advantage that the estimated parameters may be associated with data-derived distributions and, thus, with probability values.

Although we have motivated our derivation of linear estimators beginning with the need to minimize interference, this report does not describe methods for estimating the interference between the target location and the rest of the brain. This problem, which is essentially that of describing receiver operator characteristics for source estimators, is addressed elsewhere [25]. In addition, the conclusions drawn in the paper regarding estimator bias are obtained from a restricted statistical model, based on the assumption of a single point source in the presence of instrumental (white) noise. A more general setting would include the influence of other brain sources ("brain noise") on estimator bias.

Finally, it is worth noting that nothing we have proposed permits us to circumvent the nonuniqueness problem, i.e., suitably arranged linear source combinations may always be found that will mimic any other source combination. The methods we have investigated here assume, however, that satisfactory models for many problems may be obtained from simple, point-like equivalent sources, since these are what the linear estimators are searching for.

APPENDIX

In this section, we provide detailed calculations on the extrema of several scanning estimators, both in the noise-free case and in the presence of instrumental (white) noise. We do not consider the case of correlated signals arising from the brain at locations other than the target ("brain noise"), and our conclusions should be interpreted with that limitation in mind.

We consider as the statistical model

$$\mathbf{v}(t) = \mathbf{g}_{\mathbf{r}_0} q(t) + \boldsymbol{\eta}(t) \tag{A.1}$$

$$q \sim N(0,1), \quad \boldsymbol{\eta} \sim \mathbf{N}(\mathbf{0}, \sigma^2 \mathbf{I}) \tag{A.2}$$

$$\mathbf{R}_v = \mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T + \sigma^2 \mathbf{I}. \tag{A.3}$$

The general problem is as follows: Given a scanning beamformer with weight vectors $\mathbf{w}_r$, $\mathbf{r} \in \Omega$ and a single scalar source $q_{\mathbf{r}_0}$, find the estimator

$$\hat{\mathbf{r}} = \arg\max_{\mathbf{r}} \left(\mathbf{w}_{\mathbf{r}}^T E(\mathbf{v}\mathbf{v}^T)\mathbf{w}_{\mathbf{r}}\right) \tag{A.4}$$

where $E(\mathbf{v}\mathbf{v}^T) = \mathbf{R}_{\mathbf{v}}$. However, we can solve a simpler problem by assuming that $E(\hat{\mathbf{r}}) = \mathbf{r}_0$ and then determine if it is true that $\left(\partial\left(\mathbf{w}_{\mathbf{r}}^T \mathbf{R}_v \mathbf{w}_{\mathbf{r}}\right)/\partial \mathbf{w}\right)\big|_{\mathbf{w}=\mathbf{w}_{\mathbf{r}_0}} = 0$. In this Appendix, we consider only the first derivative since it is sufficient for our purposes to determine if the scanning estimators show an extremum at the target location. Because the source is normalized in the statistical model given by (A.1)–(A.3), the signal-to-noise ratio (SNR) is parameterized by σ. Our conclusions are thus independent of SNR.

A. Adaptive Weight Vector Normalized Estimator

We will consider first the case of the adaptive weight vector normalized estimator in the presence of noise. Other scalar cases may be solved using similar methods to those detailed here.

Begin with $\hat{q}^2 = E_{A-WVN}(q^2) = (\mathbf{g}^T\mathbf{R}_v^{-1}\mathbf{R}_v\mathbf{R}_v^{-1}\mathbf{g}/\mathbf{g}^T\mathbf{R}_v^{-2}\mathbf{g}) = (\mathbf{g}^T\mathbf{R}_v^{-1}\mathbf{g}/\mathbf{g}^T\mathbf{R}_v^{-2}\mathbf{g})$. Then

$$\frac{1}{2}\frac{\partial \hat{q}^2}{\partial \mathbf{g}} = \frac{\mathbf{R}_v^{-1}\mathbf{g}\left(\mathbf{g}^T\mathbf{R}_v^{-2}\mathbf{g}\right) - \left(\mathbf{g}^T\mathbf{R}_v^{-1}\mathbf{g}\right)\mathbf{R}_v^{-2}\mathbf{g}}{\left(\mathbf{g}^T\mathbf{R}_v^{-2}\mathbf{g}\right)^2}. \tag{A.5}$$

From the matrix inversion lemma [20]

$$\mathbf{R}_v^{-1} = \left(\sigma^{-2}\mathbf{I} - \left(\frac{\sigma^{-4}}{1+\sigma^{-2}\mathbf{g}_{\mathbf{r}_0}^T\mathbf{g}_{\mathbf{r}_0}}\right)\mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T\right). \tag{A.6}$$

