Standardized low resolution brain electromagnetic tomography (*s*LORETA): technical details

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Abstract

Scalp electric potentials (EEG) and extracranial magnetic fields (MEG) are due to the primary (impressed) current density distribution that arises from neuronal post-synaptic processes. A solution to the inverse problem, i.e. the computation of images of electric neuronal activity based on extracranial measurements, would provide important information on the time course and localization of brain function. In general, there is no unique solution to this problem. In particular, an instantaneous, distributed, discrete, linear solution capable of exact localization of point sources is of great interest, since the principles of linearity and superposition would guarantee its trustworthiness as a functional imaging method, given that brain activity occurs in the form of a finite number of distributed "hot spots". Despite all previous efforts, linear solutions at best produced images with systematic non-zero localization errors. A solution is reported here, which yields images of standardized current density with zero localization error. The purpose of this paper is to present the technical details of the method, allowing researchers to test, check, reproduce, and validate the new method (*s*LORETA).

Introduction

This study is strictly limited to EEG/MEG inverse solutions of the type: instantaneous, distributed, discrete, and linear. The generic form of the inverse problem follows. There are N_E instantaneous extracranial measurements. There are N_V voxels in the brain. Typically, the voxels are determined by subdividing uniformly the solution space, which is usually taken as the cortical grey matter volume or surface. At each voxel there is a point source, which may be a vector with three unknown components (i.e., the three dipole moments), or a scalar (unknown dipole amplitude, known orientation). The cases considered here correspond to $N_V \gg N_E$.

In 1984, Hämäläinen and Ilmoniemi (1) were the first to report an instantaneous, distributed, discrete, linear solution to the EEG/MEG inverse problem: the well known minimum norm solution. However, the minimum norm solution is notorious for totally misplacing actual deep sources onto the outermost cortex, as demonstrated in (3), (2), and (8).

The problem of excessively large errors of localization remained unsolved until the introduction of the method known as LORETA (low resolution brain electromagnetic tomography) in 1994 (18). LORETA has fairly good accuracy in localizing test sources even when they are deep. The overall average localization error is smaller than one grid unit (see e.g. (3), (2), and (8)).

A series of papers published in 1998 and 1999 (see (19)-(23)) introduced for the first time the method of high time resolution statistical parametric mapping for tomographic images of electric neuronal activity. The idea was to adopt the methods of statistical inference for the localization of brain function as used in PET and fMRI studies. This methodology was applied to high time resolution, time varying LORETA images.

In the present study a new tomographic method for electric neuronal activity is introduced, where localization inference is based on images of standardized current density. The method is denoted as standardized low resolution brain electromagnetic tomography (*s*LORETA). Unlike the method recently introduced by Dale et al. (6), which has systematic non-zero localization error, *s*LORETA has zero localization error.

Method

Case 1: EEG with unknown current density vector

The equation of interest takes the form:

$$\Phi = \mathbf{KJ} + c\mathbf{1} \qquad \text{Eq. 1}$$

In Eq. 1, $\Phi \in \mathbb{R}^{N_E \times 1}$ is a vector containing scalp electric potentials measured at N_E cephalic electrodes, with respect to a common, arbitrary reference electrode located anywhere on the body.

The primary (impressed) current density $\mathbf{J} \in \mathbb{R}^{(3N_V) \times 1}$ is defined as:

$$\mathbf{J} = \left(\mathbf{J}_1^T, \mathbf{J}_2^T, \mathbf{J}_3^T, ..., \mathbf{J}_{N_V}^T \right)^T \qquad \text{Eq. 2}$$

where $\mathbf{J}_l \in \mathbb{R}^{3\times1}$ for $l = 1...N_V$. At the l^{th} voxel, $\mathbf{J}_l^T = \left(J_l^x, J_l^y, J_l^z\right)$ contains the three unknown dipole moments.

The superscript "T" denotes transpose.

The lead field $\mathbf{K} \in \mathbb{R}^{N_E\times(3N_V)}$ has the following structure:

$$\mathbf{K} = \begin{pmatrix} \mathbf{k}_{1,1} & \mathbf{k}_{1,2} & \cdots & \mathbf{k}_{1,N_V} \\ \mathbf{k}_{2,1} & \mathbf{k}_{2,2} & \cdots & \mathbf{k}_{2,N_V} \\ \cdots & \cdots & \cdots & \cdots \\ \mathbf{k}_{N_E,1} & \mathbf{k}_{N_E,2} & \cdots & \mathbf{k}_{N_E,N_V} \end{pmatrix} \qquad \text{Eq. 3}$$

with $\mathbf{k}_{i,l} \in \mathbb{R}^{1\times3}$, for $i = 1...N_E$, and for $l = 1...N_V$. Note that $\mathbf{k}_{i,l} = \left(k_{i,l}^x, k_{i,l}^y, k_{i,l}^z\right)$, where $k_{i,l}^x$ is the scalp electric potential at the i^{th} electrode, due to a unit strength X-oriented dipole at the l^{th} voxel; $k_{i,l}^y$ is the scalp electric potential at the i^{th} electrode, due to a unit strength Y- oriented dipole at the l^{th} voxel; and $k_{i,l}^z$ is the scalp electric potential at the i^{th} electrode, due to a unit strength Z- oriented dipole at the l^{th} voxel.

