Published in final edited form as:

J Neural Eng. 2011 October ; 8(5): 056002. doi:10.1088/1741-2560/8/5/056002.

Hierarchical beamformer and cross-talk reduction in electroneurography

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Abstract

Electroneurography (ENG) is a method of recording neural activity within nerves. Using nerve electrodes with multiple contacts the activation patterns of individual neuronal fascicles can be estimated by measuring the surface voltages induced by the intraneural activity. The information about neuronal activation can be used for functional electric stimulation (FES) of patients suffering of spinal chord injury, or to control a robotic prosthetic limb of an amputee. However, the ENG signal estimation is a severely ill-posed inverse problem due to uncertainties in the model, low resolution due to limitations of the data, geometric constraints, and the difficulty to separate the signal from biological and exogenous noise. In this article, a reduced computational model for the forward problem is proposed, and the ENG problem is addressed by using beamformer techniques. It is shown that the beamformer algorithm can be interpreted as a version of the classical Backus-Gilbert algorithm. Furthermore, we show that using a hierarchical statistical model, it is possible to develop an adaptive beamformer algorithm that estimates directly the source variances rather than the voltage source itself. The advantage of this new algorithm, e.g., over a traditional adaptive beamformer algorithms is that it allows a very stable noise reduction by averaging over a time window. In addition, a new projection technique for separating sources and reducing cross-talk between different fascicle signals is proposed. The algorithms are tested on a computer model of realistic nerve geometry and time series signals.

Keywords

neural recording; electrostatic inverse problem; regularization; hierarchical model; neural prosthetics

1 Introduction

Minimally invasive recording of electromagnetic signals of the peripheral nerves is a challenging problem with enormous potentials in biomedical engineering. The intact

peripheral nerves of an amputee carry both afferent and efferent information that could be used to control a robotic prosthetic limb; functional electric stimulation (FES) of intact muscles of spinal cord injury patients could make use of the nerve signal, helping e.g., to regain bladder control or improve mobility in a case of a foot drop ([13, 15]).

Chronically implanted microelectrodes for recording neural signals have been tested, and success to maintain their functionality for extensive periods of time has been reported in the literature [17]. However, the long-term stability has been achieved mostly with intracortical electrodes as a part of brain computer interfaces with minimal risk for movement-induced damage such as chronic inflammatory responses due to tethering of the array ([3, 18]). In peripheral nerves, the movement induced instability and damage is likely to be a more significant issue. Indeed, it has been reported that invasive methods to read the nerve signal by intruding the protective perineurium may incur damage to the nerve and increase the risk of infections ([11]), and therefore non-penetrating methods have an appeal. On the other hand, identifying the neuronal activity of different fascicles within a nerve from measurements on the surface of the nerve poses a remarkable challenge from the point of view of both data collection and interpretation ([9, 10, 14, 19, 20]).

The inverse problem of data interpretation in electroneurography (ENG) suffers from all possible shortcomings: the data are insufficient for identifying a unique source distribution; the signal is corrupted by both exogenous and biological noise that are difficult to identify and model; the problem is ill-posed, meaning that even small errors may propagate to the computed estimates and if not properly regularized, the estimates are useless. Being an electromagnetic inverse source problem, ENG has several characteristics in common with the widely studied EEG and MEG modalities ([2, 12]), therefore it is no wonder that computational methods developed for brain imaging have found their way to peripheral nerve imaging, see, e.g. [20, 21]. Nonetheless, numerical simulations reveal that improvement of the resolution of the inversion algorithms, in particular when several fascicles are simultaneously activated remains to be a challenge.

The identification of nerve activation by voltage measurements relies on a computational model that, while simple enough to not require excessively expensive computations to be suitable for real time processing, still accounts for sufficient details of the signal generation to capture the complexity of the signal. The need for a relatively fast computational forward model is particularly relevant when there is a danger that the cuff electrodes may move with respect to the nerve due to movements of the patient.

In the present article, a computational forward model based on Maxwell's equations is first presented. It is shown that with relatively natural symmetry assumptions about the nerve structure, it is possible to reduce the three-dimensional computational problem into a two-dimensional model by averaging the voltages over the axial direction. This model is then used to investigate the resolution of a variant of the beamformer algorithm ([16]) similar to the one applied in [20] to the ENG problem. A significant problem in ENG is the poor signal-to-noise ratio. Since the time series signal itself due to nerve activity is noisy, a simple signal averaging cannot be used to reduce the noise. In this article, we demonstrate that by modeling the signal by a hierarchical statistical model with unknown spatial variance, it is possible to modify the problem so that the beamformer algorithm estimates directly the spatial covariance from the squared average of the signal. This formulation allows an effective noise reduction and the resulting algorithm is significantly robust to high additive noise. Finally, a new adaptive algorithm for reducing cross-talk between estimates of different source activities is proposed, and its viability is demonstrated with simulations based on a realistic dynamic model for neuronal stimulation.

2 Reduced static model

Let $\Omega \in \mathbb{R}^3$ denote a cylindrical domain modeling the segment of the nerve within the cuff equipped with strip electrodes. The cross section of the cylinder is denoted by D and the length of it by h . The coordinate system is chosen so that the z -axis is parallel to the axis of the cylinder, the plane $z = 0$ cutting it in the middle so that we may write $\Omega = D \times [-h/2, h/2]$. In our computational model, D is a rectangle, and the electrodes are strips parallel to z -axis along the long edges of the bottom rectangle, see Figure 1.

We separate the neuronal activity into a spatial and temporal part, the spatial part being governed by Maxwell's equations under quasi-static approximation, allowing to express the electric field in terms of a voltage potential. Let $u = u(x, y, z)$ denote the voltage potential in Ω . If $\sigma = \sigma(x, y, z)$ is the electric conductivity in Ω , Maxwell's equations at steady state yield

$$\nabla \cdot (\sigma \nabla u) = \Phi$$

, where $\Phi = \Phi(x, y, z)$ is modeling the sources within Ω . Because the sources are the active nodes of Ranvier within the cuff region under the electrodes, we shall model them by a finite number of focal sources,

$$\Phi(x, y, z) = \sum_{j=1}^n \alpha_j \delta(x - x_j) \delta(y - y_j) \delta(z - z_j)$$

, where $(x_j, y_j) \in D$, $-h/2 < z_j < h/2$, see Figure 1. The potential in Ω may depend on sources outside the domain Ω . The effect of these sources is modeled by appropriate boundary conditions.