Let $a = \sigma^{-2}\mathbf{g}_{\mathbf{r}_0}^T\mathbf{g}_{\mathbf{r}_0}$ Then, after substitution into (A.6), multiplication, and rearrangement of terms, we get

$$\mathbf{R}_v^{-2} = \sigma^{-4}\left(\mathbf{I} - \frac{\sigma^{-2}(2+a)}{(1+a)^2}\mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T\right). \tag{A.7}$$

It will also be useful to see that from (A.6)

$$\mathbf{g}_{\mathbf{r}_0}^T\mathbf{R}_v^{-1}\mathbf{g}_{\mathbf{r}_0} = \frac{a}{(1+a)} \tag{A.8}$$

and from (A.7)

$$\mathbf{g}_{\mathbf{r}_0}^T\mathbf{R}_v^{-2}\mathbf{g}_{\mathbf{r}_0} = \frac{\sigma^{-2}a}{(1+a)^2}. \tag{A.9}$$

Now, we have established the preliminaries to evaluate $(\partial\hat{q}^2/\partial\mathbf{g})\big|_{\mathbf{g}=\mathbf{g}_0}$. Substituting (A.8) and (A.9) into (A.5), we obtain the equation shown at the bottom of the page.

The solution is found when the numerator is $\mathbf{0}$ or

$$\mathbf{n} = \left(\sigma^{-2}I - \frac{\sigma^{-4}}{1+a}\mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T\right)\mathbf{g}_{\mathbf{r}_0}\frac{\sigma^{-2}a}{(1+a)^2} - \frac{\sigma^{-4}a}{(1+a)} \times \left(I - \frac{\sigma^{-2}(2+a)}{(1+a)^2}\mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T\right)\mathbf{g}_{\mathbf{r}_0}$$

which, after some rearrangement, becomes

$$\mathbf{n} = \sigma^{-4}\mathbf{g}_{\mathbf{r}_0}\left[\frac{a}{(1+a)^3} - \frac{a}{(1+a)^3}\right] \equiv 0.$$

Therefore, we have demonstrated that given the statistical model in (A.1)–(A.3), the minimum variance weight vector normalized estimator is unbiased with respect to source location. In addition, based on this equation, we can conclude that the estimator remains unbiased in the limit as $\sigma \to 0$.

B. Nonadaptive Weight Vector Normalized

Let $\hat{q}^2 = E_{NA-WVN}(q^2) = (\mathbf{g}^T\boldsymbol{\Gamma}^{-1}\mathbf{R}_v\boldsymbol{\Gamma}^{-1}\mathbf{g}/\mathbf{g}^T\boldsymbol{\Gamma}^{-2}\mathbf{g})$, where $\boldsymbol{\Gamma} = \mathbf{G}\mathbf{G}^T$. Then

$$\frac{\partial\hat{q}^2}{\partial\mathbf{g}} = \frac{2\left(\left(\mathbf{g}^T\boldsymbol{\Gamma}^{-2}\mathbf{g}\right)\mathbf{S}\mathbf{g} - (\mathbf{g}^T\mathbf{S}\mathbf{g})\boldsymbol{\Gamma}^{-2}\mathbf{g}\right)}{\left(\mathbf{g}^T\boldsymbol{\Gamma}^{-2}\mathbf{g}\right)^2} \tag{A.10}$$

and $\mathbf{S} = \boldsymbol{\Gamma}^{-1}\mathbf{R}_v\boldsymbol{\Gamma}^{-1}$. The solution is found at

$$\begin{aligned}\frac{\partial\hat{q}^2}{\partial\mathbf{g}}\bigg|_{\mathbf{g}=\mathbf{g}_{\mathbf{r}_0}} &= 0 \Leftrightarrow \left(\mathbf{g}_{\mathbf{r}_0}^T\boldsymbol{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}\right)\mathbf{S}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0} \\ &= \left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{S}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}\right)\boldsymbol{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}.\end{aligned} \tag{A.11}$$

$$\frac{1}{2}\frac{\partial\hat{q}^2}{\partial\mathbf{g}}\bigg|_{\mathbf{g}=\mathbf{g}_0} = \frac{\left(\sigma^{-2}I - \frac{\sigma^{-4}}{1+a}\mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T\right)\mathbf{g}_{\mathbf{r}_0}\frac{\sigma^{-2}a}{(1+a)^2} - \frac{\sigma^{-4}a}{(1+a)}\left(I - \frac{\sigma^{-2}(2+a)}{(1+a)^2}\mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T\right)\mathbf{g}_{\mathbf{r}_0}}{\left(\mathbf{g}^T\mathbf{R}_v^{-2}\mathbf{g}\right)^2}.$$

