Electromagnetic Source Imaging: Backus–Gilbert Resolution Spread Function-Constrained and Functional MRI-Guided Spatial Filtering

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Abstract: Electromagnetic source imaging techniques are usually limited by their low spatial resolution, even though these techniques have high temporal resolution. Our heuristic analysis shows that the spatial ambiguity of electromagnetic source localization arises from interference from other sources. In this paper, we suggest a new inverse solution based on the principle of spatial filtering to effectively suppress the interference from other sources, especially from the far sources. By means of this approach, functional MRI information can also be effectively integrated into the inverse solution to further improve spatial accuracy of source localization. Most importantly, the results of source localization by this approach are not significantly biased by incompatible fMRI information. Our simulations and experimental results using electroencephalography based on a realistic head model show that the Backus–Gilbert resolution spread function-constrained and functional MRI-guided spatial filtering suggested in this paper provide high spatial accuracy and resolution of source localization, even in the presence of multiple simultaneously active sources. *Hum Brain Mapp* 29:627–643, 2008. © 2007 Wiley-Liss, Inc.

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INTRODUCTION

Currently, electroencephalography (EEG) and magnetoencephalography (MEG) are the only noninvasive techniques that are capable of directly measuring the electrical dynamics of the human brain at the time scale of neurons (milliseconds), but these techniques are usually considered to have low spatial resolution. While it is impossible to precisely reconstruct a three-dimensional dynamic source image from a two-dimensional EEG surface potential or MEG magnetic field topography [Helmholtz, 1853], the spatial accuracy or resolution limit of source reconstruction using these techniques has not been well documented. For

example, to what level of spatial accuracy can we trust our electromagnetic source imaging results? Is there an optimal approach to provide the best solution among the various inverse solutions? In this paper, we will attempt to address these questions.

The difficulty with electromagnetic source localization is that inverse solutions are not unique. During the past decades, various inverse approaches based on different criteria have been proposed, from the single dipole/multiple dipole approach to the recently described distributed current dipole models [see Baillet et al., 2001; Michel et al., 2004 for current reviews and references therein]. Presently, the distributed current dipole models fall into two general categories of inverse solutions. The first follows the global criterion that the potentials/fields reproduced by the estimated sources will have the smallest errors in relation to the observed data, with some prior knowledge or assumptions to constrain the spatial or temporal distribution of the source [Tikhonov, 1963]. These algorithms broadly belong to the weighted minimum norm (WMN) method and its derivatives [Dale and Sereno, 1993; Goronidnitsky et al., 1997; Hamalainen and Ilmoniemi, 1984; Pascual-Marqui et al., 1994; Trujillo-Barreto et al., 2004; Yamashita et al., 2004], and the so-called “optimal resolution kernel method” [Grave de Peralta Menendez et al., 1997]. The two main drawbacks of approaches based on the global criteria are (1) that the source interference in the source space of these inverse solutions is not generally controlled and might be significant, even when the estimated sources exactly reproduce the measured data, and (2) the source distribution assumptions used to regularize the inverse solution are usually biased, due to a lack of physiological grounding, or are unsuitable for certain real situations.

The second type of inverse solution follows the local criterion that the estimated source should be close to the true source at each site, that is, it minimizes the source power with a unit gain at each site based on the principle of spatial filtering, sometimes called beamforming [Gross et al., 2001; Robinson and Vrba, 1998; Sekihara et al., 2002; van Veen et al., 1997]. Using this criterion it is possible to suppress the source interference site by site in the source space. A significant difference from the former global approaches is that the spatial filtering does not require any prior knowledge or assumption about the source distribution. Another noteworthy difference between these two categories is that the former inverse solutions are usually linear and model-driven,¹ whereas the latter inverse solutions are nonlinear and data-driven.

However, there are also several drawbacks to spatial filtering methods: (1) minimization of the source power at a specific site does not guarantee that the estimated source power would be closest to the true source power at that

site, since contributions from the other sources might strengthen or weaken the source power at that site; (2) although minimization of the source power at the sites of the pass band reduces the contribution from the stop band of the spatial filter, the stop band responses are usually still significant; (3) cancellation of temporally correlated sources; (4) without explicit constraints, it is inconvenient to adopt confirmative information about source distribution from other modalities.

To improve the spatial accuracy and resolution of electromagnetic source imaging, the combination with other high spatial resolution modalities has been proposed, especially with functional MRI (fMRI), which provides high spatial resolution (millimeters) by detecting the hemodynamic changes induced by neuronal activity inside the brain [Dale et al., 2000; Liu et al., 1998; Phillips et al., 2002; Sato et al., 2004; Schoenfeld et al., 2003]. Although fMRI responses have been found to be approximately linearly related to the underlying neural electrical power in a local region [Logothetis et al., 2001; Wan et al., 2006], the general relationship between the neural current generators and fMRI signals is not clear. There are several gaps between fMRI activation maps and the electrical generators of electromagnetic fields: (1) the variable hemodynamic response efficiency on the different regions dissociates the quantitative relationship between fMRI signals and the neuronal activities [Logothetis and Wandell, 2004]; (2) fMRI activity spots do not quite match the positions of current sources due to the intrinsic venous vascular effect of fMRI signals, especially at low field strengths [Disbrow et al., 2000]; (3) the finite fMRI signal-to-noise ratio (SNR) makes some current sources invisible in the fMRI technique, especially at low field strengths [Liu et al., 1998]; (4) the electromagnetic field cancellation renders some fMRI-activated regions invisible in electromagnetic source imaging [Nunez and Silberstein, 2000]. These discrepancies argue against directly constraining the estimated source distribution using the fMRI information, as has been done previously [Dale et al., 2000; Liu et al., 1998; Phillips et al., 2002; Sato et al., 2004; Schoenfeld et al., 2003]. In short, it is not a trivial challenge to effectively make use of fMRI information in electromagnetic source imaging [Dale and Halgren, 2001; Nunez and Silberstein, 2000].

In this paper, we present a novel method based on the principle of spatial filtering to largely avoid the drawbacks of spatial filtering mentioned earlier and to provide high spatial accuracy and resolution of source localization. The improvement of spatial filtering in the current method is focused on two main points: (1) directly constraining the stop band responses of the spatial filter to effectively suppress the contributions from other sources, especially from the far sources; (2) indirectly imposing fMRI information as prior information about the source distribution to further improve the spatial accuracy of source localization, in such a way as to avoid the drawbacks of fMRI-biased constraints mentioned earlier. Our simulations and experimental results demonstrate that this spread function-constrained

¹The inverse operator is stereotyped throughout the entire source space and independent of the observed data.

and fMRI-guided spatial filtering method significantly improves spatial accuracy and resolution of electromagnetic source imaging, even in the presence of multiple simultaneously active sources. Most importantly, while the source localization is not significantly biased by invisible or incorrect fMRI information, it is significantly improved by the true fMRI information.