On the lateral sides $S = \partial\Omega \times [-h/2, h/2]$ of the cylinder, we assume homogenous Neumann boundary conditions,

$$\sigma \frac{\partial u}{\partial n} \Big|_S = 0$$

, which is tantamount to assuming that the cuff is an insulator. On the top and bottom of the cylinder, however, the current flux does not vanish. In fact, if we assume that a saltatory potential signal propagates along an axon passing through the cuff, the active nodes of Ranvier outside Ω will induce a current through the parallel ends of the cylinder. To account for this phenomenon, we write

$$\sigma \frac{\partial u}{\partial n} \Big|_{x=\pm h/2} = \psi_{\pm}(x, y)$$

, where $\psi_{\pm}$ is the current flux density.

To simplify the model, let us assume that the conductivity within Ω is constant in z -direction, $\sigma = \sigma(x, y)$. Define the average voltage $v = v(x, y)$,

$$v(x, y) = \frac{1}{h} \int_{-h/2}^{h/2} u(x, y, z) dz$$

. By writing

$$\begin{aligned}\nabla \cdot (\sigma \nabla u) &= \underbrace{\frac{\partial}{\partial x} \left(\sigma \frac{\partial u}{\partial x} \right) + \frac{\partial}{\partial y} \left(\sigma \frac{\partial u}{\partial y} \right)}_{=\nabla_2 \cdot (\sigma \nabla_2 u)} + \sigma \frac{\partial^2 u}{\partial z^2} \\ &= \nabla_2 \cdot (\sigma \nabla_2 u) + \sigma \frac{\partial^2 u}{\partial z^2}\end{aligned}$$

, and integrating the conductivity equation over the length of the cylinder, we obtain

$$\int_{-h/2}^{h/2} \nabla \cdot (\sigma \nabla u) dz = \nabla_2 \cdot (\sigma \nabla_2 u) + \sigma \frac{\partial u}{\partial n} \Big|_{x=h/2} + \sigma \frac{\partial u}{\partial n} \Big|_{x=-h/2}$$

, or, by denoting

$$\psi(x, y) = \frac{1}{h} (\psi_+(x, y) + \psi_-(x, y)), \quad \varphi(x, y) = \frac{1}{h} \int_{-h/2}^{h/2} \Phi(x, y, z) dz$$

, the average potential satisfies the two dimensional conductivity equation

$$\nabla_2 \cdot (\sigma \nabla_2 u) = \varphi(x, y) + \psi(x, y) \quad (1)$$

. Here, φ is the primary source that we are interested in, while the source ψ represents the flow in and out the cuff region. The source φ , representing the saltatory voltage at the nodes of Ranvier, is a sum of focal terms, while ψ , which depends on the conductivity distribution in and outside of Ω as well as on sources outside Ω , can be assumed to be spatially distributed. We refer to φ as the *primary source*, and to ψ , being the contribution of the outflow of the *Ohmic source*.

From the point of view of the inverse problem, the Ohmic source can be viewed as source noise, and without detailed information of the geometry and conductivity distribution, not much can be said about it except that is correlated to φ , and

$$\int_D \varphi dS = - \int_D \psi dS \quad (2)$$

, as can be easily verified. This, in effect, is the conservation of charge condition.

The data consists of noisy observations of the voltage potentials at positions $(x^{(i)}, y^{(i)}) \in \partial D$, $1 \leq i \leq L$, where we use a point-like approximation of the contact electrodes of the cuff.

2.1 Implementation: Effect of the Ohmic source

We implement the forward model by using a finite difference approximation of the equation (1). The domain D is modeled as a rectangle with dimensions given in Table 1. We simulate the data using a detailed fascicle model, the geometry being shown in Figure 2. The conductivities of the different tissues used in the model are given in Table 1. In the data simulation, the computational domain is divided into 320×80 pixels. A standard five point finite difference approximation with Neumann boundary condition for the differential operator in (1) is used.

To simulate the data, we assume that a selected part of a fascicle, modeling an active axon group, acts as a voltage source. The five active areas within the four fascicles are indicated in Figure 2. We may activate one source at the time because the general activation, and the corresponding data, can be expressed as a linear combination of these basic activation patterns. This activation accounts for the primary part ψ of the source. To complete the simulation, we need to decide how to model the distribution of the Ohmic source ϕ , that, in general, depends on the three dimensional structure of the nerve.

It is known that the perineurium has significantly lower conductivity than epineurium and endoneurium, and moreover, the longitudinal conductivity of endoneurium is almost one order of magnitude higher than the transversal conductivity, see Table 1. Therefore, the endoneurium is a highly preferred pathway for the Ohmic currents. This observation suggests that the fascicles might act effectively as coaxial cables, the Ohmic sources strongly shadowing the signal due to the primary activity and rendering the inverse problem more difficult to solve.

To test the effect, we run the forward model with four different hypotheses about the Ohmic source distribution. Activation of one of the five axon groups is simulated at a time, giving rise to a primary source

$$\varphi(x, y) = W_{\chi_A}(x, y)$$

, where A denotes the two dimensional representation of the fascicle containing the active axon and χ_A is its characteristic function. Let F denote the two dimensional set representing the fascicle corresponding to the active source, $A \subset F$. We consider the following Ohmic source models:

1. *Fascicle model*: The Ohmic source is distributed homogenously over F , assuming that no current leaks through the perineurium. We have

$$\psi(x, y) = -\tilde{W}_{\chi_F}(x, y), \quad W|A| = \tilde{W}|F|$$

, where $|A|$ and $|F|$ denote the areas of the sets A and F , respectively.

