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Model-Based Bayesian Signal Extraction Algorithm for Peripheral Nerves

Thomas E. Eggers¹, Yazan M. Dweiri², Grant A. McCallum¹, and Dominique M. Durand^{1,*}

¹Neural Engineering Center, Biomedical Engineering, Case Western Reserve University

²Department of Biomedical Engineering, Jordan University of science and Technology

Abstract

Objective—Multi-channel cuff electrodes have recently been investigated for extracting fascicular-level motor commands from mixed neural recordings. Such signals could provide volitional, intuitive control over a robotic prosthesis for amputee patients. Recent work has demonstrated success in extracting these signals in acute and chronic preparations using spatial filtering techniques. These extracted signals, however, had low signal-to-noise ratios and thus limited their utility to binary classification. In this work a new algorithm is proposed which combines previous source localization approaches to create a model based method which operates in real time.

Approach—To validate this algorithm, a saline benchtop setup was created to allow the precise placement of artificial sources within a cuff and interference sources outside the cuff. The artificial source was taken from five seconds of chronic neural activity to replicate realistic recordings. The proposed algorithm, Hybrid Bayesian Signal Extraction (HBSE), is then compared to previous algorithms, beamforming and a Bayesian spatial filtering method, on this test data. An example chronic neural recording is also analyzed with all three algorithms.

Main Results—The proposed algorithm improved the signal to noise and signal to interference ratio of extracted test signals two to three fold, as well as increased the correlation coefficient between the original and recovered signals by 10–20%. These improvements translated to the chronic recording example and increased the calculated bit rate between the recovered signals and the recorded motor activity.

Significance—HBSE significantly outperforms previous algorithms in extracting realistic neural signals, even in the presence of external noise sources. These results demonstrate the feasibility of extracting dynamic motor signals from a multi-fascicled intact nerve trunk, which in turn could extract motor command signals from an amputee for the end goal of controlling a prosthetic limb.

Introduction

In recent years a renewed interest in creating bidirectional, clinically viable peripheral nerve interfaces has developed. A commitment from the U.S. Dept. of Defense and DARPA to

*corresponding author. dxd6@case.edu.

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develop biological platforms to interface with the residual nerves of amputee patients has fueled this development. Previous work in this field demonstrated that residual nerves of amputees remain viable sources of motor information [1] and targets for sensory restoration [2] of phantom limbs. Thus an appropriate interface could restore both volitional movement and natural sensation of a prosthetic limb to a user. In addition, the method could be applied to extract various signals from large nerves of the autonomic nervous system, such as the vagus.

Researchers have explored many approaches for interfacing with nerves [3]. Somatic nerves of the upper limb contain many fascicles (~20) which innervate distinct muscles; to interface with residual nerves in amputee patients, an implant should recover signals from distinct fascicles within the nerve. Nerve cuff electrodes have demonstrated the desirable long-term stability necessary for a viable clinical implant [4]–[6], but classically record whole nerve activity and are less selective with lower signal-to-noise ratios (SNR) compared to penetrating electrodes. To improve selectivity, the multi-contact Flat Interface Nerve Electrodes (FINE) was designed to reshape or maintain nerves into ellipses, thereby increasing the surface area and decreasing the distance from any fiber to an outside contact [7]. Separation algorithms can be applied to multi-channel recordings to recover activity in various fascicles. The earliest work employed generic blind source separation algorithms, which proved capable of separating mixed signals in low SNR but are difficult to train reliably [8].

Recovering fascicular activity with extrafascicular electrodes shares many characteristics with electroencephalogram (EEG) source localization, in that the inverse problem can be solved to estimate source activity [9]. Various algorithms from the source localization literature, including sLORETA and FOCUSS, have been investigated by other researchers to solve this problem in rat nerves [10], utilizing the known cuff/nerve geometry to create a lead field matrix [11]. Another early study investigating the FINE in rabbits used beamforming, in which a transformation matrix was created by inverting the lead field matrix [12]. A Bayesian algorithm (BSFE), based on an MEG source localization method [13] which utilized knowledge of baseline and interfering sources, was then implemented [14] to create improved spatial filters. Both methods were tested on acute data and showed promising results, and in a recent chronic study binary state gait classification was achieved [15]. However, an end goal of this work is to predict proportional motor activity in order to control a prosthetic limb. The BSFE algorithm did improve the SNR sufficiently for accurate classification of ankle movement but only over a limited dynamic range of the recovered signal.

To address this shortcoming, a hybrid algorithm which combined these two approaches was developed, herein called Hybrid Bayesian Signal Extraction (HBSE). This algorithm operates over predefined time windows and solves the inverse problem at each segment, as opposed to developing static spatial filters as in previous work. In order to operate in real time, which is critical for use in prosthesis control, a beamforming algorithm provided the initial source estimate for another iterative source localization algorithm. To test this algorithm, we developed a saline bath benchtop system which allowed the generation of realistic neural signals in arbitrary locations within the cuff. The signal recovery results from

HBSE were compared to beamforming and Bayesian spatial filter (BSFE) algorithms and are presented, along with results from a chronic experiment trial.