FORWARD PROBLEM

In the following sections, lowercase bold letters denote row vectors and uppercase bold letters denote matrices. The lead field $\mathbf{a}_i(\mathbf{x})$ of the sensor i , describing the sensor sensitivity from a unit current source at $\mathbf{x}$, is a three-element vector where each element corresponds to each of the three orthogonal dipole components. For the current sources $\mathbf{J} = (j(\mathbf{X}_1), j(\mathbf{X}_2), \dots, j(\mathbf{X}_n))$, where n is the number of sources, the measured signal from the sensor i is $v_i = \mathbf{A}_i^T \mathbf{J} + \varepsilon_i$, where $\mathbf{A}_i^T$ denotes the transpose of $\mathbf{A}_i = (\mathbf{a}_i(\mathbf{x}_1), \mathbf{a}_i(\mathbf{x}_2), \dots, \mathbf{a}_i(\mathbf{x}_n))$ and ε_i is observation noise. By collecting all sensors, it becomes

$$\mathbf{v} = \mathbf{A}\mathbf{J} + \varepsilon \quad (1)$$

where $\mathbf{v} = (v_1, v_2, \dots, v_m)^T$, $\mathbf{A} = (\mathbf{A}_1, \mathbf{A}_2, \dots, \mathbf{A}_m)^T$ and $\varepsilon = (\varepsilon_1, \varepsilon_2, \dots, \varepsilon_m)^T$, and m is the number of sensors. The matrix $\mathbf{A}$ is usually called the forward matrix or gain matrix. Generally speaking, accurate estimation of the current source at $\mathbf{x}$ is accomplished by finding an appropriate inverse operator $\mathbf{W}(\mathbf{x})$ that derives $\hat{\mathbf{j}}(\mathbf{x}) = \mathbf{W}^T(\mathbf{x})\mathbf{v}$ closest to the true current source $\mathbf{j}(\mathbf{x})$ at $\mathbf{x}$. In matrix formation, this is $\hat{\mathbf{J}} = \mathbf{W}\mathbf{v}$. Assuming both source $\mathbf{J}$ and observation noise ε are randomly distributed with zero mean, the measured data are also randomly distributed with zero mean.

SOURCE LOCALIZATION RESOLUTION AND AMBIGUITY

Here we distinguish between the two concepts of source localization resolution and ambiguity (or sensitivity). Source localization resolution refers to the fact that the observation noise maps to the source parameters errors. In contrast, source localization ambiguity refers to situations in which two different source configurations in the source space map to the same observation. Source resolution can be improved by reducing the observation noise, but source ambiguity cannot be reduced just by getting better data; only a priori or acquired knowledge can reduce it. Ultimately, the quality of the source localization depends on both the source ambiguity and resolution [Gross et al., 2003]. In the following inverse solution, the source localization ambiguity and resolution will be separately discussed and examined.

INVERSE SOLUTIONS

Mathematically, electromagnetic potential/field measurement can be thought of as representation of the brain current sources through the lead fields (the basis in the source space) by Eq. (1). If the lead fields were orthogonal, projection of an observation into a specific basis (one component of the lead fields) would lead to identification of a unique current source component. Unfortunately, the lead fields are highly correlated, especially in the case of EEG. The spatial ambiguity of the electromagnetic inverse solution is reflected in the fact that the current sources are largely smeared through the highly correlated lead fields. Thus, solving the source localization is equivalent to finding an optimal projector that minimizes the source contribution to the other positions.

Without observation noise, the estimated current sources are $\hat{\mathbf{J}} = \mathbf{R}_m \mathbf{J}$, where $\mathbf{R}_m = \mathbf{W}\mathbf{A}$, $\mathbf{R}_m$ is called the model resolution matrix [Backus and Gilbert, 1968; Grave de Peralta Menendez et al., 1997]. Thus, optimization of the estimated current sources close to the true current sources is

$$\min_{\mathbf{W}} \|\hat{\mathbf{J}} - \mathbf{J}\|^2 = \min_{\mathbf{W}} \|(\mathbf{R}_m - \mathbf{I})\mathbf{J}\|^2. \quad (2)$$

This can be achieved by minimizing the source component in each position. If one specific site at $\mathbf{x}_0$ in the source space is focused, then the optimization problem is reduced to

$$\min_{\mathbf{W}(\mathbf{x}_0)} \|\hat{\mathbf{j}}(\mathbf{x}_0) - \mathbf{j}(\mathbf{x}_0)\|^2 = \min_{\mathbf{W}(\mathbf{x}_0)} \|(\mathbf{r}_m(\mathbf{x}_0; \mathbf{x}) - \mathbf{i}_m(\mathbf{x}_0; \mathbf{x}))^T \mathbf{J}\|^2 \quad (3)$$

where $\mathbf{r}_m(\mathbf{x}_0; \mathbf{x})$ and $\mathbf{i}_m(\mathbf{x}_0; \mathbf{x})$ represent the rows of $\mathbf{R}_m$ and $\mathbf{I}$ corresponding to the point of $\mathbf{x}_0$, respectively.

If we constrain $\mathbf{r}_m(\mathbf{x}_0; \mathbf{x}) = \mathbf{i}_m(\mathbf{x}_0; \mathbf{x})$, then Eq. (3) becomes

$$\min_{\mathbf{W}(\mathbf{x}_0)} \|(\mathbf{r}_m^T(\mathbf{x}_0; \mathbf{x}))\mathbf{J}'\|^2 \quad (4)$$

where the prime symbol indicates the current source components and the model resolution vectors without the components at $\mathbf{x}_0$. It is convenient to consider a simple case of two source locations. In this case, the model resolution matrix is

$$\mathbf{R}_m = \begin{bmatrix} \mathbf{r}_{11} & \mathbf{r}_{12} \\ \mathbf{r}_{21} & \mathbf{r}_{22} \end{bmatrix}, \text{ and then the estimated sources are}$$

$$\begin{pmatrix} \hat{j}_1 \\ \hat{j}_2 \end{pmatrix} = \begin{pmatrix} \mathbf{r}_{11}\mathbf{j}_1 + \mathbf{r}_{12}\mathbf{j}_2 \\ \mathbf{r}_{21}\mathbf{j}_1 + \mathbf{r}_{22}\mathbf{j}_2 \end{pmatrix}, \text{ where } \mathbf{j}_1 \text{ and } \mathbf{j}_2 \text{ are the two true source components. With the constraint of the on-diagonal elements being the identity submatrices, the difference between the estimated and true sources becomes } \begin{pmatrix} \mathbf{r}_{12}\mathbf{j}_2 \\ \mathbf{r}_{21}\mathbf{j}_1 \end{pmatrix}.$$

Note that the discrepancy between the estimated source and the true source arises from the interference from the other sources.