In Eq. 1, c is an arbitrary constant which embodies the fact that the electric potential is determined up to an arbitrary constant; and $\mathbf{1} \in \mathbb{R}^{N_E\times1}$ is a vector of ones. The parameter c allows the use of any reference for the lead field and the measurements.

Hämäläinen, M.S., and Ilmoniemi (1) were the first to publish a particular solution to the instantaneous, distributed, discrete, linear EEG/MEG inverse problem. Their solution is known as the minimum norm inverse solution. However, the minimum norm solution is notorious for totally misplacing actual deep sources onto the outermost cortex (2).

Dale et al. (6) proposed a method in which localization inference is based on a standardization of the current density estimates. In particular, they employed the current density estimate given by the minimum norm solution, and they standardized it by using its expected standard deviation, which is hypothesized to be originated exclusively by measurement noise. The method of Dale et al. (6) produces systematic non-zero localization errors (8), even in the presence of negligible noise. This fact was not evaluated nor admitted in their original paper.

*s*LORETA is similar to the Dale et al. (6) method: it employs the current density estimate given by the minimum norm solution, and localization inference is based on standardized values of the current density estimates. However, standardization in *s*LORETA takes a completely different route (explained below). The consequence is that, unlike the Dale et al. (6) method, *s*LORETA is capable of exact (zero-error) localization.

The minimum norm inverse solution is harmonic (2), which means that the Laplacian of the current density is zero, i.e., $\nabla^2\mathbf{J}(\mathbf{r}) \equiv \mathbf{0}$, where $\mathbf{r}$ denotes volume coordinates in the brain. Therefore, the minimum norm inverse solution is very smooth. The concept of smoothness employed here is discussed in greater detail in

(8), with special emphasis on its electrophysiological interpretation. However, as previously mentioned, the minimum norm inverse solution is notorious for its incapability of correct localization of deep point sources (2).

This problem is solved by standardization of the minimum norm inverse solution, and basing localization inference on these standardized estimates.

The functional of interest here is:

$$F = \left\| \Phi - \mathbf{KJ} - c\mathbf{1} \right\|^2 + \alpha \left\| \mathbf{J} \right\|^2 \qquad \text{Eq. 4}$$

where $\alpha \geq 0$ is a regularization parameter. This functional is to be minimized with respect to $\mathbf{J}$ and c, for given $\mathbf{K}$, Φ, and α. The explicit solution to this minimization problem is (see e.g. (3)):

$$\hat{\mathbf{J}} = \mathbf{T}\Phi \qquad \text{Eq. 5}$$

where:

$$\mathbf{T} = \mathbf{K}^T \mathbf{H} \left[\mathbf{HKK}^T \mathbf{H} + \alpha \mathbf{H} \right]^+ \qquad \text{Eq. 6}$$

$$\mathbf{H} = \mathbf{I} - \mathbf{1}\mathbf{1}^T / \mathbf{1}^T \mathbf{1} \qquad \text{Eq. 7}$$

with $\mathbf{H} \in \mathbb{R}^{N_E \times N_E}$ denoting the centering matrix; $\mathbf{I} \in \mathbb{R}^{N_E \times N_E}$ the identity matrix; and $\mathbf{1} \in \mathbb{R}^{N_E \times 1}$ is a vector of ones.

For any matrix $\mathbf{M}$, $\mathbf{M}^+$ denotes its Moore-Penrose pseudoinverse (see e.g. (9)).

The centering matrix $\mathbf{H}$ in Eq. 7 is the average reference operator.

In what follows, for all EEG cases, the symbols Φ and $\mathbf{K}$ will denote the average reference transforms of the EEG measurements and the lead field, respectively. This simplifies the notation. But most important of all, the correct solution to EEG problems is based on these average reference transforms.

Therefore, when using average reference transforms of Φ and $\mathbf{K}$, Eq. 1 becomes:

$$\Phi = \mathbf{KJ} \qquad \text{Eq. 8}$$

and the functional in Eq. 4 becomes:

$$F = \left\| \Phi - \mathbf{KJ} \right\|^2 + \alpha \left\| \mathbf{J} \right\|^2 \qquad \text{Eq. 9}$$

with minimum:

$$\hat{\mathbf{J}} = \mathbf{T}\Phi \qquad \text{Eq. 10}$$

where:

$$\mathbf{T} = \mathbf{K}^T \left[\mathbf{KK}^T + \alpha \mathbf{H} \right]^+ \qquad \text{Eq. 11}$$

Standardization of the estimate $\hat{\mathbf{J}}$ requires an estimate of its variance.