2. *Leaky model*: The Ohmic current leaks through the epineurium, creating an Ohmic source localized around the active axon group. We use a Gaussian distribution to model the leak,

$$\psi(x, y) = -\tilde{W} \exp\left(-\frac{1}{2\eta^2}((x-x_0)^2 + (y-y_0)^2)\right)$$

, where (x_0, y_0) is the center of the axon group, $\eta > 0$ is a width parameter controlling the leak and $\tilde{W}$ is chosen so as to guarantee the vanishing integral condition (2).

3. *Green's model*: The Ohmic current distributes itself following the three dimensional point source field in homogenous medium with constant conductivity,

$$\psi(x, y) = -\tilde{W} \frac{1}{((x-x_0)^2 + (y-y_0)^2 + (h/2)^2)^{3/2}}$$

, $\tilde{W}$ is chosen so that the vanishing integral condition (2) is valid.

4. *Homogenous model*: The Ohmic current distributes uniformly over the whole epineurium E ,

$$\psi(x, y) = -\tilde{W}_{x_E}(x, y), \quad W|A| = \tilde{W}|E|$$

, We point out that without a three-dimensional conductivity model, it is not possible to simulate numerically the Ohmic model, and such a model is beyond the scope of the present simplified model. In Figure 3, the computed voltages with different Ohmic source models and two different primary sources are plotted. From that figure, it is obvious that the voltages in the fascicle model are strongly masked by the coaxial effect, and the more widespread the Ohmic current is, the stronger the response and horizontal localization of the source is. Also, the fascicle model may create sources that have dipolar nature, in particular if the active axon group is off-centered within the fascicle such as source 4 in Figure 2. The conclusion of this experiment is that in lack of further information about the distribution of the Ohmic current, modeling choices may have significant effects on the interpretation of the results, and the model needs to be compared with data where detailed histological information are available.

In the numerical simulations throughout this paper, we use the leaky model as the Ohmic response of the nerve.

3 Inverse problem with static data

The ENG data consist of a time series of voltage recordings at the contact electrodes. We assume that the temporal and spatial dependencies of the sources are separable, and consider first the inverse problem assuming that the data consist of a single time slice. The problem may therefore be stated as follows: **Inverse Problem I:** *Given the boundary voltage measurements*

$$b^{(i)} = v(x^{(i)}, y^{(i)}) + \text{"noise"}, \quad 1 \leq i \leq L$$

, *estimate the primary sources φ and the Ohmic sources ψ .*

We point out that the data depend on the sum of the sources, so without complementary information, it is not possible to separate the primary and Ohmic sources. Moreover, in the previous section it was demonstrated that the source separation is dependent on the distribution of the Ohmic current across the nerve. To avoid methods that rely on assumptions that may be incorrect, we seek to estimate the lumped source density $\varphi + \psi$.

3.1 Lead field computation

For the inverse problem, to avoid the most obvious inverse crime (see [7]), we discretize the epineurium using a coarser mesh, with $N = 80 \times 20$ pixels, than what is used for generating the data. Moreover, since the true conductivity distribution is unknown, in the inverse modeling we use a constant isotropic conductivity that corresponds to the transversal conductivity of the epineurium.

The lead field matrix A is defined as the matrix mapping the source densities to the electrode voltages,

$$Af=b_0, f \in \mathbb{R}^N, b_0 \in \mathbb{R}^L, A \in \mathbb{R}^{L \times N}$$

, where $f_i = \varphi(x_i, y_i) + \psi(x_i, y_i)$, with (x_j, y_j) the j th grid point in Cartesian coordinates, $1 \leq i \leq N$, and $b_j = v(x^{(j)}, y^{(j)})$, the voltage at the electrode locations, $1 \leq j \leq L$. We choose the reference voltage (ground) so that

$$\sum_{j=1}^L b_j = 0$$

To compute the lead field matrix, we use the Helmholtz reciprocity principle: Denote by $G_p(p') = G(p, p')$, $p, p' \in D$, the Neumann Green's function, defines as the solution of the problem

$$\nabla \cdot (\sigma \nabla G_p) = \delta_p \quad (3)$$

, where δ_p is Dirac's delta at p , and $p' \mapsto G(p, p')$ satisfies the boundary conditions

$$\sigma \frac{\partial G_p}{\partial n} \Big|_{\partial D} = \frac{1}{|\partial D|}$$

Obviously, the rows of the lead field matrix are, up to the ground condition, a discrete version of $G_p(p'_j)$, where $p'_j = (x_j, y_j)$ is the locations of the j th electrode. To resolve the lead fields, consider the problem of finding a function v_j satisfying

$$\nabla \cdot (\sigma \nabla v_j) = 0$$

with Neumann boundary data

$$\sigma \frac{\partial v_j}{\partial n} \Big|_{\partial D} = \frac{1}{L} \sum_{\ell=1}^L \delta_{\partial, p'_\ell} - \delta_{\partial, p'_j}, 1 \leq j \leq L$$

, where δ_{∂, p'_j} denotes the one-dimensional Dirac delta at $p'_j \in \partial D$ along the boundary of D , and the average over all electrodes is chosen as a reference (ground). Moreover, since v_j is defined up to an additive constant, we impose the extra condition

$$\int_{\partial D} v_j dS = 0$$

By Green's identity,

$$\begin{aligned}
 v_j(p) &= \int_D \left(v_j \nabla \cdot (\sigma G_p) - G_p \nabla \cdot (\sigma v_j) \right) dp' \\
 &= \int_{\partial D} \left(v_j \sigma \frac{\partial G_p}{\partial n} - G_p \sigma \frac{\partial v_j}{\partial n} \right) dS
 \end{aligned}$$

, and the boundary conditions, we find that

$$v_j(x) = G_p(p'_j) - \frac{1}{L} \sum_{\ell=1}^L G_p(p'_\ell), \quad 1 \leq j \leq L \quad (4)$$

Therefore, instead of solving the lead fields, we may alternatively solve the *sensitivity functions* v_j , which, after a finite difference discretization, requires the solution of only L linear systems. Physically, the function v_j indicates the sensitivity of the voltage difference between the j th and the reference electrode.

For later reference, Figure 4 shows two lead field vectors, or rows of the matrix A , interpreted as pixel images. Not surprisingly, the fields are almost flat except for a region around the corresponding electrode. This behavior emphasizes the ill-posedness of the inverse problem: The voltage measured at a given electrode is sensitive to sources only at the proximity of the electrode.