Effective suppression of the interference from other sources can theoretically be achieved by optimally adjusting the model resolution spread function (RSF) compo-

nents according to the corresponding source strength. Unfortunately these sources are not known a priori. To partially suppress the interference from other sources, we can optimize a model RSF, such as the Backus–Gilbert method [Backus and Gilbert, 1968, 1970]. Obviously, this approach alone is not enough to effectively suppress the interference from other sources in terms of various possibilities of source distribution. Therefore, we additionally suggest minimizing the estimated source power at the point of interest at x_0 , similar to the other spatial filtering approaches, to restrict intensification by the other sources. Although optimization of the estimated source power itself does not guarantee minimization of the interference from other sources (note that the contribution from the other sources might also attenuate the estimated source power), the combination of the two approaches would largely suppress the source interference. Therefore, in this paper, we suggest a novel method based on the principle of spatial filtering to effectively suppress the interference from other sources by combining minimization of the estimated source power with a unit gain constraint at x_0 [van Veen et al., 1997] and suppression of the side lobes of the RSF by penalizing the off-central elements of $r_m(x_0; x)$ [Backus and Gilbert, 1968, 1970]. In mathematical formation,

$$\min_{W(x_0)} \{ \varepsilon \| \hat{j}(x_0) \|^2 + \lambda \| r_m k \|^2 \},$$

$$\text{subject to } r_m(x_0; x_0) = i_m(x_0; x_0) \quad (5)$$

where $k = \text{diag}(k_1, k_2, \dots, k_n)$ denotes the weighted kernel that penalizes the model resolution matrix components other than at the point of interest. Again it is helpful to consider the previous simple example. In that case, if the other source power is large, then minimizing the source power alone would not be sufficient to obtain the optimal solution; it is also necessary to reduce the model resolution matrix component associated with the other location.

By minimizing the corresponding Lagrange function (see Appendix), the inverse solution can be derived as

$$W(x_0) = \frac{(C_v + \lambda S)^{-1} A(x_0)}{A^T(x_0)(C_v + \lambda S)^{-1} A(x_0)} \quad (6)$$

where C_v denotes the data covariance matrix, $S = AHA^T$ denotes the model resolution spread matrix, and $H = kk^T$ denotes the diagonal penalization matrix. Thus the estimated source power is derived as

$$\| \hat{j}(x_0) \|^2 = \text{Tr}(W^T(x_0) C_v W(x_0)). \quad (7)$$

Without the latter item of RSF penalization in Eq. (5), the inverse solution is reduced to conventional spatial filtering [Robinson and Vrba, 1998; van Veen et al., 1997]. On the other hand, in formula it apparently differs from the Backus–Gilbert method in that the data covariance matrix replaces the noise covariance matrix in Eq. (6) [Backus

and Gilbert, 1968]. The regularization parameter λ can be determined by the trade-off curve [Backus and Gilbert, 1970] or L-curve method [Hansen, 1992].

Depending on the penalization matrix H , various inverse solutions can be derived within the above framework, as listed below.

- i. Dirichlet Spread Function: In this case $H = I$ (with no penalization of the resolution matrix), the resolution spread matrix is expressed as $S = AA^T$. The corresponding inverse solution is

$$W(x_0) = \frac{(C_v + \lambda AA^T)^{-1} A(x_0)}{A^T(x_0)(C_v + \lambda AA^T)^{-1} A(x_0)}. \quad (8)$$

This is similar to the minimum norm (MN) solution [Hamalainen and Ilmoniemi, 1984], but with normalization at each point of source space.

- ii. Identity Spread Function: In this case $S = I$, which assumes that $H = (A^T A)^{-1}$. However, this requirement of H could never be satisfied because the rank of the forward matrix A is far from full rank. The corresponding inverse solution is

$$W(x_0) = \frac{(C_v + \lambda I)^{-1} A(x_0)}{A^T(x_0)(C_v + \lambda I)^{-1} A(x_0)}. \quad (9)$$

This is the solution has been used in the dynamic imaging of coherent sources (DICS) method [Gross et al., 2001], as well as in the synthetic aperture magnetometry (SAM) method [Robinson and Vrba, 1998].

- iii. Backus–Gilbert Spread Function: In this case, $H = \text{diag}(d_1^2, d_2^2, \dots, d_n^2)$, where $d_i = |x_i - x_0|$. It is implemented to penalize the off-central elements of the resolution spread matrix. To circumvent the situation where the component of H at x_0 singularly becomes zero, it is convenient to adapt $H = \text{diag}\left(\frac{d_1^2 + \alpha^2}{\alpha^2}, \frac{d_2^2 + \alpha^2}{\alpha^2}, \dots, \frac{d_n^2 + \alpha^2}{\alpha^2}\right)$, where α is set to 1 and then the component at the point of x_0 is unit. With this constraint, the interference from sources that are much farther from the source of interest is more suppressed.

