Automated localization of magnetoencephalographic interictal spikes by adaptive spatial filtering

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Abstract

Objective: Automated adaptive spatial filtering techniques can be applied to magnetoencephalographic (MEG) data collected from people with epilepsy. Source waveforms estimated by these methods have higher signal-to-noise ratio (SNR) than spontaneous MEG data, allowing identification and location of interictal spikes. The software tool SAM2 provides an adaptive spatial filtering algorithm for MEG data that yields source images of excess kurtosis and provides source time-courses in voxels exhibiting high excess kurtosis. The sensitivity and specificity of SAM2 in epilepsy is unknown.

Methods: Interictal MEG data from 36 patients with intractable epilepsy were analyzed using SAM2, and results compared with equivalent current dipole (ECD) fit procedures.

Results: When SNR of interictal spikes was high (compared to background) with a clear single focus, in most cases there was good agreement between ECD and SAM2. With multiple foci, there was typically overlap but imperfect concordance between results of ECD and SAM2.

Conclusions: SAM2 may in some cases be equivalent to manual ECD fit for localizing interictal spikes with single locus and good SNR. Further studies are required to validate SAM2 with multiple foci or poor SNR.

Significance: In some cases, SAM2 might eventually assist or replace manual ECD analysis of MEG data.

Keywords: MEG; Automated spike localization; Adaptive spatial filtering; Epilepsy

1. Introduction

Traditionally, the analysis of clinical magnetoencephalographic (MEG) data collected in patients with epilepsy involves manual selection of interictal spikes, followed by fitting single or multiple equivalent current dipoles (ECDs) to each spike or spike-average. The locations of these interictal spike ECDs are then subjected to visual examination to assess clustering and reliability of putative interictal spike sources. This is time-consuming and requires considerable manual manipulation of data. Moreover, the reliability of this procedure is highly influenced by noise in the recordings and by the variable number of interictal spikes. A small number of interictal spikes can be easily missed in noisy recordings. Therefore, automated methods for interictal spike detection and localization are much needed to improve the efficiency, sensitivity and specificity of electromagnetic source imaging.

Several automated approaches have been proposed for EEG interictal spike detection that assume subsequent user-mediated source localization. These approaches are largely based on morphological analysis, template matching, predictive filtering and/or independent component analysis (Ossadchti et al., 2004). Morphological analysis characterizes the waveforms, frequency bands or time-frequency representations of interictal spikes (Michel et al., 1999; Gotman, 1990, 2003). Template matching

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approaches use a priori information about spike shape (embodied as a matched filter) and require good modeling of the background noise covariance. In many of these methods, high rates of false positives are reduced by context information gathered by concurrent recordings of electrooculographic, electrocardiographic, and electromyographic activity.

More recently, spike detection approaches based on independent component analysis (ICA) have also been proposed. ICA is primarily used as a spatiotemporal filter where components are selected by visual inspection. Kobayashi et al. used ICA decomposition with the RAP-MUSIC algorithm and fit dipoles to ICA sub-space (Kobayashi et al., 2002a,b). While their approach does not make use of the spatial topography of detected spikes, it requires visual interpretation of the independent components to identify the interictal sub-space, and a manual cluster analysis to discard spurious sources. Osadtchi et al. have recently described an automated method that combines ICA preprocessing, multivariate autoregressive model (MVAR) estimation of background brain activity, RAP-MUSIC and a cluster-significance thresholding procedure for localization of interictal activity that can be used for manual/operator pruning (Osadtchi et al., 2004). The result is a three-step automated method, namely (1) independent component analysis (ICA) with component picking, thresholding and spike detection (based on peak-picking of ICA projections); (2) dipole modeling of detected spikes; and (3) elimination of dipoles that fail to cluster based on statistical criteria. Alternative techniques using adaptive and nonadaptive spatial filtering, as well as scalar and vector beam forming, have also been under development for the analysis of interictal MEG datasets (Sekihara et al., 2004, 2005).