For $\mathbf{R}_v = \mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T + \sigma^2\mathbf{I}$, the left term in (A.11) becomes

$$\begin{aligned}&\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}\right)\mathbf{S}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}\\&=\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}\right)\mathbf{\Gamma}^{-1}\left(\sigma^2 I+\mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T\right)\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\\&=\sigma^2\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}\right)\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}\\&\quad+\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\right)\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}\right)\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\end{aligned}$$

and the right term in (A.11) becomes

$$\begin{aligned}&\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{S}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}\right)\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}\\&=\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-1}\left(\sigma^2 I+\mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T\right)\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\right)\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}\\&=\sigma^2\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}\right)\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}\\&\quad+\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\right)^2\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}.\end{aligned}$$

Since, in general, $\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\right)\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}\right)\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\neq\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\right)^2\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}$, the nonadaptive weight vector normalized estimator yields a biased location estimator.

C. Distortionless Estimator

Let $\hat{q}^2 = E_D(q^2) = \left(\mathbf{g}^T\mathbf{\Gamma}^{-1}\mathbf{R}_v\mathbf{\Gamma}^{-1}\mathbf{g}/\left(\mathbf{g}^T\mathbf{\Gamma}^{-1}\mathbf{g}\right)^2\right)$. Then

$$\frac{\partial\hat{q}^2}{\partial\mathbf{g}}=\frac{\left(2\left(\mathbf{g}^T\mathbf{\Gamma}^{-1}\mathbf{g}\right)^2\mathbf{S}\mathbf{g}-\left(\mathbf{g}^T\mathbf{S}\mathbf{g}\right)\frac{\partial}{\partial\mathbf{g}}\left(\mathbf{g}^T\mathbf{\Gamma}^{-1}\mathbf{g}\right)^2\right)}{(\mathbf{g}^T\mathbf{\Gamma}^{-1}\mathbf{g})^2}\tag{A.12}$$

where $\mathbf{S} = \mathbf{\Gamma}^{-1}\mathbf{R}_v\mathbf{\Gamma}^{-1}$, and $(\partial/\partial\mathbf{g})\left(\mathbf{g}^T\mathbf{\Gamma}^{-1}\mathbf{g}\right)^2 = 4\left(\mathbf{g}^T\mathbf{\Gamma}^{-1}\mathbf{g}\right)\mathbf{\Gamma}^{-1}\mathbf{g}$. For equation (A.12) to be $\mathbf{0}$, it is sufficient to show that the numerator be equal to zero

$$\begin{aligned}\left.\frac{\partial\hat{q}^2}{\partial\mathbf{g}}\right|_{\mathbf{g}=\mathbf{g}_{\mathbf{r}_0}}&=0\Leftrightarrow\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\right)\mathbf{S}\mathbf{g}_{\mathbf{r}_0}\\&=2\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{S}\mathbf{g}_{\mathbf{r}_0}\right)\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}.\end{aligned}\tag{A.13}$$

Equation (A.13) cannot be true. To see this, rearrange (A.13) and left-multiply both sides by $\mathbf{g}_{\mathbf{r}_0}^T$ to obtain $\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{S}\mathbf{g}_{\mathbf{r}_0}/2\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{S}\mathbf{g}_{\mathbf{r}_0}\right)\right)=\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}/\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\right)\right)\Leftrightarrow 1/2 = 1$, which is a contradiction. Thus distortionless beamformers cannot be unbiased location estimators. Following the same argument, this conclusion follows even in the presence of noise.

D. Lead Field Normalized Minimum Norm

Consider the lead field normalized minimum norm in the noise-free case. Rewriting the weight vector from Table III, we have $\hat{q}^2 = E_{MN}(q)^2 = \tilde{\mathbf{g}}^T\mathbf{\Gamma}^{-1}\mathbf{R}_v\mathbf{\Gamma}^{-1}\tilde{\mathbf{g}}$, $\tilde{\mathbf{g}} = |\mathbf{g}|^{-1}\mathbf{g}$. Then, $(\partial\hat{q}^2/\partial\tilde{\mathbf{g}})|_{\tilde{\mathbf{g}}=\tilde{\mathbf{g}}_{\mathbf{r}_0}} = 2\mathbf{\Gamma}^{-1}\mathbf{R}_v\mathbf{\Gamma}^{-1}\tilde{\mathbf{g}}_{\mathbf{r}_0} \neq \mathbf{0}$ unless $\tilde{\mathbf{g}}_{\mathbf{r}_0} = \mathbf{0}$, which means that this estimator is biased.