- iv. Gaussian Spread Function: Beyond the essential idea of the Backus–Gilbert method to suppress the interference from other sources, there are many options for penalizing the off-central elements of the resolution matrix. For example, in the Gaussian penalization matrix, $H = \text{diag}\left(e^{\frac{d_1^2}{\alpha^2}}, e^{\frac{d_2^2}{\alpha^2}}, \dots, e^{\frac{d_n^2}{\alpha^2}}\right)$, when α is set to 1 then the component at the point x_0 is unity. However, the rapid increase of the elements in the Gaussian spread function with the distances increasing usually results in the matrix $(C_v + \lambda S)$ singular. Hence, we will not discuss it further in this paper.

fMRI-GUIDED EEG/MEG INVERSE SOLUTION

As mentioned earlier, theoretically the bias of the estimated source at a specific site arises from the interference from other simultaneously active sources. Without a priori knowledge of the source distribution, an appropriate method is to minimize the current source power with a unit gain and penalize the model RSF, in order to suppress the interference from other simultaneously active sources, especially those far away from the point of interest. If it is possible to acquire some additional brain activity information through other modalities such as fMRI, then it is helpful to specifically draw more weights on those regions showing strong fMRI activation compared to other locations in the brain. This would effectively suppress the contribution from other active current sources. In contrast, if the activated regions inferred from fMRI signals originally have no current sources, the strategy of drawing more weights on these regions would not significantly bias the estimated source distribution, since originally there is no interference from that point to the other locations. More specifically, we can use the statistical parameter mapping results from the fMRI data, like T or F values, to incorporate into the weighted resolution matrix. Namely, the fMRI-weighted matrix is set to $\mathbf{H}_{\text{fMRI}} = \text{diag}(e^{t_1}, e^{t_2}, \dots, e^{t_n})$, where t_i represents the corresponding T or F values at the points within the activated regions and zeros outside these regions as well as at the point of interest. Finally, the penalization matrix becomes $\mathbf{H}_{\text{fMRI}} \times \mathbf{H}$, where $\mathbf{H}$ is defined in the previous session, and it could be each of those diagonal penalization matrices. In the latter part of this paper, only the case of the BG spread function will be discussed. The essential difference from the other methods combining fMRI information is that the current method does not directly impose the fMRI information into the source space, but only into the source interference space, in which the sources interfere with each other through the inverse operator. Consequently, the EEG/MEG source localization would not be significantly biased by false or invisible fMRI information, but it would be significantly improved by true fMRI information.

NOISE-NORMALIZED STATISTICAL SOURCE LOCALIZATION

Source localization resolution is dependent upon the observation noise. To account for the noise effect, the projected noise distribution in the source space is also calculated using Eq. (6), with the noise covariance matrix replacing the data covariance matrix. The ratio of the estimated source and noise power at each position is indexed as the function of noise-normalized source distribution [Robinson and Vrba, 1998; van Veen et al., 1997]. The noise-normalized power is F -distributed with three degrees of freedom for the numerator, and the degrees of freedom for the denominator is the number of time samples used to calculate the noise covariance matrix [Dale et al., 2000].

The corresponding source orientation is computed from the first principle eigenvector of the estimated source covariance matrix [Gross et al., 2001].

COVARIANCE MATRIX ESTIMATION

In practice, the data and noise covariance matrix are estimated from the measured data. The major difference in covariance matrix estimation from the other spatial filtering (or beamforming) methods is that in the current method, the current sources and observation noises are assumed to be zero-mean and Gaussian. This gives rise to the observed zero-mean and Gaussian data due to the linearity of the forward problem. Hence, the estimated covariance matrix is acquired as $\mathbf{C}_v = \frac{1}{N-1} \sum_{j=1}^N \mathbf{V}_j \mathbf{V}_j^T$, where N is the repeated number on observation of the same spatial spectrum and $\mathbf{V}_j$ is the j th observed data. Actually Eq. (6) requires only that $(\mathbf{C}_v + \lambda \mathbf{S})$, not $\mathbf{C}_v$, be nonsingular. Hence, it is not necessary that N must at minimum exceed the number of elements in the data vector. However, a large repeated number should be better to accurately estimate the covariance matrix.

REALISTIC HEAD MODEL

The simulations used in this paper were generated using a real EEG system with 56 scalp electrodes (64 channel BrainAmp, Brain Products GmbH, Munich, Germany) on an individual subject, the same as in the later real experimental setting. A high-resolution T1-weighted MRI image obtained by a 1.5 T scanner (176 sagittal slices of 256×256 matrix, isotropic voxel size: 1 mm, repeat time, TR: 2,000 ms; echo time, TE: 4 ms and flip angle, FA: 15°) was used to generate the head model. A 3D digitizer (Polhemus Iso-track) was used to detect the electrode positions over the subject's scalp outside the scanner room. The reconstructed electrodes' coordinates were matched to the head surface extracted from the subject's T1-weighted MRI image with respect to the anatomical landmarks of the head (nasion, right and left-preauricular points). The mismatch of electrodes' positions is within 3.5 ± 2.5 mm.

A realistic head model was generated by segmenting the high-resolution T1-weighted MRI image into skin, skull, and CSF. The skin segment was obtained by a simple threshold method, and the CSF segment was obtained from the combination of the three compartments of gray matter, white matter, and CSF segmented by SPM2 (Wellcome Department of Imaging Neuroscience, UCL), while the skull segment was obtained by hand-tracing each slice. The three segments were respectively meshed using 1,260 vertexes and 2,500 triangles (Fig. 1). The distributed source model was generated uniformly within the gray and white matter with a grid resolution of $6 \times 6 \times 6$ mm³ (the total number of grids was 6,418) and it was orientation-unconstrained [the fact that the electrode positions generally mismatch the true positions on the subject head results in

Figure 1.

The meshed surfaces of the CSF, skull, and skin of an individual subject's head (from innermost to outermost). Each surface was generated in the same coordinate system with 1,260 vertexes and 2,500 triangles. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

estimated sources probably emerging in the white matter, see detailed discussion in Hillebrand and Barnes, 2003]. The forward matrix A was computed using the boundary element method (BEM) with Galerkin weighting method and linear basis function² [Mosher et al., 1999]. The relative conductivities for the skin, skull, and brain (including CSF) were conventionally set to 1:1/80:1 [Rush and Driscoll, 1969]. The EEG signals were transformed with an average reference.

SIMULATIONS

A series of simulations with a single dipole source or multiple dipole sources, which were at a specific time point or at a specific frequency point, were carried out to evaluate the performance of the proposed method. In each simulation the dipoles randomly have the same strength and orientation except for specification. In the cases of simulations without noise, the normalized source powers were calculated like a noise-normalized source power calculation by setting the noise covariance matrix to an identity matrix.³ The regularization parameter λ in Eq. (6) was

²<http://neuroimage.usc.edu/brainstorm/>.