An alternative approach to automated interictal spike localization with adaptive spatial filtering is proposed in this paper. This method uses adaptive spatial filtering to reconstruct the time-course of activity in specific voxels in the brain and to examine voxels that exhibit excess kurtosis in the estimated time-course. The spatial locations of voxels with high excess kurtosis are assumed to be sources of interictal spikes. The time series of the voxel estimates with high excess kurtosis can be thresholded to detecting interictal spikes. This procedure, described in greater detail below, was implemented using the Synthetic Aperture Magnetometry kurtosis (SAM(g)) software tools provided by VSM MedTech Ltd/CTF Systems (Port Coquitlam, BC).

For this study, we examined MEG data from a group of patients with epilepsy of diverse etiology. We compared the localization of interictal spikes obtained by adaptive spatial filtering procedures and by equivalent dipole fit. The object of this comparison was twofold: (1) to determine how closely the results of our automated method matched those of manual ECD procedures and (2) to understand how and why results of these two procedures might differ for specific cases.

2. Methods

MEG recordings from 36 consecutive patients who were referred to the UCSF Biomagnetic Imaging Laboratory were assembled under procedures approved by the UCSF Committee on Human Research. The patients carried a variety of diagnoses including cortical dysplasia and medial temporal lobe epilepsy; all had medically refractory (and in some cases surgically refractory) epilepsy. The majority of the recordings were interictal, but in a few cases a seizure was captured during the MEG session (Cases 2, 20, and 27). Data were recorded from each patient in a passband of dc −75 Hz (300 Hz sample rate) using a CTF 275-channel whole cortex MEG helmet. These data had already been subjected to manual spike marking and dipole fit as part of routine clinical investigation. Spikes were marked at their onset. As a general rule, during manual dipole fitting, dipoles having greater than 10% residual variance were rejected.

Estimation of sources with high excess kurtosis was determined using adaptive spatial filtering by SAM(g) software tools. To perform this analysis, spontaneous MEG data with a bandwidth of dc to at least 70 Hz was obtained from patients and divided into 2-min segments. For each patient, segments were selected for analysis that represented a range of states (e.g., awake and asleep) and degree of epileptic activity (e.g., with many spikes and few spikes by ECD), and segments with significant muscle artifact were avoided; the number of segments selected varied among patients. An estimate of the source activity at each coordinate in the brain was calculated from the MEG data as \( \hat{S}(i) = \mathbf{w}^T \mathbf{m}(i) \), where \( \mathbf{r} \) is the position of the voxel, \( S_r(t) \) is the strength of the dipole moment at location \( \mathbf{r} \), \( \mathbf{w} \) denotes the transpose of a vector of spatial filtering co-efficient that operates on the data, and \( \mathbf{m}(t) \) is the data vector of magnetic field measurements at time \( t \).

Therefore, an estimate of source power at each voxel in the brain is given by \( S_r^2(t) = |\mathbf{w}^T \mathbf{m}(t)|^2 \) and integrating over time yields source variance \( S_r^2 = \mathbf{w}^T \mathbf{C}_r \mathbf{w} \), where the covariance matrix is \( \mathbf{C} = \mathbf{M} \mathbf{M}^T / T \), with \( \mathbf{M} \) being the spatiotemporal data matrix and \( T \) the total integration time. Solving for \( \mathbf{w} \) by minimizing source variance, subject to \( \mathbf{w}^2 \mathbf{b} = 1 \), yields \( \mathbf{w} = \mathbf{C}^{-1} \mathbf{b} / \mathbf{b}^T \mathbf{C}^{-1} \mathbf{b} \), where \( \mathbf{b} \) is the forward solution for a unit current dipole at position \( \mathbf{r} \), computed assuming a multiple local-sphere spherical volume conductor model. The noise covariance is assumed to be a scaled identity matrix. The scale was set to equal to the minimum eigenvalue of the source covariance matrix. No regularization was necessary for inversion of the covariance matrices.