Note that Eq. 9 can be derived from a Bayesian formulation of the inverse problem (see e.g. (5), Eq. 1.88 therein). In this view, the *actual* source variance (*prior*) $\mathbf{S_J} \in \mathbb{R}^{(3N_V) \times (3N_V)}$ is equal to the identity matrix, i.e.:

$$\mathbf{S_J} = \mathbf{I}, \mathbf{I} \in \mathbb{R}^{(3N_V) \times (3N_V)} \qquad \text{Eq. 12}$$

In addition, from the Bayesian point of view, the electric potential variance is due to noisy measurements:

$$\mathbf{S}_{\mathrm{F}}^{noise} = \alpha\,\mathbf{H} \qquad \text{Eq. 13}$$

Note that in Eq. 13, the average reference operator **H** plays the role of the identity matrix in the subspace spanned by the measurement space.

It is usually assumed that activity of the actual sources and the noise in the measurements are uncorrelated.

Based on the linear relation in Eq. 8, making use of Eqs. 12 and 13, and taking into account the independence of actual source activity and measurement noise, the electric potential variance $\mathbf{S}_{\mathrm{F}} \in \mathbb{R}^{N_E \times N_E}$ then is:

$$\mathbf{S}_{\mathrm{F}} = \mathbf{K}\mathbf{S}_{\mathbf{J}}\mathbf{K}^T + \mathbf{S}_{\mathrm{F}}^{noise} = \mathbf{K}\mathbf{K}^T + \alpha\,\mathbf{H} \qquad \text{Eq. 14}$$

See e.g. (10), Eqs. 1.5.1-1.5.6 therein.

Due to the linear relation in Eq. 10, and making use of Eq. 14, the variance of the *estimated* current density is:

$$\mathbf{S}_{\hat{\mathbf{J}}} = \mathbf{T}\mathbf{S}_{\mathrm{F}}\mathbf{T}^T = \mathbf{T}\left(\mathbf{K}\mathbf{K}^T + \alpha\,\mathbf{H}\right)\mathbf{T}^T = \mathbf{K}^T\left[\mathbf{K}\mathbf{K}^T + \alpha\,\mathbf{H}\right]^+\mathbf{K} \qquad \text{Eq. 15}$$

See e.g. (10), Eqs. 1.5.1-1.5.6 therein, and (9).

Note that the variance of the *estimated* current density is equivalent to the Backus and Gilbert (4) resolution matrix, which is obtained by plugging Eqs. 8 and 11 into 10:

$$\hat{\mathbf{J}} = \mathbf{T}\mathbf{K}\mathbf{J} = \mathbf{K}^T\left[\mathbf{K}\mathbf{K}^T + \alpha\,\mathbf{H}\right]^+\mathbf{K}\mathbf{J} = \mathbf{R}\mathbf{J} = \mathbf{S}_{\hat{\mathbf{J}}}\mathbf{J} \qquad \text{Eq. 16}$$

with:

$$\mathbf{S}_{\hat{\mathbf{J}}} = \mathbf{R} = \mathbf{K}^T\left[\mathbf{K}\mathbf{K}^T + \alpha\,\mathbf{H}\right]^+\mathbf{K} \qquad \text{Eq. 17}$$

where **R** is the resolution matrix.

Note that the variance of the *estimated* current density in Eqs. 15 and 17 is <u>not</u> the *posterior* variance in the Bayesian formulation (see e.g. (5), Eq. 1.94).

In contrast, according to Dale et al. (6), the variance of the *estimated* current density is based on the assumption that the only source of variation is measurement noise. This means that Eq. 14 now is:

$$\mathbf{S}_{\mathrm{F}}^{Dale} = \mathbf{S}_{\mathrm{F}}^{noise} \qquad \text{Eq. 18}$$

and Eq. 15 now is:

$$\mathbf{S}_{\hat{\mathbf{J}}}^{Dale} = \mathbf{T}\mathbf{S}_{\mathrm{F}}^{Dale}\mathbf{T}^T = \mathbf{T}\mathbf{S}_{\mathrm{F}}^{noise}\mathbf{T}^T \qquad \text{Eq. 19}$$

Note that unlike the approach of Dale et al. (6), *s*LORETA takes into account two sources of variation: mainly the variation of the actual sources, and then finally, if any, the variation due to noisy measurements.

Finally, *s*LORETA corresponds to the following estimates of standardized current density power:

$$\hat{\mathbf{J}}_l^T\left\{\left[\mathbf{S}_{\hat{\mathbf{J}}}\right]_{ll}\right\}^{-1}\hat{\mathbf{J}}_l \qquad \text{Eq. 20}$$

where $\hat{\mathbf{J}}_l \in \mathbb{R}^{3\times1}$ is the current density estimate at the l^{th} voxel given by Eqs. 10 and 11 (for average reference transforms); and $\left[\mathbf{S}_{\hat{\mathbf{J}}}\right]_{ll} \in \mathbb{R}^{3\times3}$ is the l^{th} diagonal block of matrix $\mathbf{S}_{\hat{\mathbf{J}}}$ in Eqs. 15 or 17.