E. Nonadaptive Standardized

Let $\hat{q}^2 = E_{NA-St}(q^2) = (\mathbf{g}^T\Gamma^{-1}\mathbf{R}_v\Gamma^{-1}\mathbf{g}/\mathbf{g}^T\Gamma^{-1}\mathbf{g})$. Then

$$\frac{\partial\hat{q}^2}{\partial\mathbf{g}}=\frac{2\left(\left(\mathbf{g}^T\mathbf{\Gamma}^{-1}\mathbf{g}\right)\mathbf{S}\mathbf{g}-(\mathbf{g}^T\mathbf{S}\mathbf{g})\mathbf{\Gamma}^{-1}\mathbf{g}\right)}{(\mathbf{g}^T\mathbf{\Gamma}^{-1}\mathbf{g})^2}\tag{A.14}$$

where $\mathbf{S} = \mathbf{\Gamma}^{-1}\mathbf{R}_v\mathbf{\Gamma}^{-1}$. It is sufficient that the numerator of (A.14) be $\mathbf{0}$ at the extremum. Since $\mathbf{R}_v = \mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T + \sigma^2\mathbf{I}$, the numerator term (up to a multiple) becomes $\mathbf{n} = (\mathbf{g}^T\mathbf{\Gamma}^{-1}\mathbf{g})\mathbf{\Gamma}^{-1}\left(\sigma^2\mathbf{I}+\mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T\right)\mathbf{\Gamma}^{-1}\mathbf{g} - \left(\mathbf{g}^T\mathbf{\Gamma}^{-1}\left(\sigma^2\mathbf{I}+\mathbf{g}_{\mathbf{r}_0}\mathbf{g}_{\mathbf{r}_0}^T\right)\mathbf{\Gamma}^{-1}\mathbf{g}\right)\mathbf{\Gamma}^{-1}\mathbf{g}$. Rearranging terms, we get

$$\mathbf{n}=\sigma^2\left((\mathbf{g}^T\mathbf{\Gamma}^{-1}\mathbf{g})\mathbf{\Gamma}^{-2}\mathbf{g}-(\mathbf{g}^T\mathbf{\Gamma}^{-1}\mathbf{g})^2\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\right)\neq\mathbf{0}.\tag{A.15}$$

This confirms the result reported in [6] that sLoreta is a biased source location estimator in the presence of noise.

If we consider the noise-free case, the situation changes since now, (A.15) becomes

$$\begin{aligned}\mathbf{n}&=\sigma^2\left[\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\right)\mathbf{\Gamma}^{-2}\mathbf{g}_{\mathbf{r}_0}-\left(\mathbf{g}_{\mathbf{r}_0}^T\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\right)^2\mathbf{\Gamma}^{-1}\mathbf{g}_{\mathbf{r}_0}\right]\\&=\mathbf{0}.\end{aligned}\tag{A.16}$$

Thus, in the noise-free case, this estimator becomes unbiased.

F. Adaptive Standardized

Let $\hat{q}^2 = E_{A-St}(q^2) = (\mathbf{g}^T\mathbf{R}_v^{-1}\mathbf{R}_v\mathbf{R}_v^{-1}\mathbf{g}/\mathbf{g}^T\mathbf{R}_v^{-1}\mathbf{g}) = 1$; therefore, this estimator has no location sensitivity.

REFERENCES

[1] C. M. Michel, M. M. Murray, G. Lantz, S. Gonzalez, L. Spinelli, and R. Grave de Peralta, “EEG source imaging,” *Clinical Neurophysiol.*, vol. 115, pp. 2195–2222, 2004.

[2] M. E. Spencer, R. M. Leahy, J. C. Mosher, and P. S. Lewis, “Adaptive filters for monitoring localized brain activity from surface potential time series,” in *Conf. Rec. 26th Annu. Asilomar Conf. Signals, Syst., Comput.*, Nov. 1992, pp. 156–161.

[3] S. E. Robinson and D. F. Rose, “Current source image estimation by spatially filtered MEG,” *Biomagnetism: Clinical Aspects*, pp. 761–765, 1992.

[4] 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, no. 9, pp. 867–880, Sep. 1997.

[5] K. Sekihara, S. S. Nagarajan, D. Poeppel, A. Marantz, and Y. Miyashita, “Reconstructing spatio-temporal activities of neural sources using an MEG vector beamformer technique,” *IEEE Trans. Biomed. Eng.*, vol. 48, no. 7, pp. 760–771, Jul. 2001.