Assuming additive noise that accounts both for the exogenous measurement noise and modeling errors, we arrive at the discrete model

$$b = Af + e \quad (5)$$

, where e represents the noise.

The inverse problem turns out to be more challenging than its formal simplicity suggests. In particular, standard regularization techniques such as Tikhonov regularization and truncated SVD methods do not perform well.

3.2 Tikhonov and TSVD

The standard Tikhonov regularization method replaces the ill-posed linear system (5) to be solved for f with a nearby regularized least squares problem,

$$f_{\text{Tikh}} = \operatorname{argmin} \left\{ \|b - Af\|^2 + \alpha \|L f\|^2 \right\}$$

, where the regularization matrix L and the regularization parameter $\alpha > 0$ are determined by a priori assumptions of the properties of a feasible solution and the level of noise, respectively. The standard choices for regularization matrix L are the identity matrix or discrete approximations of differential operators.

Figure 5 (top row) shows the Tikhonov regularized solutions using the identity matrix penalty and a second order finite difference smoothness penalty with homogenous Neumann boundary conditions. The simulated data correspond to activation of sources number 1 and 4, see Figure 2. The results are a clear illustration of the fundamental problem of standard

regularization techniques with the present application: the data are more sensitive to changes in the source pixels close to the electrodes, therefore, a penalty on the source amplitude, or energy, tends to move the sources right at the boundary and under the electrodes, since the data are explained with least energy by such sources. Another way to explain the phenomenon is to notice that any linear combination of the lead fields such as those shown in Figure 4 can have maxima only under the contact electrodes.

The tendency of regularization methods to push the estimated source towards the sensors has been observed also in MEG and EEG applications, and depth weight methods have been developed to compensate for it (see, e.g., [8]). To test whether similar ideas may help in the present problem, we scale the forward matrix by pixel sensitivities. More precisely, since the fictitious data due to an activity of unit size in j th pixel alone is

$$b^{(j)} = A f^{(j)} = a^{(j)}$$

, where $f^{(j)}$ is a unit basis vector and $a^{(j)}$ is the j th column of the matrix A , the norm of $b^{(j)}$ could be a good proxy for the sensitivity to pixel values at the j th pixel. Hence, we define the scaled problem

$$\begin{aligned} b &= A f + e = A W^{-1} W f + e \\ &= \tilde{A} \tilde{f} + e \end{aligned} \quad (6)$$

, where

$$W = \text{diag}(\|b^{(1)}\|, \dots, \|b^{(N)}\|) \in \mathbb{R}^{N \times N}$$

Hoping to have an improved sensitivity to pixels away from the contacts, we seek the Tikhonov regularized solution to the weighted problem (6). The regularized solutions of the scaled problem are shown in Figure 5 (first two figures from the bottom). The effect of correcting for the sensitivity by scaling is rather minimal, and we may conclude that for standard Tikhonov regularization is not the method of choice when looking for activity localized.

It turns out that the other classical method of choice, the standard truncated singular value solution TSVD (see [6, 7]) suffers from similar shortcomings: The support of the first singular vectors of the matrix A that form an orthonormal basis in the source space clusters strongly at pixels under the electrodes, and therefore any of their linear combinations will show activity under the electrodes and almost no activity inside the nerve or between the electrodes, leading to reconstructions similar to those produced with Tikhonov regularization.

3.3 Beamformer

Beamformer algorithms originate from radar imaging, and in recent years they have been applied in various imaging modalities ([16]), including the present problem ([20]). Adaptive beamforming algorithms use the time series data and will be discussed briefly later; here we apply a version that can be applied to single time slices.

The beamformer algorithm, which assumes a random source with a given co-variance matrix,

$$\Gamma = E \{ f f^T \}$$

, tacitly assuming that the mean of f vanishes, looks for an estimator for the i th pixel value of x which is linear in the data, that is

$$\hat{f}_i = q^T b = q^T A f + q^T e$$

, where $q = \mathbb{R}^L$ is a filter vector. The criterium used for the design of the filter vector is that $\hat{f}_i$ should have statistical properties as close as possible to f_i . To this end, partition the matrix A and the vector f by writing

$$A f = a^{(i)} f_i + \sum_{\ell \neq i} a^{(\ell)} f_\ell = a^{(i)} f_i + A_{-i} f_{-i}$$

. and write

$$\hat{f}_i = q^T a^{(i)} f_i + q^T (A_{-i} f_{-i} + e) = q^T a^{(i)} f_i + R_i \quad (7)$$

.

A good statistical approximation for f_i calls for the variance of the f_i -dependent part to be equal to the variance of f_i , which is the reason for requiring that

$$q^T a^{(i)} = 1$$

.

In order to minimize the variance of the residual part R_i , we observe that

$$\begin{aligned} E \{ R_i^2 \} &= E \left\{ \left(q^T (A f + e) \right)^2 \right\} - E \left\{ \left(q^T a^{(i)} f_i \right)^2 \right\} \\ &= q^T \left(A \Gamma A^T + \sigma^2 I \right) q - \Gamma_{ii}, \end{aligned}$$

, This implies that the optimal filter vector $q = q^{(i)}$ must be the solution of the following constrained minimization problem:

$$q^{(i)} = \operatorname{argmin} \left\{ q^T \left(A \Gamma A^T + \sigma^2 I \right) q \right\} \text{ subject to } q^T a^{(i)} = 1$$

.

The vectors $q^{(i)}$ can be found using by the method of Lagrange multipliers going through the following steps:

1. Solve $(A[A^T + \sigma^2 I]z = -a^{(i)},$
2. Set $q^{(i)} = (z^T a^{(i)})^{-1} z$

Repeating this process for all pixels yields the imaging matrix Q ,

$$Q^T = [q^{(1)} q^{(2)} \dots q^{(N)}]$$

which can be used to compute the beamformer solution for the inverse problem

$$\hat{x} = Qb \quad (8)$$

We apply the beamformer algorithm to the current problem, assuming that the source covariance matrix is a constant multiple of identity matrix, that is,

$$[= \gamma I, \gamma > 0$$

, and therefore,

$$A[A^T + \sigma^2 I] = \gamma(AA^T + \tau I), \tau = \frac{\sigma^2}{\gamma}$$

, where τ is the effective regularization parameter. In the computed example below, we assume that the noise level, expressed in terms of its standard deviation, is 5% of the maximum of the contact voltages. In the calculation of the beamformer filter, the value of the regularization parameter τ does not have a significant effect on the solutions, hence can be chosen rather loosely. In the computed examples, the value $\tau = 10^{-10}$ was used.