Note that the pseudo-statistic in Eq. 20 has the form of an "*F*" statistic.

Note that Eq. 20 is different in form from the Dale et al. (6) standardization (see (6), Eq. 7 therein). The Dale et al. (6) standardized estimates are:

$$\hat{\mathbf{J}}_l^T \left[Diag\left(\left[\mathbf{S}_{\hat{\mathbf{J}}}^{Dale}\right]_{ll} \right) \right]^{-1} \hat{\mathbf{J}}_l \qquad \text{Eq. 21}$$

where $\left[\mathbf{S}_{\hat{\mathbf{J}}}^{Dale}\right]_{ll} \in \mathbb{R}^{3\times3}$ is the l^{th} diagonal block of matrix $\mathbf{S}_{\hat{\mathbf{J}}}^{Dale}$ in Eq. 19; and for any symmetric matrix $\mathbf{M}$, $Diag(\mathbf{M})$ is the diagonal matrix formed by the diagonal elements of $\mathbf{M}$.

Case 2: EEG with known current density vector orientation, unknown amplitude

This case usually corresponds to the inverse problem when the cortical surface is completely known. Voxels are now distributed along the cortical surface, and the dipoles at each voxel have known orientation (perpendicular to the cortical surface). The unknowns correspond to the amplitudes, which may take positive, zero, or negative values. The dipole orientations (*defined as unit length vectors with three components*) can be incorporated into the lead field $\mathbf{K}$ in Eq. 8. Details can be found in (3).

In this case Eq. 8 has the same form, but now $\mathbf{J} \in \mathbb{R}^{N_V\times1}$ since it only contains one unknown scalar per voxel, and $\mathbf{K} \in \mathbb{R}^{N_E\times N_V}$ since it includes the dipole orientation at each voxel. Details can be found in (3). All the derivations employed in Eqs. 8-17 remain formally identical.

However, *s*LORETA now corresponds to the following estimates of standardized current density power:

$$\frac{\left(\hat{J}_l\right)^2}{\left[\mathbf{S}_{\hat{\mathbf{J}}}\right]_{ll}} \qquad \text{Eq. 22}$$

where the scalar $\hat{J}_l$ is the current density amplitude estimate at the l^{th} voxel; and the scalar $\left[\mathbf{S}_{\hat{\mathbf{J}}}\right]_{ll}$ is the l^{th} diagonal element of matrix $\mathbf{S}_{\hat{\mathbf{J}}} \in \mathbb{R}^{N_V\times N_V}$.

Note that the pseudo-statistic in Eq. 22 has the form of an "*F*" statistic.

Case 3: MEG

The equations for the MEG case have identical form to Eqs. 8-17, 20, and 22, depending on the case of unknown dipole moments, or only unknown amplitudes.

Note that the average reference does not apply to MEG.

The only change corresponds to the equations for the MEG lead field, which are different to those for the EEG.

Head models

Simulations were carried out in a three-shell spherical head model registered to the Talairach human brain atlas (11), available as a digitized MRI from the Brain Imaging Centre, Montreal Neurological Institute. Registration between spherical and realistic head geometry used EEG electrode coordinates reported by Towle et al. (12).

In one set of practical, realistic, simulations, the solution space was restricted to cortical gray matter and hippocampus, as determined by the corresponding digitized Probability Atlas also available from the Brain Imaging Centre, Montreal Neurological Institute. A voxel was labeled as gray matter if it met the following three conditions: its probability of being gray matter was higher than that of being white matter, its probability of being gray matter was higher than that of being cerebrospinal fluid, and its probability of being gray matter was higher than 33%. Only gray matter voxels that belonged to cortical and hippocampal regions were used for the analysis. A total of 6430 voxels at 5mm spatial resolution were produced under these neuroanatomical constraints. At each voxel, three unknown values (the three dipole moments) were estimated, making a total of 6430x3=19290 unknowns. 25 electrodes (in EEG experiments), or 25 magnetometer sensors (in MEG experiments) were used. In both cases, sensors and electrodes were placed in the same locations.

In the second set of practical, realistic, simulations, the solution space was restricted to the cortical surface, represented as 12980 triangles (voxels) (13). This case corresponded to unknown current density amplitude (but with known orientation), making a total of 12980 unknowns. 101 electrodes (in EEG experiments), or 101 magnetometer sensors (in MEG experiments) were used. In both cases, sensors and electrodes were placed in the same locations.

Comparison of imaging methods

The minimum norm solution, the method of Dale et al. (6), and *s*LORETA were compared in terms of localization errors and spatial spread. The methods were tested with point sources located at the voxels. For the case corresponding to 3 unknowns per voxel, an arbitrary (random) orientation of the test source was employed. The test sources were used to generate the measurements (forward equation (Eq. 8)), which were then given to the imaging methods. Simulations included "noise free" and "noisy" measurements.