For each coordinate, the excess kurtosis \( g_2 \) in the estimated source time-course is determined as a measure of spikiness. Excess kurtosis is computed from each source waveform as \( g_2 = \frac{1}{N} \sum [S(t) - \bar{S}]^4 / \sigma^4 - 3 \), where \( \sigma \) is the standard deviation and \( T \) is the number of time samples. A functional image is made up of the \( g_2 \) values corresponding to each voxel. For our subjects, SAM(g) images were
computed for a ROI of $x = \{-10.0, 10.0\; \text{cm}\}$, $y = \{-9.0, 9.0\; \text{cm}\}$, $z = \{0.0, 14\; \text{cm}\}$, relative to the head frame, in 5 mm steps; this ROI enclosed the entire head, in all cases. SAM($g_2$) analysis was performed for a frequency range of 20–70 Hz in order to provide optimal image contrast for interictal spike activity. The data were analyzed in 2-min segments from which covariances and kurtoses were computed. A list of the local maxima in the SAM($g_2$) images was saved, and SAM virtual sensors (source waveform estimates) were computed for each location for viewing source activity in the dc −75 Hz range. Virtual sensor waveforms were examined and rejected if significant muscle artifact was present.

The peak of each spike in the 20–70 Hz source time series was marked using an adaptive threshold-crossing algorithm. The adaptive thresholding procedure for spike detection was to take a voxel time series for peaks of the kurtosis images (SAM($g_2$) virtual sensors). Then, a peak-to-rms ratio was computed across the time series; this is the ratio of the absolute value of the waveform to the rms ($\sigma$) at each time-point. Typically, thresholding at a peak-to-rms ratio of five gave good detection of spikes. Note that this peak-to-rms threshold is a tunable feature, although we kept it at the default of five for the cases discussed here. All spikes identified by SAM($g_2$) were reviewed manually and were rejected if they represented artifact or normal background patterns (e.g., sharpened alpha). Spikes with a low degree of kurtosis (less than two) were typically rejected. Two exceptions are noted in Table 1, and in these two cases, spikes with a lower degree of kurtosis were kept because of their plausibility; since $g_2$ is a measure of outliers in the distribution of amplitudes, very frequent interictal spikes may yield a smaller $g_2$ than do rare spikes, so in some cases automatic rejection of spikes with low kurtosis is not warranted. The SAM($g_2$) image and dipole markers were co-registered with the corresponding MRI of each patient.

We then compared the relative location of the SAM($g_2$) maxima to the fits from manual dipole marking. See Fig. 1 for an example of MEG waveforms and a simultaneous SAM($g_2$) virtual sensor waveform. For each subject, the concordance between SAM($g_2$) results and ECD fit results was reviewed and rated using the following schema (based loosely on a similar schema used to rate spike concordance in MEG/EEG datasets (Lin et al., 2003) and modified by R. Knowlton [personal communication]):

- **I. Concordant, ECD+/SAM+:** SAM($g_2$) and ECD results both yielded foci in the same location (lobar concordance)
- **II. Concordant, ECD+/SAM+ overlap:** SAM($g_2$) and ECD both yielded foci that had significant overlap, but not 100% agreement (e.g., one method suggested frontal and temporal foci, and the other suggested frontal only)
- **III. Concordant, ECD-/SAM-:** neither SAM($g_2$) nor ECD fit yielded a focus (i.e., no spikes found with either method)
- **IV. Discordant, ECD+/SAM-:** ECD found a focus but SAM($g_2$) found no focus or was uninterpretable
- **V. Discordant, ECD-/SAM+:** ECD found no focus or was uninterpretable; SAM($g_2$) found a focus
- **VI. Discordant, ECD+/SAM+ no overlap:** SAM($g_2$) and ECD both yielded foci, but disagreed on location (e.g., one method suggested a frontal focus and one suggested a temporal focus)

We then calculated the three-dimensional coordinates of the centroid of each spike cluster, of the averaged spike for each cluster, and of the corresponding SAM($g_2$) peak.

**3. Results**

Table 1 is a case summary table containing lobar concordance ratings for each case. Because lobar concordance is a qualitative and imprecise construct, for the concurrent and discordant overlap cases this is followed by several quantitative calculations for each of the most prominent ECD clusters for each case: (1) the distance between the centroid of the cluster and the SAM($g_2$) maximum, (2) the distance between the averaged spike for the cluster and the SAM($g_2$) maximum, and (3) the difference between (1) and (2). Of the 36 cases reviewed, in five cases the results of one technique or the other were not reliable because of artifact, so concordance ratings could not be determined for these cases; they appear at the bottom of the table. Note that for one of these cases with severe dental artifact that precluded manual ECD fits, SAM($g_2$) was nonetheless able to find a clinically plausible focus (Case 36).