Figure 6 shows four source estimates obtained using the beamformer algorithm for different simulated source configurations. The positions of the true sources in these simulations are marked by dots. Evidently, the source localization is relatively good when the data correspond to a single active source (numbers 1 and 4 in Figure 2), or when two active sources are well separated. However, two nearby active sources (numbers 2 and 3 in Figure 2) are not distinguishable and are therefore estimated as a single source. It turns out that this lack of resolution is not as critical as it may seem at first, and may be overcome, to some extent, with additional information from time series data.

We close this section by pointing out the formal similarity of the beamformer algorithm as described here and the classical Backus-Gilbert algorithm (BG) for solving linear ill-posed problems [1]. Both approaches seek to estimate the unknown vector one component at the time, optimizing to minimize the cross-talk between pixels. While the beamformer algorithm penalizes for cross talk from all stop band pixels with equal weight, the BG algorithm introduces a distant-dependent penalty.

4 Time series data

The computed simulations demonstrate that the spatial resolution of the beam-former estimates with single time slice data may be insufficient to separate sources in fascicles close to each others or within the same fascicle, although the data may contain enough information for statistically significant separation of signals originating from distinct sources. Moreover, the noise level in the ENG data is substantial [20], so effective noise reduction techniques are of key importance. In this section, we elaborate further the beamformer algorithm, with an emphasis on the prior covariance of the source. In particular, we propose a new kind of beamformer algorithm that is based on a hierarchical statistical model, and a novel source separation filter that projects the measured signal to directions corresponding to single source activation. The filter, combined with the hierarchical beamformer, is tested with simulated realistic time series data that is described in the Appendix.

4.1 Adaptive beamformer

As an introduction, we discuss briefly the adaptive beamformer [16], in which the time series data is utilized for computing the beamformer matrix.

The beamformer algorithm using a single time slice data assumes the prior covariance Γ to be known, a common choice being $\Gamma = \gamma \mathbf{I}$, which implicitly assumes that the pixels are mutually independent and have equal variance. The idea behind the adaptive beamformer is to use the data over several time slices, assuming that the underlying process is stationary, that is, each time slice represents a recording of random sources that are independent and identically distributed.

More precisely, let $t_1 < t_2 < \dots < t_M$ denote a time sequence of consecutive registration times, and $F^1, F^2, \dots, F^M$ be a stationary stochastic process modeling the corresponding voltage source vectors. We assume that

$$\mathbb{E}\{F^j\} = 0, \mathbb{E}\{F^j(F^j)^\top\} = \Gamma$$

.

If $f^1, f^2, \dots, f^M$ is a realization of the process, it follows from the Law of Large Numbers that, when M is large,

$$\frac{1}{M} \sum_{j=1}^M f^j \approx 0, \frac{1}{M} \sum_{j=1}^M f^j(f^j)^\top \approx \Gamma$$

.

If the additive noise is independent of the source, as we will assume here, we have

$$\frac{1}{M} \sum_{j=1}^M e^j(f^j)^\top \approx 0, \frac{1}{M} \sum_{j=1}^M f^j(e^j)^\top \approx 0$$

, and we approximate the noise covariance matrix $\mathbf{C}$ with

$$\frac{1}{M} \sum_{j=1}^M e^j (e^j)^\top \approx C$$

Introducing in correspondence with each time instance t_j the rank one matrix

$$b^j (b^j)^\top = A \begin{bmatrix} f^j (f^j)^\top \end{bmatrix} A^\top + \begin{bmatrix} e^j (f^j)^\top \end{bmatrix} A^\top + A \begin{bmatrix} f^j (e^j)^\top \end{bmatrix} + e^j (e^j)^\top \quad (9)$$

, averaging over all such rank one matrices and arranging the observations b^j into a matrix,

$$B = \begin{bmatrix} b^1 & \dots & b^M \end{bmatrix}, \quad b^j = A f^j + e^j$$

, we find that

$$\frac{1}{M} \sum_{j=1}^M b^j (b^j)^\top = \frac{1}{M} B B^\top \approx A \Gamma A^\top + C$$

The matrix appearing in the right hand side is the same one used in the single time slice beamformer algorithm. An important feature of the matrix B is that it is obtained directly from the data, and it automatically accounts for the underlying covariance matrix Γ . In particular, if some of the pixels are mutually correlated, the ensuing correlation structure is encoded automatically into the algorithm.

4.2 Hierarchical beamformer and source variance estimation

The adaptive beamformer algorithm addresses the difficulty of assigning a value to the signal covariance matrix Γ . Numerical experiments with simulated data indicate that in the present problem, the adaptive beamformer does not improve the spatial resolution, in particular when realistic signal-to-noise ratios are used. A common strategy for reducing the amplitude of the external noise is to average the signal over a moving window. In the present application, however, averaging leads to a significant loss of the signal, since the neuron firings are independent and the voltages cancel each other.

A much more useful piece of information than the voltage source amplitude itself is the variance of the source. To estimate the source variance, we propose a hierarchical model and show that under certain hypotheses, it is possible to estimate the variance using a beamformer algorithm that is very robust with noise.

Following the setup for the adaptive beamformer algorithm, let $F^1, F^2, \dots, F^M$ denote a time series of identically distributed random variables representing the source with zero mean and covariance Γ , and independent of the additive noise. Instead of assigning the covariance matrix, we write a statistical model for it, assuming that

$$\Gamma = \begin{bmatrix} \gamma_1 & & \\ & \ddots & \\ & & \gamma_N \end{bmatrix}, \quad \gamma_j > 0$$

, with the diagonal elements γ_j mutually independent and having a constant variance. From the Bayesian perspective, this amounts to introducing a hierarchical model with a hyperprior, where the variances, but not the signal components, are identically distributed.