In the minimum norm solution case, the imaging method is based on Eqs. 20 and 22, but without standardization, which is achieved by setting the variance to the identity matrix, i.e., $\mathbf{S}_{\hat{\mathbf{j}}} \equiv \mathbf{I}$.

In the minimum norm solution and in *s*LORETA, the regularization parameter α in the previous equations was estimated by cross-validation. Exact details and equations for a practical implementation of the cross-validation method can be found in (14).

In the Dale et al. (6) method, the parameter α is interpreted as the variance of the noise in the measurements, and this value was determined by the simulation design. In the "noise free" case, a very small value of α was used, typically in the order of 10^{-10} times the power of the scalp field produced by the test source with lowest scalp field power.

Localization error was defined as the distance between the actual test source and the location of the maximum in the imaging method. The spatial spread was defined identically as in (3), which corresponds to a measure of spatial standard deviation of the imaging method centered at the actual test source, and not at the imaging method's own maximum, since this would unjustifiably favor the method's performance.

Results

Figures 1a-1h summarize localization error, spatial spread, and estimated activity values for the three imaging methods (minimum norm, Dale, and *s*LORETA).

Note that the estimated activity values at test source locations cannot be compared among the different imaging methods, since these values are in different units for the different imaging methods. However, this feature is very informative for comparing the quality of the different methods. For example, from Fig 1a, the ratios of estimated source activity (maximum to minimum) were 850, 103, and, 30, for minimum norm, Dale, and *s*LORETA, respectively. This means that with *s*LORETA, some sources (especially deep ones) will be underestimated. However, *s*LORETA out-performs tremendously the minimum norm and the Dale methods in this aspect.

In all noise free simulations, only *s*LORETA has exact, zero error localization. In all noisy simulations, *s*LORETA has by far the lowest localization errors. In most cases, the spatial spread (i.e. "blurring") of *s*LORETA is smaller than that of the Dale method.

Figure 1a

Variable	Valid N	Mean	Median	Minimum	Maximum	Lower Quartile	Upper Quartile	Std.Dev.
MNE	6430	37.83832	32.78719	0.00000	140.3567	21.79449	48.21825	22.17381
MNSSD	6430	52.19853	49.57677	29.37124	96.0995	43.22689	59.34685	11.85655
MNMaxAtPoint	6430	0.00132	0.00072	0.00002	0.0170	0.00034	0.00180	0.00150
DaleE	6430	33.49835	30.82207	0.00000	104.0432	21.79449	43.01163	15.89892
DaleSSD	6430	55.25780	54.72793	37.51842	86.7242	49.27447	60.61464	7.97651
DMaxAtPoint	6430	0.73773	0.64132	0.04674	4.7933	0.42049	0.93426	0.46353
LORE	6430	0.00000	0.00000	0.00000	0.0000	0.00000	0.00000	0.00000
LORSSD	6430	55.91575	55.66131	37.46555	79.1693	52.21046	59.50099	5.50024
LORMaxAtPoint	6430	0.00109	0.00092	0.00015	0.0045	0.00063	0.00145	0.00060

Figure 1b

Variable	Valid N	Mean	Median	Minimum	Maximum	Lower Quartile	Upper Quartile	Std.Dev.
MNE	6430	39.88576	33.54102	0.00000	144.6548	22.36068	50.49752	25.05183
MNSSD	6430	54.08980	51.30133	30.05812	100.7998	44.34347	61.70680	12.82109
MNMaxAtPoint	6430	0.00124	0.00068	0.00002	0.0117	0.00033	0.00171	0.00135
DaleE	6430	33.58242	30.82207	0.00000	104.0432	21.79449	43.01163	16.05038
DaleSSD	6430	55.78534	55.27424	37.20245	88.7353	49.70205	61.29503	8.08541
DMaxAtPoint	6430	24.60999	21.34088	1.34483	158.8102	14.14819	31.15955	15.45903
LORE	6430	4.58698	0.00000	0.00000	50.2494	0.00000	7.07107	6.29806
LORSSD	6430	56.84441	56.65639	36.48186	78.5615	53.17038	60.61004	5.70991
LORMaxAtPoint	6430	0.00104	0.00087	0.00010	0.0037	0.00058	0.00140	0.00058

Figure 1c

Variable	Valid N	Mean	Median	Minimum	Maximum	Lower Quartile	Upper Quartile	Std.Dev.
MNE	6430	39.04392	32.40370	0.00000	118.3216	18.70829	54.08327	24.91432
MNSSD	6430	51.74000	51.28205	22.53735	93.9798	40.37547	60.93124	13.88708
MNMaxAtPoint	6430	0.00161	0.00059	0.00000	0.0312	0.00021	0.00188	0.00260
DaleE	6430	32.01096	26.92582	0.00000	105.1189	16.58312	44.15880	19.78573
DaleSSD	6430	56.59331	56.32226	28.19129	90.9237	45.52004	66.56503	13.19172
DMaxAtPoint	6430	0.85813	0.47528	0.00115	14.9132	0.19275	1.08481	1.12301
LORE	6430	0.00000	0.00000	0.00000	0.0000	0.00000	0.00000	0.00000
LORSSD	6430	55.07968	54.83463	32.32223	85.2298	51.05409	58.79261	6.57732
LORMaxAtPoint	6430	0.00102	0.00076	0.00000	0.0063	0.00044	0.00137	0.00080