**3.1. Concordant cases**

Of the 31 cases rated, 18 had good lobar/multilobar concordance between SAM($g_2$) and ECD (rated concordant, ECD+/SAM+). Generally, for these cases, the distance between SAM($g_2$) peak and centroid of ECD dipole cluster was less than 2.5 (average 1.71, standard deviation 0.89); in the case (Case 15) where it was much higher, there were broad opercular spikes whose dipoles had a large scatter, and the region identified by SAM($g_2$) was large and relatively ill-defined, so it is not surprising that there was some disagreement. Cases 1, 4, 5, and 8 are examples of this pattern, and are shown in Figs. 1–4. Five cases had overlap in results from the two methods (rated concordant, ECD+/SAM+ overlap). Six cases had no spikes identified by either ECD or SAM($g_2$) (rated discordant, ECD-/SAM-): although strictly speaking, concordance is good, note that this rating signals a lack of positive findings with either method.

**3.2. Discordant cases**

In two cases, ECD found a focus and SAM($g_2$) did not (rated discordant, ECD+/SAM); in one of these, ECD...
could model poorly formed focal sharp waves seen on EEG and MEG, but SAM($g_2$) did not detect a focus. In the other case, MEG recorded generalized spike and slow wave complexes maximal on left with poor dipole fits on ECD and left frontal spikes with good dipole fits on ECD; SAM($g_2$) did not find a focus. There were no cases that fit the last two rating patterns (i.e., no cases were rated as discordant, ECD−/SAM+ or discordant, ECD+/SAM+ no overlap).

We found that running the SAM($g_2$) analysis for a single case took several hours, albeit without active user attention, depending on the number of segments analyzed and the traffic on the computing cluster used to run it, and analyses were therefore sometimes run overnight for expediency. Manual review of the output (examination of virtual sensor spikes) took an additional hour, on average.

4. Discussion

In 18 of the 31 interpretable cases (58%), ECD and SAM($g_2$) found foci, and agreement between ECD dipoles and SAM($g_2$) results was excellent. If we include the 6/31 where neither method identified a focus, we found full concordance in 24/31 or 77% of cases (though note that for one of these cases, Case 18, a SAM($g_2$) maximum with kur-
Fig. 1. Case 1. (Top panel) SAM(g2) results (red-orange region), including two SAM(g2) maxima, one shown in green and one in yellow, superimposed on anatomic brain MRI (relevant axial, coronal, and sagittal views shown). Kurtosis values for the maxima are also displayed; kurtosis is 14.8 for the yellow maximum (corresponding to virtual sensor V1) and 16.5 for the green (corresponding to virtual sensor V0). Red-orange color scale indicates degree of kurtosis. ECD dipoles and SAM(g2) maxima do not always appear on the same slices of the MRI but do show good lobar agreement. (Bottom panel) Simultaneous MEG (green = a group of right-temporal channels, blue = a group of left-temporal channels), EEG (first eight black channels), and SAM(g2) virtual sensor (last two black channels, labeled V0 and V1) waveforms. The V0 channel corresponds to the green maximum and the V1 channel corresponds to the yellow maximum. The light blue vertical cursor is placed on a left-temporal spike that can be seen in MEG, EEG, and virtual sensor waveforms.
tosis <2 but good colocalization with results of manual ECD fit was included). In another 5/31 cases there was overlap between the results from the two methods, yielding 29/31 or 94% of cases with some concordance. Of the five overlap cases, one (Case 20) was multifocal by both ECD and SAM($g_2$), but different foci were identified with the two methods. In two cases (Cases 19, and 22) ECD indicated a unilateral temporal focus while SAM($g_2$) indicated bitemporal maxima. In Case 23, ECD and SAM($g_2$) agreed on the high kurtosis/high SNR foci (right-temporal and orbitofrontal), and though SAM($g_2$) did identify occipital maxima, they had much lower kurtosis in comparison; in fact, the kurtosis value for these was below the cutoff of two that was used to keep or discard other maxima and if we chose instead to discard these low kurtosis maxima as invalid, the case would demonstrate full concordance. As for the discordant cases, in two cases only did SAM($g_2$) fail where ECD succeeded, and in one of these cases the ME findings were relatively weak, limited to several sharp waves with low SNR. In one case with dental artifact, ECD was not successful but SAM($g_2$) was able to yield a result that was in agreement with other clinical...