To derive an algorithm to estimate the variances, consider the linear observation model (5), f having equal distribution with the variables F^k . The expectation of the voltage squared, measured at j th electrode, $b_j = e_j^\top b$, conditioned on the diagonal vector γ of the matrix Γ , is

$$\overline{b_j^2} = E \left\{ \left(e_j^\top b \right)^2 \right\} = e_j^\top A \Gamma A^\top e_j + \sigma^2$$

It is a straightforward matter to check that

$$\overline{b_j^2} = \sum_{k=1}^N \left(A_{jk} \right)^2 \gamma_k + \sigma^2$$

, or in vector notation,

$$\overline{b^{\odot 2}} = A^{\odot 2} \gamma + \sigma^2 c$$

, where the operation $\odot 2$ denotes pointwise second power of the array and c is a vector with entries equal to one. In particular, given the observations b^j corresponding to the realizations f^j of the sources F^j over a time window of length M , we may consider the approximation

$$\overline{b^2} \approx \frac{1}{M} \sum_{j=1}^M \left(b^{(j)} \right)^2$$

In particular, we have a linear model for the unknown variances γ_j , and we may apply the beamformer algorithm to the data $\overline{b^{\odot 2}} - \sigma^2 c$ with the forward model defined by the matrix $A^{\odot 2}$. A particularly attractive feature of this formulation is that in the averaging process, the random signal does not cancel out, while the additive noise contributes only to a background value that is easy to take into account in the data.

4.3 Beamformer and source separation

A typical problem of classical beamformer algorithms is the tendency to merge together several sources which are simultaneously active, with the identification of signals originating from different sources hampered by cross-talk. This has been a strong motivation

to look for a variant that minimizes the cross-talk between different sources that are simultaneously activated. The derivation of the source separation formula is based on the assumption of static data, but it is applied to the dynamic time series data.

Consider the beamformer filter matrix (8) $\mathbf{Q} \in \mathbb{R}^{N \times L}$, represented in terms of its column vectors $\mathbf{u}^{(l)} \in \mathbb{R}^N$,

$$\mathbf{Q} = [\mathbf{u}^{(1)} \mathbf{u}^{(2)} \dots \mathbf{u}^{(L)}]$$

, where L is the number of electrodes. The beamformer estimate of the voltage distribution corresponding to single time slice data $\mathbf{b} \in \mathbb{R}^L$ is

$$\hat{\mathbf{f}} = \mathbf{Q} \mathbf{b} \in \text{span} \{\mathbf{u}^{(1)}, \dots, \mathbf{u}^{(L)}\}$$

Assume that the nerve contains K distinct sources, and data with only one single source active at a time is collected. Let $\mathbf{b}^{(j)}$ denote the data corresponding to activity in the j th source, $1 \leq j \leq K$, and by $\hat{\mathbf{f}}^{(j)}$ the corresponding beamformer estimate. We refer to these estimates

$$\hat{\mathbf{f}}^{(j)} = \mathbf{Q} \mathbf{b}^{(j)}, \quad 1 \leq j \leq K$$

, as single source estimates, and we normalize them to have unit length

$$\mathbf{v}^{(j)} = \frac{1}{\|\hat{\mathbf{f}}^{(j)}\|} \hat{\mathbf{f}}^{(j)}, \quad 1 \leq j \leq K$$

The data vectors $\mathbf{b}^{(j)}$ can be regarded as training data, collected under controlled conditions. We do not specify the noise level in the data, but we assume that it is appropriately taken into account when constructing the beamformer filter matrix. The training data does not require the knowledge of the true location of the sources, but only the information that only a single source at the time is active.

Consider now a time slice data $\mathbf{b} \in \mathbb{R}^L$ of unknown activation pattern, and define

$$\hat{\mathbf{f}} = \mathbf{Q} \mathbf{b}$$

Since $\mathbf{b}$ is a linear combination of the single source activations, we call $\hat{\mathbf{f}}$ a mixed source estimate. We want to find a representation of the mixed source estimate in terms of the single source estimates of the form

$$\widehat{f} = \sum_{j=1}^K \alpha_j v^{(j)}, \quad (10)$$

, where the coefficients α_j serve as indicators of the contribution of the corresponding single source. The key step for finding a representation of this type (10) is the identification of a suitable orthonormal basis for the vector space spanned by the single source estimates. The cross-talk matrix $\mathbf{C} \in \mathbb{R}^{K \times K}$, defined as

$$C_{jk} = (v^{(j)})^T v^{(k)}$$

, is the Gramian of the normalized single source estimates, and its entries are the cosines of the angles between these vectors. Let $\mathbf{R} \in \mathbb{R}^{K \times K}$ be the Cholesky factor of $\mathbf{C}$,

$$\mathbf{C} = \mathbf{R}^T \mathbf{R}$$

and let $\mathbf{V} \in \mathbb{R}^{K \times K}$ be the matrix whose columns are the single source estimate vectors

$$\mathbf{V} = \begin{bmatrix} v^{(1)} & \dots & v^{(K)} \end{bmatrix}$$

.

Since the matrix $\mathbf{D}$, defined as

$$\mathbf{D} = \mathbf{V} \mathbf{R}^{-1}$$

, which satisfies

$$\begin{aligned} \mathbf{D}^T \mathbf{D} &= \mathbf{R}^{-T} \mathbf{V}^T \mathbf{V} \mathbf{R}^{-1} \\ &= \mathbf{R}^{-T} \mathbf{C} \mathbf{R}^{-1} = \mathbf{I} \end{aligned}$$

, has the same column space as the matrix $\mathbf{V}$, its columns form an orthonormal basis for the vector space spanned by the single source estimates which contains all mixed source estimates. It follows from the orthogonality of the columns of $\mathbf{D}$ that $\mathbf{D}\mathbf{D}^T$ is the projection matrix onto the span of the single source estimates; furthermore, since any mixed vector is already in that space, we have

$$\widehat{f} = \mathbf{D} \mathbf{D}^T \widehat{f}$$

, and from the definition of $\mathbf{D}$,

$$\widehat{f} = \mathbf{V} \mathbf{R}^{-1} \mathbf{D}^T \widehat{f}$$

, from which it follows that

$$\alpha = R^{-1} D^T Q b \quad (11)$$

This is the source separation formula that we shall use with simulated time series data.