³The estimated spatial spectrum in the source space is weighted by the lead field $A(x_0)$. For locations far from any scalp electrode, the elements of $A(x_0)$ are generally small, so the estimated source power will be large. Inversely, for locations close to an electrode, the elements of $A(x_0)$ are large, so the estimated source power will be small. To compensate this non-uniform effect, the source power must be normalized even in the cases of noiseless simulations.

determined by the trade-off curve. The value was set to $\lambda = \eta = \text{Tr}(C_v)/\text{Tr}(S)$ throughout these simulations. The fMRI-activated regions of interest (ROIs) were assumed to be spheres with radius of 20 mm and the fMRI weights were uniformly set to 1,000, approximately corresponding to a T or F value of 7. The source spatial accuracy was quantified as the distance between the peak of the estimated source profile and the true source position, whereas the source spatial resolution was evaluated by the full width at half maximum (FWHM) of the estimated source profile, which was fitted with a Lorentzian line shape function [Gross et al., 2003].

SINGLE DIPOLE SOURCES

Three samples of the single-dipole source simulations in the visual, motor, and prefrontal cortex are shown in Figure 2. All spatial filtering methods addressed in this paper exactly reconstructed the true source positions and orientations with no exceptions (500 simulations, the other data are not shown). Only the widths of the point spread functions (PSF) or FWHMs are slightly different (Fig. 12). The identity spread function (ID) gives a narrower PSF than the Dirichlet spread function (DI) and the Backus–Gilbert spread function (BG). These accurately estimated results are consistent with the fact that the single dipole source has no interference from other sources, but the reason why the contributions from the single source to the other positions are also efficiently suppressed is not yet clear (see Discussion).

MULTIPLE DIPOLE SOURCES

In most cases, cognitive activation probably involves a cortical network comprising several simultaneously active sources, not just a single active source. Hence, the multiple dipole source simulations are important to evaluate the potential application of the proposed method in real experiments. Without losing generality, we simply chose two-dipole sources as examples; 500 couples of dipole sources uniformly distributed within the source grids were randomly selected (Fig. 3). The performance of the proposed Backus–Gilbert spread function-constrained method was compared with the other spread function methods. The properties dependent on the fMRI information compatibility and the regularization parameter λ were first investigated with no noise effect, and then with the observation noise effect.

Six sets of calculations were carried out using the same simulated source database to compare the methods and to investigate the fMRI information compatibility effect. These are (1) DI; (2) ID; (3) BG with no fMRI information; (4) BG with completely mismatching fMRI information; (5) BG with partially compatible fMRI information; (6) BG with fully compatible fMRI information. The invisible fMRI activated regions were randomly selected in each simulation.

Figure 2.

The single dipole source simulations at the sites of the prefrontal cortex (a), the motor cortex (b), and the visual cortex (c) (unthresholded). From left to right: the true single-dipole sources, the results of the Backus–Gilbert spread function (BG) method, the identity

spread function (ID) method, and the Dirichlet spread function (DI) method. All methods provide exact source localization at the true source positions.

RSF CONSTRAINTS

The simulation results are shown in Figure 4. The FWHM distribution at the bottom of Figure 4 is only collected from those reconstructed dipoles with spatial errors smaller than 40 mm. The source spatial accuracy and resolution by the BG spatial filter (with no fMRI information) are significantly better than the DI and ID spatial filters (t -test, $P < 0.012$). About 50% of the dipoles (30% having zero spatial errors) were precisely localized within the range of 10 mm by the BG method (the FWHM is 5.8 ± 2.5 mm), while only 28% (10% having zero spatial errors) were localized within the same range by the DI method (the FWHM is 8.9 ± 3.2 mm), and only 5% (no dipoles with zero spatial errors) were localized within the same range by the ID method (the FWHM is 11.2 ± 4.6 mm). About 30% of dipoles could not be reconstructed or were localized over 40 mm away from the true source positions in the BG method, while 46 and 48% dipoles could not be

accurately localized in the DI and ID methods, respectively. These simulation results demonstrate that the Backus–Gilbert spread function-constrained spatial filter is much more effective in suppressing the interference from other sources than the Dirichlet and identity spread function-constrained spatial filters are. One example is shown in Figure 5, in which the two dipoles have different strengths but the same orientation.

fMRI INFORMATION

Equipped with different fMRI information, the spatial accuracy and resolution of source localization by the Backus–Gilbert RSF-constrained spatial filter would be varied. In particular, the invisible fMRI information could adversely affect the results [Liu et al., 1998]. To evaluate the extent to which our proposed method of incorporating fMRI information in the electromagnetic source imaging

Figure 3.

The uniformly random source distribution ($N = 500 \times 2$) used in the two-dipole source simulations [(a), the positions index source grids]. The distribution of the two-dipole source distances is Gaussian [(b), mean = 78.5 mm, variance = 29.0 mm].

utilizes true fMRI information and resists incorrect fMRI information, we compared the results of simulations from sets (3–6) defined earlier (Fig. 4). The source localization spatial errors (accuracy) between the case with no fMRI information and the case with completely mismatching fMRI

information were not significantly different (t -test, $P > 0.36$). The accuracy in the case with fully compatible fMRI information was significantly better than that in the partially compatible fMRI information case (t -test, $P < 0.03$), which in turn was better than that found in cases with no

Figure 4.

The distribution of the distances between the peaks of estimated sources and the true source positions (top), and the distribution of estimated sources' FWHMs (bottom, in which the distances between the peaks of estimated sources and the true source

positions are lower than 40 mm) in the six sets of two-dipole source simulations: (1) DI; (2) ID; (3) no fMRI BG; (4) completely fMRI-mismatched BG; (5) partially fMRI-compatible BG; (6) fully fMRI-compatible BG.

Figure 5.

One example of the two-dipole source simulations (maximum projected images, unthresholded): One dipole source is placed at the site of the visual cortex and the other one is placed at the site of the motor cortex. From top to bottom: the true two-dipole sources, BG-fMRI, BG, ID, and DI.

Figure 6.

The estimated source orientation difference distribution (mean = 4.5°) in the case of two-dipole source simulations using the BG spatial filtering with fully compatible fMRI information. The angle is defined as the difference between the estimated source orientation and the true source orientation ($[0^\circ, 180^\circ]$).

fMRI information or completely mismatching fMRI information (t -test, $P < 0.07$). In contrast, the spatial resolutions (FWHMs) show no significant differences among the four types (t -test, $P > 0.42$). Moreover, the estimated dipole source orientations are quite close to the true source orientations (Fig. 6). Taken together, these results show that the method of imposing fMRI information onto the source interference space greatly improves the spatial accuracy of source localization when compatible fMRI information is used, and does not significantly bias the results when incompatible fMRI information is used. The spatial resolutions (FWHM), however, do not significantly vary with the fMRI information compatibility.