Figure 1d

Variable	Valid N	Mean	Median	Minimum	Maximum	Lower Quartile	Upper Quartile	Std.Dev.
MNE	6430	44.27823	35.35534	0.00000	166.2077	20.61553	63.44289	30.57528
MNSSD	6430	60.91795	58.75015	23.72672	121.0887	45.67004	73.79142	18.58118
MNMaxAtPoint	6430	0.00133	0.00040	0.00000	0.0313	0.00012	0.00152	0.00233
DaleE	6430	33.24084	27.38613	0.00000	148.1553	16.58312	45.27693	21.59598
DaleSSD	6430	59.52341	59.46867	28.68398	107.2327	47.85251	70.34295	13.95973
DMaxAtPoint	6430	17.20670	9.43516	0.16072	299.3523	3.98560	21.80584	22.43950
LORE	6430	14.24706	7.07107	0.00000	147.3092	0.00000	18.70829	20.14731
LORSSD	6430	60.77054	60.49491	35.43527	102.4891	56.06658	65.47762	7.50177
LORMaxAtPoint	6430	0.00083	0.00056	0.00000	0.0063	0.00027	0.00118	0.00078

Figure 1e

Variable	Valid N	Mean	Median	Minimum	Maximum	Lower Quartile	Upper Quartile	Std.Dev.
MNE	100	28.98679	25.36807	0.00000	91.1744	14.34387	39.08800	19.36050
MNSSD	100	53.90649	48.95036	23.76909	100.3630	41.37335	65.95370	18.61981
MNMaxAtPoint	100	0.00742	0.00317	0.00037	0.0666	0.00124	0.00961	0.01051
DaleE	100	42.29466	33.04389	0.00000	166.5460	19.13596	49.98529	35.84860
DaleSSD	100	71.99582	71.43313	26.98512	110.9749	57.10882	84.82082	18.75077
DMaxAtPoint	100	0.20637	0.15743	0.01566	0.6211	0.09072	0.32076	0.14919
LORE	100	0.00000	0.00000	0.00000	0.0000	0.00000	0.00000	0.00000
LORSSD	100	62.80766	62.93061	27.10507	95.0718	52.24510	74.24862	16.19637
LORMaxAtPoint	100	0.00628	0.00494	0.00169	0.0227	0.00310	0.00861	0.00423

Figure 1f

Variable	Valid N	Mean	Median	Minimum	Maximum	Lower Quartile	Upper Quartile	Std.Dev.
MNE	100	35.9899	31.8368	0.00000	167.1248	20.6669	43.8966	25.68608
MNSSD	100	69.1564	67.4566	40.32875	142.7591	57.5730	77.9292	16.18904
MNMaxAtPoint	100	0.0048	0.0020	0.00036	0.0606	0.0009	0.0048	0.00816
DaleE	100	70.0574	51.9784	2.44020	167.3185	24.4963	120.5450	51.44283
DaleSSD	100	110.5303	112.2489	70.58756	130.1740	104.4996	118.6246	11.71376
DMaxAtPoint	100	2.0920	1.7073	-1.13414	7.0096	0.5953	3.4344	1.91975
LORE	100	5.9143	0.0000	0.00000	167.1248	0.0000	4.5863	18.62143
LORSSD	100	71.6598	71.5749	42.62740	138.2016	62.4085	80.4276	13.43835
LORMaxAtPoint	100	0.0037	0.0026	0.00079	0.0226	0.0015	0.0043	0.00354

Figure 1g

Variable	Valid N	Mean	Median	Minimum	Maximum	Lower Quartile	Upper Quartile	Std.Dev.
MNE	100	24.14936	18.00278	0.00000	74.9658	8.30879	38.12478	20.31740
MNSSD	100	51.29687	48.30866	17.19826	111.1994	36.99803	62.50606	19.73759
MNMaxAtPoint	100	0.00816	0.00442	0.00011	0.0744	0.00102	0.01176	0.01065
DaleE	100	24.72421	18.61624	0.00000	121.7062	8.83806	31.34624	23.32379
DaleSSD	100	63.19210	57.17276	20.47453	116.9826	48.07145	76.21105	21.03505
DMaxAtPoint	100	1.01759	0.84079	0.05285	3.7928	0.29971	1.54114	0.83204
LORE	100	0.00000	0.00000	0.00000	0.0000	0.00000	0.00000	0.00000
LORSSD	100	59.88620	61.28746	23.63058	101.2460	49.22148	69.53170	16.08875
LORMaxAtPoint	100	0.00666	0.00586	0.00092	0.0241	0.00281	0.00957	0.00440

