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Strategies for statistical thresholding of source localization maps in magnetoencephalography and estimating source extent

Kostiantyn Maksymenko[a,b], Bernard Giusiano[a], Nicolas Roehri[a], Christian-G. Bénar[a,*], Jean-Michel Badier[a]

[a] Aix Marseille Univ, Inserm, INS, Institut de Neurosciences des Systèmes, Marseille, France
[b] Project-Team Athena, INRIA Sophia Antipolis, France

HIGHLIGHTS

- Different strategies are compared for defining a threshold on MEG source maps.
- Parametric and adaptive thresholding were compared on simulated data.
- Adaptive thresholds were the best, across a range of signal to noise ratios.
- Extent of active cortex can be retrieved with performance close to optimal.

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ABSTRACT

Background: Magnetoencephalography allows defining non-invasively the spatio-temporal activation of brain networks thanks to source localization algorithms. A major difficulty of MNE and beamforming methods, two classically used techniques, is the definition of proper thresholds that allow deciding the extent of activated cortex.
New method: We investigated two strategies for computing a threshold, taking into account the difficult multiple comparison issue. The strategies were based either on parametric statistics (Bonferroni, FDR correction) or on empirical estimates (local FDR and a custom measure based on the survival function).
Results: We found thanks to the simulations that parametric methods based on the sole estimation of H_0 (Bonferroni, FDR) performed poorly, in particular in high SNR situations. This is due to the spatial leakage originating from the source localization methods, which give a 'blurred' reconstruction of the patch extension: the higher the SNR, the more this effect is visible.
Comparison with existing methods: Adaptive methods such as local FDR or our proposed 'concavity threshold' performed better than Bonferroni or classical FDR. We present an application to real data originating from auditory stimulation in MEG.
Conclusion: In order to estimate source extent, adaptive strategies should be preferred to parametric statistics when dealing with 'leaking' source reconstruction algorithms.

1. Introduction

Magnetoencephalography (MEG) and electroencephalography (EEG) can localize neural electrical activity based on noninvasive measurements of neuronal electromagnetic signals. Their excellent time resolution provide a unique window on the dynamics of human brain functions. However, the only way to localize the putative electric sources in the brain is through the solution of an ill-posed inverse problem, which can only be solved by introducing strong *a priori* assumptions on the generation of EEG and MEG signals (Baillet et al., 2001).

Many solutions for solving the inverse problem have been proposed in the literature (reviews in Baillet et al., 2001; Michel et al., 2004). Different classes of solutions exist, based on a limited number of dipolar sources (equivalent dipoles), on sources placed along the cortex or on a regular grid within the brain volume (distributed sources) or based on spatial filtering (beamforming).

A major difficulty for distributed sources and beamforming is to find a threshold that will determine the number of active regions and their extent. In particular, extracting the correct extent

* Corresponding author.
E-mail address: christian.benar@univ-amu.fr (C.-G. Bénar).

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of active cortical sources is an important issue, in order to estimate which brain regions are involved in a given paradigm (after registration to an atlas), or in presurgical evaluation of epilepsy, where the clinicians have to decide on the amount of cortex to be resected (Rosenow and Lüders, 2001). Several authors have presented strategies for estimating source extent (e.g. Kincses et al., 1999; Hillebrand and Barnes, 2011; Becker et al., 2017). Within a statistical framework, a hypothesis test can be performed for each brain source followed by thresholding, which results in a heavy multiple comparison problem (of the order of several thousand sources). Thus, Grova and colleagues have shown that there can exist in some conditions a possible threshold, as the work is based on receiver operating characteristics that tests all possible thresholds (Grova et al., 2006), but does not evaluate a way to actually estimate the threshold in real-life situations (even though Otsu thresholding was proposed for visualization purposes).

Several parametric and non-parametric methods have been proposed to take into account the multiple comparison problem in general (Goeman and Solari, 2014; Efron, 2005) and in neuroscience in particular (Nichols and Hayasaka, 2003; Genovese et al., 2002). However, most attention so far has been directed towards multiple comparison in the analysis of fMRI data, and much less towards EEG/MEG thresholding at the source level (Pantazis et al., 2005). Unlike fMRI, which directly measures every voxel in the brain, EEG/MEG data reconstruction is based on an inverse operator. Such operator can change the noise properties and produce a leakage effect, which reduces spatial resolution (Grave De Peralta Menendez et al., 1997). Random field theory and permutation methods were analyzed in Pantazis et al. (2005), including a non-parametric framework for setting the threshold, but in practice the parametric methods are often reduced to simple thresholding according to *p*-values.