4.3.1 Resolution of the method—In view of the limited capability of the plain beamformer algorithm to identify more than a few independent sources, it is of interest to ask whether the cross talk reduction method has similar limitations. To answer this question, observe that the normalized vectors $v^{(j)}$ are by definition in the range of the imaging matrix Q , and therefore the maximum number of independent source vectors cannot exceed the column rank of this matrix. It is also easy to argue that by placing one fascicle right under each electrode, the imaging matrix should be able to distinguish between such sources, indicating that the column rank of Q must be L , the number of electrodes. In particular, this means that the theoretical maximum number of identifiable sources equals L . The numerical rank of the matrix C may be lower than L , and therefore the full theoretical limit may not be achieved. In conclusion, the true resolution of the proposed method is geometry dependent.

Figure 7 shows the singular values of the imaging matrix Q calculated using the lead field matrix A and the pointwise square of it, $A^{\odot 2}$. We observe that the singular values of the former decrease much more rapidly than those of the latter, suggesting that the hierarchical beamformer is likely to be more robust in the sense that in the presence of noise, the vectors $v^{(j)}$ are less likely to be confused.

4.4 Source separation with simulated data

To simulate the time series data, let $f^{(j)} \in \mathbb{R}^N$, $1 \leq j \leq 5$ denote source vectors that correspond to the five sources indicated in Figure 2, including the Ohmic source computed using the leaky model. The time dependent source model assumes that the spatial and temporal dependencies are separable,

$$f(t) = \sum_{j=1}^5 f^{(j)} g^{(j)}(t)$$

, and the time dependent parts $g^{(j)}(t)$ are generated as explained in the Appendix. The data is generated by applying the lead field matrix A and adding Gaussian noise.

Consider a discretely sampled time series data arranged data matrix (13). Using the source separation formula (11) derived in the previous section, we compute the matrix

$$R^{-1} D^T Q B = \begin{bmatrix} \alpha_1(t_1) & \alpha_1(t_2) & \cdots & \alpha_1(t_m) \\ \vdots & & & \vdots \\ \alpha_5(t_1) & \alpha_5(t_2) & \cdots & \alpha_5(t_m) \end{bmatrix}$$

The rows of this matrices are the time series of the contributions of the single source components to the mixed source estimates.

Figures 8–9, show side to side the time dependent signal $g^{(j)}(t)$ of each of the five active sources, referred to as “channels”, for two different pairs of fascicles firing while the remaining three are inactive, and the estimates for the channels obtained by this method. In these estimates, the additive Gaussian had a low variance, the variance σ being 1% of the maximum voltage amplitude over all electrodes and all the time period. A particularly striking feature of the algorithm is its ability to identify equally well contributions from sources which are spatially well separated (Figure 8) as well as from sources close to each other, or even inside the same fascicle (Figure 9).

To demonstrate the robustness of the hierarchical beamformer, we increase significantly the noise level in the signal, from 1% to 20% of the overall maximum of the signal amplitude. Figure 10 shows the voltage data at the electrode number 16, corresponding to the low and the high noise amplitude. In Figure 11, the cross talk reduced reconstructions using the plain beam former and the hierarchical beamformer are shown. In computing the hierarchical beamformer, we average the squared voltages over a window of 2000 registrations, which decreases the effective sampling frequency from 20 kHz to 10 Hz. While the plain beamformer seems to lose completely the information, the hierarchical version is able to resolve the activity pattern without problems.

Finally, we test the algorithm’s ability to resolve more than two active signals. In Figure 12, all five sources are activated. We observe that the cross talk between the channels is not significant, while differences in the amplitude occur. Notably, the amplitude of the first channel is relatively low, which is probably due to the geometry of the simulated nerve: the first source is located far from any single electrode.

5 Discussion

The article proposes a simplified two dimensional computational model for the electroneurography problem. The source in this model consists of a spatially well localized primary part and a wider distributed volume current contribution. While the Ohmic volume current portion is not of particular interest for identification of active sources, the model suggests that it may have a significant effect on the data, in particular if the conductivity structure of the nerve is such that the fascicles act as coaxial cables. In order to have a more reliable picture of the return current distribution, a detailed three dimensional nerve model should be used. This research is part of a future work.

The beamformer algorithm used in this study differs from standard beamformers by explicitly including a priori probability distribution of the source density. Although the basic beamformer algorithm implemented for our static examples does not make explicit use of the Bayesian approach, the new interpretation is fundamental in the development of the hierarchical beamformer. By assuming a non-constant distribution of the variance of the source, it is possible to write a hierarchical model where the variances, rather than the signal itself, become the primary unknown. This novel perspective has the significant advantage to allow an effective noise reduction by averaging without leading to a reduction of the useful signal level itself, thus rendering the algorithm remarkably robust. Moreover, the variance gives direct information about the spatial distribution of the firing rate rather than of the instantaneous voltage sources which represent neuron noise.

Another significant contribution of the article is the novel source separation technique that significantly reduces the cross talk between channels, making it possible to distinguish between signals from sources that are remarkably closer to each other than the resolution limit of the traditional beamformer algorithm. The source separation algorithm requires

training data; it will be a topic for future research to investigate the possibility of adaptively updating the training data.

Acknowledgments

This work was partly supported by NIH grant RO1NS03284-14S1. Erkki Somersalo was partly supported also by NSF grant DMS1016183.

Appendix: Modeling and simulation of the neuron firing

In modeling time dependent sources, we assume that the spatial and temporal dependencies are separable. Consider the model in Figure 2 with five possible active sources, and denote by $f^{(j)} = f^{(j)}(x, y)$, $1 \leq j \leq 5$, the corresponding distributions, which contain both the primary and the Ohmic part. Each source has its own temporal activity pattern, denoted by $g^{(j)}(t)$, and under the assumption of separability, the total activity becomes

$$F(x, y, t) = \sum_{j=1}^5 f^{(j)}(x, y) g^{(j)}(t)$$

The temporal dependency corresponds to firing of a large number of single neurons within the activation area, so it is natural to model each $g^{(j)}(t)$ as a mutually independent stochastic process.