Figure 1h

Variable	Valid N	Mean	Median	Minimum	Maximum	Lower Quartile	Upper Quartile	Std.Dev.
MNE	100	24.45986	18.66037	2.27264	112.0305	7.42037	33.5709	21.15045
MNSSD	100	51.35619	47.54100	21.34614	113.7560	37.58425	63.7877	19.03778
MNMaxAtPoint	100	0.00643	0.00365	0.00004	0.0361	0.00088	0.0095	0.00759
DaleE	100	26.01610	16.77787	0.00000	140.5733	7.61179	28.2769	27.68495
DaleSSD	100	63.01346	56.41088	27.18239	118.5519	45.99483	79.7158	22.79567
DMaxAtPoint	100	95.85396	77.37389	3.74402	399.8879	27.72483	148.8874	88.56923
LORE	100	0.86365	0.00000	0.00000	24.3981	0.00000	0.0000	3.73665
LORSSD	100	58.08502	57.12851	30.12392	105.6818	46.83195	67.9525	14.95321
LORMaxAtPoint	100	0.00574	0.00516	0.00037	0.0165	0.00234	0.0084	0.00392

Figure 1: "a-h" summarize in tabular form localization error, spatial spread, and estimated activity values for the three imaging methods (minimum norm, Dale, and *s*LORETA). (a) EEG, 6430 voxels, 3 unknowns per voxel, 25 electrodes, 6430 test sources with random orientation, no noise. (b) Same as (a), but with additive random noise (noise scalp field standard deviation equal to 0.12 times the test source with lowest scalp field standard deviation). (c) MEG, 6430 voxels, 3 unknowns per voxel, 25 sensors, 6430 test sources with random orientation, no noise. (d) Same as (c), but with additive random noise (noise scalp field standard deviation equal to 7.21 times the test source with lowest scalp field standard deviation). (e) EEG, 12980 voxels, 1 unknown per voxel, 101 electrodes, 100 randomly selected test sources, no noise. (f) Same as (e), but with additive random noise (noise scalp field standard deviation equal to 0.082 times the test source with lowest scalp field standard deviation). (g) MEG, 12980 voxels, 1 unknown per voxel, 101 sensors, 100 randomly selected test sources, no noise. (h) Same as (g), but with additive random noise (noise scalp field standard deviation equal to 8.49 times the test source with lowest scalp field standard deviation). MNE: minimum norm localization error (mm); MNSSD: minimum norm spatial standard deviation (mm); MNMaxAbs: estimated minimum norm activity value at test source location (arbitrary units); DaleE: Dale localization error (mm); DaleSSD: Dale spatial standard deviation (mm); DMaxAbs: estimated Dale activity value at test source location (arbitrary units); LORE: *s*LORETA localization error (mm); LORSSD: *s*LORETA spatial standard deviation (mm); LORMaxAbs: estimated *s*LORETA activity value at test source location (arbitrary units). Note that the estimated activity values at test source locations cannot be compared among the different imaging methods (see text for explanation).

Discussion

Properties of *s*LORETA for EEG and MEG with unknown current density vector

The main properties of *s*LORETA, for both EEG and MEG, based on estimates of activity given by Eq. 20 are:
1. Exact, zero error, localization for test dipoles located at voxel positions, in the absence of noisy measurements.
2. Exact, zero error, localization of test dipoles *with arbitrary orientation*, located at voxel positions, in the absence of noisy measurements.
3. Exact, zero error, localization of test dipoles *with arbitrary orientation*, located at voxel positions, in the absence of noisy measurements, even under regularization $(\alpha > 0)$.
4. Exact, zero error, localization even for dipoles corresponding to a non-connected grid. For example, *cortical and non-connected subcortical grey matter can now be modeled as the solution space*. The error remains zero.

Properties of *s*LORETA for EEG and MEG with known current density vector orientation, unknown amplitude

The main properties of *s*LORETA based on estimates of activity given by Eq. 22 are:
1. Exact, zero error, localization of test dipoles located at voxel positions, in the absence of noisy measurements.
3. Exact, zero error, localization of test dipoles located at voxel positions, in the absence of noisy measurements, even under regularization $(\alpha > 0)$.
4. Exact, zero error, localization even for dipoles corresponding to non-connected grids. For example, *cortical and non-connected subcortical grey matter can now be modeled as the solution space*. The error remains zero.
5. These results mean that the distribution of voxels can be quite arbitrary. For example, voxels do not have to be uniformly distributed from the geometrical point of view, although they should be uniformly distributed from the "*grey matter density*" point of view. Furthermore, different types of voxels may exist, some with unknown current density vector, and some with known current density orientation but unknown amplitude.