The objective of the current article is to propose and validate statistical strategies for thresholding source localization maps in MEG. We used two linear inverse methods – minimum norm estimate and beamforming (linearly constrained minimum variance). For different patch/SNR configurations we reconstructed source activity and applied different statistical thresholds in order to obtain the estimated patch location, which were compared with the simulated patch.

2. Materials and methods

In the following, we assume that the brain surface model is defined, with a description of every source position and orientation. In general, if orientation is not fixed, methods could be easily generalized using a three-dipole source representation.

2.1. Minimum norm estimate (MNE)

The observation model is:

$$x = As + n, \tag{1}$$

where $x \in \mathbb{R}^N$ is an observation vector (EEG or MEG) at the fixed time moment, N is a number of sensors; $s \in \mathbb{R}^M$ is the vector of source amplitudes, M is the number of sources; $A \in \mathcal{M}_{N,M}$ is the gain matrix; $n \in \mathbb{R}^N$ is the measurement noise.

The prior hypotheses are: $n \sim \mathcal{N}(0, C)$, $s \sim \mathcal{N}(0, R)$, i.e. both n and s are normally distributed vectors with zero mean and covariance matrices C and R respectively. This leads to (Baillet et al., 2001):

$$\hat{s} = (A^T C^{-1} A + R^{-1})^{-1} A^T C^{-1} x = Wx. \tag{2}$$

It can be also shown that:

$$(A^T C^{-1} A + R^{-1})^{-1} A^T C^{-1} = RA^T (ARA^T + C)^{-1}. \tag{3}$$

It is more efficient to use the second expression because it requires the inversion of a matrix that is square in the number of sensors, compared to square in the number of sources (Liu et al., 2002). In practice, the *a priori* source covariance matrix is unknown and we can add a regularization parameter by writing $R = \frac{R}{\lambda^2}$. This results in

$$W = RA^T (ARA^T + \lambda^2 C)^{-1}. \tag{4}$$

It should be noted that after some manipulations (whitening and scaling) we can use the following approximation:

$$\lambda^2 \approx \frac{1}{SNR}, \tag{5}$$

where SNR is the (power) signal-to-noise ratio of the whitened data, but in practice we can only estimate this value of SNR (Hämälä inen, 2010).

2.2. Beamforming (BF)

The data model is the same as for MNE but we will represent it in another way (Van Veen and Buckley, 1996; Van Drongelen et al., 1996):

$$x = \sum_{i=1}^{M} A(q_i) s(q_i) + n, \tag{6}$$

where q_i corresponds to the location of ith source, $s(q_i)$ is associated dipole amplitude, and $A(q_i) \in \mathbb{R}^N$ the corresponding column of the leadfield matrix.

Every source amplitude is assumed to be a random variable with mean $\bar{s}(q_i) = \mathbb{E}[s(q_i)]$ and variance $R(q_i) = \mathbb{E}[(s(q_i) - \bar{s}(q_i))^2]$. Moreover, we assume that all sources are uncorrelated, and that sensor-level noise is zero mean with covariance matrix Q. We can calculate the mean and the covariance matrix of the observed data vector x:

$$\bar{x} = \sum_{i=1}^{M} A(q_i) \bar{s}(q_i) \tag{7}$$

$$C(x) = \sum_{i=1}^{M} A(q_i) R(q_i) A^T(q_i) + Q \tag{8}$$

For every source q_i the objective is to construct an operator (spatial filter) $W(q_i) \in \mathbb{R}^N$, such as $\hat{s}_i = W^T(q_i)x$. An ideal spatial filter satisfies:

$$W^T(q_i) A(q_j) = \begin{cases} 1, & \text{if } i = j, \\ 0, & \text{if } i \neq j. \end{cases} \tag{9}$$

In that case we obtain:

$$\begin{aligned} \hat{s}(q_i) &= W^T(q_i)x \\ &= \sum_{j=1}^{M} W^T(q_i) A(q_j) s(q_j) + W^T(q_i) n \\ &= s(q_i) + W^T(q_i) n, \end{aligned} \tag{10}$$

In the absence of noise this would lead to perfect reconstruction of the source activity. But in the context of the EEG/MEG signals, when $M > N$, the perfect filter is not possible. The idea of linearly constrained minimum variance (LCMV) filtering (Van Veen and Buckley, 1996) is to find $W(q_i)$ which minimizes the variance of the filter output while satisfying the constraint:

$$\begin{cases} \min\limits_{W(q_i)} \mathrm{Var}(\hat{s}_i), \\ W^T(q_i) A(q_i) = 1. \end{cases} \tag{11}$$