THE REGULARIZATION PARAMETER

Like the Backus–Gilbert method [Backus and Gilbert, 1970], the regularization parameter λ is a trade-off between inverse resolution and stability. In the case of the BG spread function constrained spatial filter, a relatively higher regularization parameter value would increase the source localization resolution (accuracy), but decrease its stability. Alternatively, a relatively smaller value would increase its stability, but decrease its resolution. Our simulations confirm this anticipation with the parameter values 0.01η , η , and 100η ($\eta = \text{Tr}(C_v)/\text{Tr}(S)$), in the condition of fully compatible fMRI information (Fig. 7). When the parameter value is 100η , although the source spatial accuracy

(mean, $\mu = 4.9$ mm; standard deviation, $\sigma = 8.5$ mm, spatial errors within 40 mm) and spatial resolution (FWHM, $\mu = 4.6$ mm, $\sigma = 3.3$ mm) are slightly better than the case of η (spatial accuracy, $\mu = 5.6$ mm, $\sigma = 8.2$ mm, not significantly different $P > 0.6$; FWHM, $\mu = 6.1$ mm, $\sigma = 3.6$ mm, significantly different, $P < 0.25$), the ratio of unrecoverable dipole sources does increase (28 and 16% in the cases of 100η and η , respectively). When the parameter value is changed to 0.01η , the source spatial accuracy and resolution are apparently reduced (spatial accuracy, $\mu = 10.8$ mm, $\sigma = 9.3$ mm, $P < 0.20$; FWHM, $\mu = 7.8$ mm, $\sigma = 3.2$ mm, $P < 0.22$). Among the unrecoverable dipole sources (17%), most were localized with spatial errors larger than 40 mm, which is different from the other two cases where most were missed. Therefore, we confirm that selection of the regularization parameter value close to η gives optimal balance between the spatial accuracy and stability. These simulations also indicate that the results are not sensitive to the regularization parameter λ .

SNR-DEPENDENT SPATIAL RESOLUTION

In this section, we investigate the source spatial resolution dependence on the observation noise. The observation noise was assumed to be additive, Gaussian, and spatially uncorrelated. The noise covariance matrix is expressed as $C_e = I \frac{\text{Tr}(C_e)}{m \text{SNR}^2}$, where I is the identity matrix, m is the number of channels, and SNR is the assumed signal to noise ratio. We chose six SNR ratios (2, 5, 7, 10, 15, and 20, in addition to inf) in our simulations. One-hundred pairs of dipole sources were selected from those simulations where the estimated sources are exactly located at the true source positions using the Backus–Gilbert RSF-constrained spatial filtering with fully compatible fMRI information. In each simulation case, the random noise with the same variance was added to the EEG data, which were generated from the assumed sources through the gain matrix, and the simulations were repeated 50 times. The spatial resolution (FWHM) within each SNR ratio was averaged. The results are shown in Figure 8. The estimated source spatial accuracy did not significantly change with SNR. The averaged FWHM (characterizes spatial resolution) decreased with increasing SNR and decreased more slowly from an SNR of 10. These results imply that even at a moderately low SNR (around 10), this proposed method would robustly reconstruct the current sources.

THREE DIPOLE SOURCES

The simulation results would be more complex with more multiple dipole sources due to an increase in source interference. Here we give an example of simulations with three dipole sources. The sources were simultaneously placed on one side of the brain at the sites of the visual cortex, temporal cortex, and prefrontal cortex (Fig. 9a). The estimated results show that only the BG-constrained and fMRI-guided spatial filtering method could accurately

Figure 7.

The effects of regularization parameter λ on the estimated sources in the case of two-dipole source simulations using the BG spatial filtering with fully compatible fMRI information ($\eta = \text{Tr}(\mathbf{C}_v)/\text{Tr}(\mathbf{S})$). The distribution of the distances between the

peaks of estimated sources and the positions of true sources (top), and the distribution of estimated sources' FWHMs (bottom, in which the distances between the peaks of estimated sources and the true source positions are lower than 40 mm).

reconstruct the multiple simultaneously active sources (Fig. 9b). In the BG alone spatial filtering method, the source positions at the prefrontal and temporal cortex were mismatched with the true source positions and the source at the site of visual cortex was missed (Fig. 9c), while the DI and ID methods provided extensively diffuse source distributions that even emerged on the opposite side, far away from the positions of true sources (Fig. 9d,e).

REAL EXPERIMENTAL APPLICATION

We applied the Backus–Gilbert RSF-constrained and fMRI-guided spatial filtering method to a real experiment. A right-handed normal male subject (age 22 years) participated after giving informed consent in accordance with Tohoku University Institutional Review Board. The subject performed a fast repetitive right-hand grasping movement that was cued by right-field visual checkerboard stimuli

flickering at 4 Hz. This visual stimulus-cued hand movement continued for 8 s, followed by a rest stage of fixation for 16 s. This cycle was repeated 30 times. The subject practiced synchronizing his hand movement to visual stimuli prior to fMRI and EEG recordings. fMRI and EEG data were recorded separately.

The T_2^* -weighted fMRI images were acquired using a 1.5 T scanner, equipped with a circular head coil (Siemens Magnetom Symphony, Erlangen, Germany), with a gradient echo planar sequence (repeat time, TR: 2,000 ms; echo time, TE: 40 ms; flip angle, FA: 85°; field of view, FOV: 192 mm; voxel size, $3.0 \times 3.0 \times 6.0 \text{ mm}^3$; 20 sagittal slices with 0.6 mm gap and bandwidth, 2,170 Hz/pixel). The fMRI images preprocessing (realignment, slice timing adjustment, coregistration, and spatial smoothing with 6-mm isotropic FWHM Gaussian kernel) and statistical analysis based on the individual subject's brain were carried out using statistical parametric mapping (SPM2, Wellcome

Figure 8.

The FWHM depends on SNR in the case of two-dipole source simulations using the BG spatial filtering with fully compatible fMRI information (100 pairs of two-dipole sources; the squares indicate the mean, and error bars indicate the standard deviation).

Department of Imaging Neuroscience, UCL). For convenience, the statistical results are transformed and shown in the MNI template brain (corrected $P < 0.001$, Fig. 11a).