A Generalization

Suppose there exist reasons to *believe* that the *actual* (*prior*) current density variance is the diagonal, positive definite matrix **W**. This situation arises for example, in some approaches that force fMRI hot spot locations onto the EEG/MEG inverse solution (see for example (6)). In this case, Eq. 8 can be rewritten as:

$$\mathrm{F} = \left(\mathbf{K}\mathbf{W}^{1/2}\right)\left(\mathbf{W}^{-1/2}\mathbf{J}\right) \qquad \text{Eq. 23}$$

where the new unknown variable $\left(\mathbf{W}^{-1/2}\mathbf{J}\right)$ has been "pre-standardized" to have the identity matrix as its variance. This transformed variable plays the role of $\mathbf{J}$ in all equations above, and $\left(\mathbf{K}\mathbf{W}^{1/2}\right)$ plays the role of the lead field in all equations above. All else proceeds identically with these new formal substitutions.

Note that the final *s*LORETA image corresponds to standardized estimates of activity (Eqs. 20 or 22) for the pre-standardized current density $\left(\mathbf{W}^{-1/2}\mathbf{J}\right)$.

Note that this approach can be applied to any *actual* (*prior*) current density variance $\mathbf{W}$, as long as it is positive definite, and there exists a meaningful decomposition:

$$\mathbf{W} = \left(\mathbf{W}^{1/2}\right)^T \left(\mathbf{W}^{1/2}\right) \qquad \text{Eq. 24}$$

for the square root matrix $\mathbf{W}^{1/2}$. For example, this is the case of the classical LORETA method (2), where $\mathbf{W}^{-1/2}$ embodies a discrete spatial Laplacian operator that achieves smoothness between neighboring voxels.

Estimating the regularization parameter a

The regularization parameter a cannot be estimated from the functional in Eq. 8. However, it can be estimated via the cross-validation functional. This has been published in (14), in a reply to comments made to the paper in (2), which includes the detailed derivation of the method, and a set of equations that can be used efficiently in practice.

*s*LORETA in experimental designs (statistical analysis of tomographic images)

Although *s*LORETA calculations produce pseudo-statistics, it is highly recommended to *not* use these values as actual statistics in testing of hypotheses in experimental designs.

Unlike the approach of Dale et al. (6), which makes use of their statistics for hypothesis testing, it is recommended to use *s*LORETA pseudo-statistic values as *estimates of activity*, and to apply standard techniques such as in statistical non-parametric mapping (SnPM) (7) for the analysis of experimental designs.

*s*LORETA in testing for absolute activation

Note that tests for absolute activation with *s*LORETA can be performed by using the modified pseudo-statistics:

$$\left\{\left[\mathbf{S}_{\hat{\mathbf{J}}}\right]_{ll}\right\}^{-1/2}\hat{\mathbf{J}}_l \qquad \text{Eq. 25}$$

or:

$$\frac{\hat{J}_l}{\sqrt{\left[\mathbf{S}_{\hat{\mathbf{J}}}\right]_{ll}}} \qquad \text{Eq. 26}$$

which correspond to Eqs. 20 and 22, respectively.

These pseudo-statistics should be used in an experimental design where there are N independent *s*LORETA images. For example, in a visual event related potential study with $N = 10$ subjects, consider the 10 *s*LORETA images at the P100 latency.

In Eq. 25, $\left\{\left[\mathbf{S}_{\hat{\mathbf{J}}}\right]_{ll}\right\}^{-1/2}$ denotes the unique symmetric inverse square root matrix of $\left[\mathbf{S}_{\hat{\mathbf{J}}}\right]_{ll}$. The pseudo-statistic in Eq. 26 has the form of a univariate Student's *t*-statistic, and the pseudo-statistic in Eq. 25 has the form of a Mahalanobis transform (10).

In the case of unknown amplitudes only, significant absolute activation is based on testing for zero mean of the pseudo-statistic in Eq. 26. SnPM can be used to correct for multiple comparisons and to bypass assumptions of Gaussianity.

In the case of unknown current density vector, significant absolute activation is based on testing for zero mean of the "*max-statistic*" of the pseudo-statistic in Eq. 25. This corresponds to the maximum of the absolute value among the three components. The "*max-statistic*" reduces three numbers per voxel to a single number per voxel. This is then used in SnPM to correct for multiple comparisons and to bypass assumptions of Gaussianity.

Conclusions

1. Localization error can not be improved beyond the present result. It is zero. Up to the present, no other instantaneous, distributed, discrete, imaging method for EEG/MEG has been published (to the best of the author's knowledge) that achieved perfect localization. All other previously published methods at best produced systematic non-zero localization errors (see (2), (6), (15), (16), (17)).
2. If the aim is localization, this new method, denoted as *s*LORETA, at least has perfect first order localization.
3. A distributed imaging method capable of exact localization of point sources is of great interest, since the principles of linearity and superposition would guarantee its trustworthiness as a functional imaging method, given that brain activity occurs in the form of a finite number of distributed "hot spots".
4. The detailed information provided here allows the reader to reproduce, check, test, and validate the previous claims.

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