Fig. 2. Case 4. Manually fit dipoles (yellow arrows) and SAM($g_2$) results (red-orange region with green maxima), superimposed on anatomic brain MRI (axial slices shown). Color scale indicates degree of kurtosis. Simultaneous MEG (green = a group of right-temporal channels, blue = a group of left-temporal channels), EEG (black channels), and SAM($g_2$) virtual sensor waveforms (red channels) are also shown. In this case, both manual ECD fit and SAM($g_2$) documented left central-temporal spikes and rare right-temporal spikes. The top panel shows two spikes seen in the SAM($g_2$) virtual channels V2/V3, the first with a corresponding visible MEG/EEG spike (marked with dark blue vertical cursor), and the second with no corresponding visible MEG/EEG spike (marked with grey vertical cursor). The SAM($g_2$) maximum appears on the MSI image as a green dot labeled 46.4 (the corresponding kurtosis value). The bottom panel shows a spike seen in the SAM($g_2$) channel V1 (marked with dark blue vertical cursor) with maximum that mapped to the opposite hemisphere (shown on MSI image as green dot, labeled with its kurtosis value, 51.3); this spike is apparent in retrospect on the MEG but is not easily discerned.
information, so in this case SAM\(g_2\) provided information when ECD did not, instead of merely replicating its results.

The placement of manual markers for ECD fits was based upon spike onset as visible in the MEG sensor waveforms, but in several cases spike onsets appeared later in the MEG sensor waveforms than in the SAM virtual sensor waveforms. The difference between dipole scatter for the automated and manually placed spike markers might in such cases be attributable to the SAM\(g_2\) virtual sensors emphasizing an earlier portion of the spike, before excitation has spread, and so in these cases it is conceivable, though unproven, that the SAM\(g_2\) virtual sensors may in fact be closer to spike origin than are ECD fit locations. Analogous observations were recently made in a group of epilepsy patients with polymicrogyria, where abnormal sulcation of the epileptogenic lesions may cause MEG to miss the onset of spikes because they are radially orient- ed; instead, in these cases, MEG may pick up mainly propagated activity, while simultaneous EEG records spike onsets more accurately because of the unusual cortical geometry (Bast et al., 2005). The precise situations and patient populations for whom SAM\(g_2\) might offer theoretical advantages over routine MEG with ECD fit are unknown.

This study demonstrates that SAM\(g_2\) may, in many cases, be equivalent to the ECD fit, especially for localizing MEG interictal spikes when there is a single spike locus and good SNR. In most such cases, we were able to obtain good quality ECD fits using SAM\(g_2\) for automated spike detection followed by user review of the selected spikes. When multiple interictal spike foci were present and ECD scatter high, SAM\(g_2\) might indicate a larger region instead of a tight maximum, or might indicate multiple regions that did not overlap perfectly with the multiple ECD foci. Our results suggest that tools like SAM\(g_2\) could be used to improve the efficiency of routine clinical analysis of MEG studies in epilepsy patients. Current anal-
ysis protocols are labor intensive and sensitive to error. Though its results do require thoughtful interpretation by the user, SAM(g) could help increase the efficiency of this process: for example, manual dipole fitting could follow first-pass data analysis and localization using SAM(g). SAM(g) could also provide additional channels for spike detection and morphological analysis. Further testing will be necessary to determine the sensitivity and specificity of SAM(g) in cases with single and multiple foci, and to test SAM(g) and manual ECD fit against gold standards such as ictal electrocorticography or seizure relief following resection of a putative focus.

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