Each source in the nerve is assumed to have a time dependent firing rate $a^{(j)}(t)$. Fixing j , we drop the super-index and write $a(t) = a^{(j)}(t)$. Over a short time period Δt , we assume that the number of firings over $[t, t + \Delta t)$ of individual neurons in the source is Poisson distributed,

$$P \{ \# \text{ of firings in } [t, t + \Delta t) = n \} = \frac{(a(t) \Delta t)^n}{n!} e^{-a(t) \Delta t}$$

Letting Δt approach zero, it follows that probability density of the random variable

$$s = \text{waiting time to next firing}$$

, conditioned to the last firing at t is

$$\pi(s|t) = a(t+s) \exp\left(-\int_t^{t+s} a(\tau) d\tau\right)$$

Hence, given that the latest neuron firing takes place at t , the next firing time is $t + s$, where s can be drawn by solving the equation

$$\int_t^{t+s} a(\tau) d\tau = -\log w, \quad w \sim \text{Uniform}([0, 1])$$

In our computed simulations, we use piecewise constant firing rate patterns alternating periods of low and high activity, with firing rate

$$a(t) = \begin{cases} 20\text{s}^{-1} & \text{for low activity} \\ 800\text{s}^{-1} & \text{for high activity} \end{cases}$$

For each active source, we generate its own activation pattern and draw its random firing sequence $\tau_0 < \tau_1 < \dots < \tau_N$. We then compute the signal as

$$g^{(j)}(t) = \sum_{j=1}^N \sigma(t - \tau_j), \quad (12)$$

, where $\sigma(t)$ is an action potential wave form as shown in Figure 13. We collect the simulated data by sampling the electrode voltages at a frequency of 20 kHz, and subsequently added independent Gaussian noise. The simulated data are organized into a matrix

$$\mathbf{B} = [b(t_1) \quad b(t_2) \quad \dots \quad b(t_m)], \quad (13)$$

, where $t_1 < \dots < t_m$ are the instances at which the voltages have been sampled.

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Figure 1.

A schematic picture of the measurement geometry. The nerve within the cuff is assumed to have a constant conductivity in the axial direction (left). Within the fascicles, the nodes of Ranvier act as sources of the potential. When the saltatory action potential passes through the neurons, the nodes of Ranvier act as current sources or sinks, inducing an Ohmic current that may leak out of the domain Ω through the planes $z = \pm h/2$ (right).

Figure 2.

The structure of the nerve used in the simulations. The fascicles are modeled by ellipses surrounded by a thin insulating perineurium. The active axon groups are inside the fascicles and numbered as indicated. The 22 contact electrode locations are marked in the figure.

Figure 3.

Computed voltages with different Ohmic source models using two different sources. In the top row, the activated axon group is the one labeled by “1” in Figure 2, while in the bottom row, the source “5” was active. On the left are the voltages at the eleven upper electrodes, on the right those at the lower electrodes. Legend abbreviations: FM = fascicle model; LM = leaky model, GM = Green’s model, HM = homogenous model.

Figure 4. Two lead fields, or sensitivity vectors, corresponding to electrodes 1 and 19, interpreted as voltage source distributions over the cuff intersection. Any linear estimator seeks to estimate the source distribution as a linear combination of the lead fields, leading to a strong bias towards the edges.

Figure 5.

Regularized reconstructions using Tikhonov regularization. The data was generated by activating two of the sources, numbers 1 and 4 in Figure 2. In the top figure, the penalty matrix is the identity, and in the second figure from the top, second order smoothness penalty is used. In the third figure from the top, white noise prior is used, and the columns of the forward matrix have been weighted by the inverse of their norm to compensate the different sensitivity. In the bottom figure, the weight with the smoothness prior is used. In each figure, the positions of the true sources are indicated dots.

Figure 6.

Beamformer estimates with simulated data corresponding to single sources (second and third from top) and with two sources (two bottom figures). The source locations are indicated by black dots. Gaussian white noise with standard deviation equal to 5% of the maximum computed noiseless voltage was added.

Figure 7.
The singular values, scaled with the largest of them, of the imaging matrix Q calculated using the lead field matrix A (squares) and the pointwise square $A^{\odot 2}$ (dots).

Figure 8.

Filtered estimates with simulated dynamic data with two active sources well separated. The left column shows the input time series in each source location, see Figure 2, referred to as channels. The results with the beamformer and filtering are shown in the right column.

Figure 9.

Filtered estimates with dynamic data with two nearby sources. The left column shows the input time series $g^{(j)}(t)$, $1 \leq j \leq 5$ (referred to as “channel”) in each source location as indicated in Figure 2. The results with the beamformer and filtering are shown in the right column.

Figure 10.

Simulated signal measured at the electrode number 16 corresponding to low additive noise (left) and high additive noise (right). The noise levels are 1% and 20 % of the maximum of voltage amplitudes over all electrodes and over the whole time period.

Figure 11.

Filtered estimates with dynamic data with two nearby sources and high additive noise. The left column shows the signal estimates. In the right column, the same time series data is squared and averaged over a window of 2000 frames and the beamformer is computed using the squared lead field to estimate the source variance.

Figure 12.

Filtered estimates with dynamic data with five active sources. The initial activation time from top to bottom is 1 s, 2 s, 3 s, 4 s, and 5 s, respectively, and the activations cease at 7 s, 7.5 s, 8 s, 8.5 s, and 9 s, respectively.

Figure 13.
The action potential σ used in (12) to calculate the activation pattern.

Table 1

Geometric and electromagnetic parameter values used in the computational model for simulating the data.

Cuff geometry		Conductivities [S/m]	
Width	12 mm	Epineurium	0.083
Breadth	3 mm	Perineurium	0.002
Discretization step	0.0375 mm	Endoneurium (transversal)	0.083
Number of electrodes	2×11	Endoneurium (longitudinal)	0.571