The same EEG system was used as in the previous simulations. The EEG data were sampled at 256 Hz with a band-pass filter (BPF) between 0.5 and 125 Hz. The impedances of all channels were maintained below 5 k Ω . To reduce noise, after artifact removal, the steady-state evoked potentials and selected control EEG data at rest with the same duration as the activated state were averaged across trials. The topography at one peak of the oscillatory evoked potentials is shown in Figure 10. Spectrograms (Hanning window segment length 1 s, overlapping by half a segment length) in the activated and rest states were calculated using Welch's method of spectral density estimation [Welch, 1967]. The spectrum of the steady state evoked potentials is highest at the visual stimulation frequency (4 Hz) and its harmonic frequency (8 Hz). We selected the spectrum band at the range of 4.0 ± 1.0 Hz to estimate the current sources. Finally, the data and noise covariance matrix were averaged across successive data segments.

The Backus–Gilbert RSF-constrained spatial filtering with and without fMRI information was applied to estimate the EEG current sources. The results are also transformed and shown in the MNI template brain (Fig. 11b,c). The fMRI-activated regions are primarily located at Pre-SMA (supplementary motor area, $[-2, -8, 68]$), left SMC (primary sensorimotor cortex, $[-42, -24, 54]$), and left V1

(primary visual cortex, $[-8, -96, -6]$), regions consistent with the previous functional imaging study [Jenkins et al., 1994]. It is usually difficult to separately localize synchronously active sources using spatial filtering [van Veen et al., 1997, but see Gross et al., 2001]. Although the

Figure 9.

One example of the three-dipole source simulations (unthresholded): One dipole source is placed at the site of the visual cortex, another one is placed at the site of the temporal cortex, and the third one is placed at the site of the prefrontal cortex. From top to bottom: the true dipole sources, BG-fMRI, BG, ID, and DI.

The EEG topography at one peak of steady-state evoked potentials of right-hand movements cued by right-field visual stimulation flickering at 4 Hz and the spectrum of the two selected channels (C_1 and O_1).

the other sources at the site of the single source, this single source might have interference at other sites. To investigate the underlying reason, we compared the RSF and the estimated source distribution from the single and multiple

It may initially seem strange that the DI and ID methods could precisely reconstruct the true sources in the single-dipole source simulations, but would usually fail in the multiple-dipole source simulations. In the single-dipole source simulations, although there is no interference from

Figure 12.

The resolution spread function (RSF, upper) profile and the point spread function (PSF, lower) profile normalized by their maximum in the case of a single-dipole source simulation at the site of the

visual cortex (see Fig. 2c). (a) ID; (b) DI; (c) BG. The PSF profiles are fitted by a Lorentzian line shape function [gray lines, the widths are 0.8, 2.7, and 4.9 mm, respectively, from (a) to (c)].

source simulations. As shown in Figure 12, it is apparent that the estimated source distribution narrowly concentrates at the single source position in the DI and ID methods, but the elements of RSF are quite large even at positions far from the single source.⁴ It turned out that the precise localization of the single sources using these methods is not caused by “good” narrow-band spatial filters, but by the property of orthogonality between the resolution matrix rows and the single source vector. The orthogonal property is conserved across a variety of single sources. This orthogonal property results from the strategy of minimization of source power at each site of source space using spatial filtering. In this sense, stereotyped (model-driven) inverse operators might not be appropriate to effectively suppress the source interference in terms of the variety of sources, even in the single source situations. However, in two-dipole source situations, this orthogonal property is not generally maintained and the source interference on the other positions is also significant and extensive using the ID and DI methods (Fig. 13). Therefore, the way to suppress the source interference in the multiple active sources is to restrict the RSF width. In this paper,

we suggest using the Backus–Gilbert RSF constraint to fulfill this goal.

fMRI Information Integration

In cases where the sources are spatially close, the Backus–Gilbert RSF constraint alone is not sufficient to suppress the mutual source interference. As seen in the real experimental example, using this constraint alone, the active sources in the motor cortex could not be separated and correctly reconstructed. In these situations, incorporating the fMRI information into the Backus–Gilbert RSF constraint is essential to suppress their mutual source interference. Our simulations demonstrated that the benefit of this method of integrating fMRI information is that it resists the false or invisible fMRI information bias. Generally speaking, this approach of source reconstruction conservatively utilizes the fMRI information as the possible source locations. However, in some cases, the regions having strong fMRI responses would be certain to have active sources. Therefore, the combination of both sides would be the next step in imposing the fMRI information onto both the source space and source interference space. In addition, the cancelled current sources could not be retrieved by the currently proposed method. This issue can only be solved by proper experimental design to avoid potential/field cancellation.

⁴Here RSF is defined as $RSF(x, x_0) = \frac{1}{3} \text{Tr}[W(x)A(x_0)]$.

Figure 13.

The resolution spread function (RSF, upper) profile and the noise-normalized source power in the example of a two-dipole source simulation (see Fig. 5). The total number of source grids is 6,418. The true dipole sources are placed at the grids num-

bered 1,848 and 5,715. (a) the RSF at the 1,848th grid; (b) the RSF at the 5,715th grid; (c) the normalized source power. The ratio of the true dipole source powers at the 1,848th and 5,715th grids is 1:1/4.

Reconstruction of Correlated Sources

The notorious drawback of conventional spatial filtering is correlated source cancellation [van Veen et al., 1997, but see Gross et al., 2001]. This usually limits its application in situations where there are multiple correlated active sources. The correlated source cancellation results from larger mutual source interference between the correlated sources than the uncorrelated sources [see Eq. (29) in van Veen et al., 1997]. As shown earlier, in the EEG system the source interference in spatial filtering without the spread function constraint is generally significant even when the sources are far from each other. A proper constraint on the spread function gives rise to effective suppression of source interference regardless of source correlation. Therefore, our proposed method can precisely reconstruct the correlated sources as well. Gross et al. [2001] also proposed a way of suppressing the source interference to localize coherent sources (the same as the identity spread function-constrained spatial filtering in this paper). However, the results of our simulations with the EEG system show that its efficiency is limited, even more so than the DI method, in which the spread function is not penalized. Compared with the MEG system, the frequent failures of the ID method in

the EEG system might be partially caused by much more highly correlated EEG lead fields. Recently, the modification of the conventional spatial filtering methods to alleviate the correlated source cancellation has also been addressed by using higher order covariance matrices [Huang et al., 2004] or the “dual source model” [Brookes et al., 2007]. However, the success of their methods was largely dependent on the features of correlated sources.