[6] K. Sekihara, M. Sahani, and S. S. Nagarajan, “Localization bias and spatial resolution of adaptive and nonadaptive spatial filters for MEG source reconstruction,” *Neuroimag.*, vol. 25, pp. 1056–1067, 2005.

[7] J. C. Mosher, R. M. Leahy, and P. S. Lewis, “EEG and MEG: Forward solutions for inverse methods,” *IEEE Trans. Biomed. Eng.*, vol. 46, no. 3, pp. 245–259, Mar. 1999.

[8] L. H. Loomis and S. Sternberg, *Advanced Calculus*. Reading, MA: Addison-Wesley, 1968, p. 85.

[9] A. Tarantola, *Inverse Problem Theory*. Amsterdam, The Netherlands: Elsevier, 1987, pp. 461–526.

[10] R. Pascual-Marqui, C. M. Michel, and D. Lehmann, “Low resolution electromagnetic tomography: A new method for localizing electrical activity in the brain,” *Int. J. Psychophysiol.*, vol. 18, pp. 49–65, 1994.

[11] T. A. Crowley, C. D. Haupt, and D. B. Kynor, “A weighting matrix to remove depth bias in the linear biomagnetic inverse problem with applications to cardiology,” in *Proc. Tenth Int. Conf. Biomag.*, 1996, pp. 197–200.

[12] G. E. Backus and J. F. Gilbert, “Numerical applications of a formalism for geophysical inverse problems,” *Geophys. J. R. Astron. Soc.*, vol. 13, pp. 247–276, 1967.

[13] R. Grave de Peralta and S. L. Gonzalez Andino, “Backus and Gilbert method for vector fields,” *Human Brain Mapping*, vol. 7, pp. 161–165, 1999.

[14] T. J. Loredo and R. I. Epstein, “Analysing gamma-ray burst spectral data,” *Astrophys. J.*, vol. 336, pp. 896–919, 1989.

[15] R. Grave de Peralta, O. Hauk, S. L. Gonzalez Andino, H. Vogt, and C. Michel, “Linear inverse solutions with optimal resolution kernels applied to the electromagnetic tomography,” *Human Brain Mapping*, vol. 5, no. 6, pp. 454–467, 1997.

[16] G. Borgiotti and L. J. Kaplan, “Superresolution of uncorrelated interference sources by using adaptive array technique,” *IEEE Trans. Antennas Propagat.*, vol. AP-27, no. 6, pp. 842–845, Nov. 1979.

[17] R. D. Pascual-Marqui, “Standardized low resolution brain electromagnetic tomography (sLORETA): Technical details,” *Methods and Findings in Experimental and Clinical Pharmacology*, vol. 24D, pp. 5–12, 2002.

[18] S. E. Robinson and J. Vrba, “Functional neuroimaging by synthetic aperture magnetometry (SAM),” in *Recent Advances in Biomagnetism*. Sendai, Japan: Tohoku Univ. Press, 1999, pp. 302–305.

[19] 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.

[20] M. Scherg, P. Berg, D. Weckesser, E. Hoechstetter, H. Bornfleth, N. Ille, and T. Bast, “Multiple source analysis of MEG and EEG data: Tools for validation,” in *Proc. 14th Int. Cong. Biomag.*, 2004, p. 112.

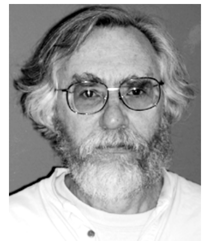
[21] J. C. Mosher and R. M. Leahy, “Recursive MUSIC: A framework for EEG and MEG source localization,” *IEEE Trans. Biomed. Eng.*, vol. 45, no. 11, pp. 1342–1354, Nov. 1998.

[22] R. E. Greenblatt and M. E. Pflieger, “Randomization-based hypothesis testing from event-related data,” *Brain Topograph.*, vol. 16, no. 4, pp. 225–232, 2004.

[23] S. Haykin, *Adaptive Filter Theory*. Englewood Cliffs, NJ: Prentice-Hall, 1991, p. 480.

[24] K. V. Mardia, J. T. Kent, and J. M. Bibby, *Multivariate Analysis*. London, U.K.: Academic, 1979, p. 62.

[25] M. E. Pflieger, R. E. Greenblatt, and J. Kirkish, “Regional resolving power of combined MEG/EEG,” *Neurol. Clin. Neurophysiol.*, vol. 79, Nov. 2004.



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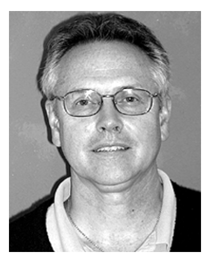

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