Spatial Accuracy and Resolution of Electromagnetic Source Imaging

The spatial accuracy and resolution limit of electromagnetic source imaging might be uncertain. It varies case-by-case, depending on the true source distribution. We could not guarantee the estimated source spatial accuracy given any electromagnetic measurement. However, the optimal inverse solution of electromagnetic source imaging does exist in a statistical sense. As has been shown here, the Backus–Gilbert RSF-constrained and fMRI-guided spatial filtering is better than the other spatial filtering methods examined in this paper. In our two-dipole source simulations, 70% of sources could be precisely localized within 10 mm spatial accuracy. With increasing complexity of

source distribution, the spatial accuracy deteriorated. Finally, the spatial accuracy and resolution also depends on the brain, skull, and skin conductivities [Oostendorp et al., 2000], the mismatches of electrode/sensor positions [Hillebrand and Barnes, 2003], the number of sensors [Vrba and Robinson, 2001], and the measured data SNR [Liu et al., 1998] in real experiments. Although in this paper we only discussed its application in the EEG system, our method could be also applied in the MEG system, likely with better source spatial accuracy and resolution because of the absence of the skull smearing effect.

CONCLUSION

In this paper, we describe an improved spatial filtering method that combines Backus–Gilbert methodology with fMRI information to accurately reconstruct dynamic electromagnetic source imaging. Through effective suppression of source interference, this new method can be used to obtain better spatial accuracy and resolution than other spatial filtering methods, even in cases of correlated sources. Our method of imposing fMRI information into the source interference space resists false or invisible fMRI information bias, while using true fMRI information to improve the spatial accuracy of source localization.

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APPENDIX

The L^2 -norms in Eq. (5) can be expressed in matrix form as

$$\begin{aligned} \varepsilon[\|\hat{\mathbf{j}}(\mathbf{x}_0)\|^2] &= \varepsilon\{\text{Tr}[(\mathbf{W}^T(\mathbf{x}_0)\mathbf{v})(\mathbf{W}^T(\mathbf{x}_0)\mathbf{v})^T]\} \\ &= \varepsilon\{\text{Tr}[\mathbf{W}^T(\mathbf{x}_0)\mathbf{v}\mathbf{v}^T\mathbf{W}(\mathbf{x}_0)]\} \\ &= \text{Tr}[\mathbf{W}^T(\mathbf{x}_0)\mathbf{C}_v\mathbf{W}(\mathbf{x}_0)] \end{aligned} \quad (\text{A1})$$

where $\mathbf{C}_v = \varepsilon[\mathbf{v}\mathbf{v}^T]$ denotes the data covariance matrix, and

$$\begin{aligned} \varepsilon[\|\mathbf{r}_m\mathbf{h}\|^2] &= \text{Tr}[(\mathbf{W}^T(\mathbf{x}_0)\mathbf{A})\mathbf{k}((\mathbf{W}^T(\mathbf{x}_0)\mathbf{A})\mathbf{k})^T] \\ &= \text{Tr}[\mathbf{W}^T(\mathbf{x}_0)\mathbf{A}\mathbf{H}\mathbf{A}^T\mathbf{W}(\mathbf{x}_0)] \\ &= \text{Tr}[\mathbf{W}^T(\mathbf{x}_0)\mathbf{S}\mathbf{W}(\mathbf{x}_0)] \end{aligned} \quad (\text{A2})$$

where $\mathbf{H} = \text{diag}(k_1^2, k_2^2, \dots, k_n^2)$ and $\mathbf{S} = \mathbf{A}\mathbf{H}\mathbf{A}^T$ denotes the spread matrix. Alternatively, Eq. (5) is expressed as

$$\begin{aligned} \min_{\mathbf{W}(\mathbf{x}_0)} \{ &\text{Tr}[\mathbf{W}^T(\mathbf{x}_0)(\mathbf{C}_v + \lambda\mathbf{S})\mathbf{W}(\mathbf{x}_0)]\}, \\ \text{subject to } &\mathbf{W}^T(\mathbf{x}_0)\mathbf{A}(\mathbf{x}_0) = \mathbf{I}. \end{aligned} \quad (\text{A3})$$

The solution to Eq. (A3) can be obtained using the Lagrange multiplier method. Let $2\mathbf{L}$ be a 3×3 matrix of the Lagrange multiplier. The cost function of Eq. (A3) is

$$\begin{aligned} F(\mathbf{W}, \mathbf{L}) &= \text{Tr}[\mathbf{W}^T(\mathbf{x}_0)(\mathbf{C}_v + \lambda\mathbf{S})\mathbf{W}(\mathbf{x}_0) \\ &\quad + (\mathbf{W}^T(\mathbf{x}_0)\mathbf{A}(\mathbf{x}_0) - \mathbf{I})2\mathbf{L}]. \end{aligned} \quad (\text{A4})$$

Minimization of the cost function is to find a local extremism that satisfies

$$\frac{\partial F}{\partial \mathbf{W}} = (\mathbf{C}_v + \lambda\mathbf{S})\mathbf{W}(\mathbf{x}_0) + \mathbf{A}(\mathbf{x}_0)\mathbf{L} = 0. \quad (\text{A5})$$

Thus, the solution to Eq. (A5) is

$$\mathbf{W}(\mathbf{x}_0) = -(\mathbf{C}_v + \lambda\mathbf{S})^{-1}\mathbf{A}(\mathbf{x}_0)\mathbf{L}. \quad (\text{A6})$$

By substituting $\mathbf{W}(\mathbf{x}_0)$ in the constraint $\mathbf{W}^T(\mathbf{x}_0)\mathbf{A}(\mathbf{x}_0) = \mathbf{I}$, the Lagrange multiplier matrix $\mathbf{L}$ is obtained as

$$\mathbf{L}^T = -[\mathbf{A}^T(\mathbf{x}_0)(\mathbf{C}_v + \lambda\mathbf{S})^{-1}\mathbf{A}(\mathbf{x}_0)]^{-1} \quad (\text{A7})$$

and substituting Eq. (A7) into Eq. (A6) yields the inverse solution

$$\mathbf{W}(\mathbf{x}_0) = \frac{(\mathbf{C}_v + \lambda\mathbf{S})^{-1}\mathbf{A}(\mathbf{x}_0)}{\mathbf{A}^T(\mathbf{x}_0)(\mathbf{C}_v + \lambda\mathbf{S})^{-1}\mathbf{A}(\mathbf{x}_0)}. \quad (\text{A8})$$