Methods

Algorithm derivation

The main contribution of this work is the development of an algorithm to extract fascicle level signals from intact peripheral nerves in real time, and is described herein. This hybrid algorithm builds upon and extends two previous algorithms designed to extract MEG sources [13] and adapted to neural signals [16]. Each source can be modeled as in Eq. 1:

$$Y_i = \sum_{j=1}^{D_s} L_j * S_j + v \quad (1)$$

Where $Y_i \in \mathbb{R}^{K \times N}$ is the matrix of recorded signals from the K contacts over N time points from the i^{th} source, $S_j \in \mathbb{R}^{1 \times N}$ is the signal associated with each of the D_s pixels (i.e. target neural signal), v the noise term, and $L_j \in \mathbb{R}^{K \times 1}$ the lead field matrix for pixel j (L calculated as in [12]). The number of sources i is determined by anatomy, representing the number of independent signals to be estimated. The lead field matrix represents a 2-dimensional map of the transverse cross-section of the nerve, discretized into 10×35 pixels, which relates the current at pixel j to the recorded signal at contact K . Briefly, this lead field is calculated using a finite element model of the nerve cuff/nerve. The nerve in this model is homogenous, representing an empty epineurium ($\sigma = 0.083$ S/m), and thus no *a priori* knowledge of the fascicles or non-homogeneities of the nerve are required. The inverse problem must be solved to infer S at every pixel j given Y_i , where each source S represents a given fascicle or functional group of fascicles, whose activity will predominately occupy a subset of the total pixels. From [14], Equation 1 can be expanded such that each source instead is modeled as Eq. 2:

$$Y_i = A_i * S_i + B_i * U_i + V_i \quad (2)$$

In this model, each source i is modeled by its true source activity, S , with its mixing matrix A as well as an interference term U with its corresponding mixing matrix B . With this formulation, other sources within the cuff can be considered to be interfering noise to source i , in addition to the static channel noise V . The training phase of the algorithm requires first isolating data segments where only 1 source is active, Y_i . These factors can then be estimated taking advantage of known activity times, utilizing a paradigm known as stimulus evoked factor analysis (SEFA), as detailed in [17]. The next step involves identifying the pixels associated with each source. To do this, the following likelihood models are introduced, as in [13]:

$$p(Y_i|S) \propto \exp \left(-\frac{1}{2} \left\| \left(Y - \sum_{j=1}^{D_S} L_j * S_j \right) \right\|_{\Sigma_i}^2 \right) \quad (3)$$

$$p(S_j|\Gamma_j) \propto \exp \left(-\frac{1}{2} \text{trace}(S_j^T \Gamma_j^{-1} S_j) \right) \quad (4)$$

where $\|Q\|_{\Sigma} = \sqrt{\text{trace}(Q^T \Sigma^{-1} Q)}$ (i.e. a normalized Frobenius norm). $\Gamma_j \in \mathbb{R}$ (to be estimated) is the variance of the zero mean Gaussian signal for each individual pixel j associated with source S and Σ_i represents the combined noise term, and is given by:

$$\Sigma_i = B * B^T + C_v \quad (5)$$

The goal is to estimate the variance of each pixel for a given time window, Γ_i , rather than the dynamic source S . To do this, equations 3 and 4 are integrated over the source S to obtain $p(Y_i|\Gamma)$:

$$p(Y_i|\Gamma) = \int p(Y_i|S) p(S|\Gamma) dS \propto |\Sigma_i + L\Gamma L^T|^{-1/2} \exp \left(-\frac{1}{2} Y_i^T (\Sigma_i + L\Gamma L^T)^{-1} Y_i \right) \quad (6)$$

Taking the logarithm of this equation leads to the following cost function to be minimized:

$$C(\Gamma) = \text{trace}(Y_i * Y_i^T (\Sigma_i + L\Gamma L^T)^{-1}) + \log(\Sigma_i + L\Gamma L^T) \quad (7)$$

The first term in the equation represents the ratio between the empirical and estimated variance, which measures the accuracy with which the estimated activity matches the observed activity. The second regularizing term penalizes the estimated source's power (Γ), which favors sparse solutions. This cost function can be minimized with any nonlinear optimization technique, however a principled and quickly convergent procedure has previously been developed, which introduces two auxiliary variables, X and Z (see [13] for derivation):

$$X_j^{new} = \Gamma_j L_j^T (\Sigma_i + L\Gamma L^T)^{-1} Y_i \quad (8)$$

$$Z_j^{new} = L_j^T (\Sigma_i + L\Gamma L^T)^{-1} L_j \quad (9)$$

$$\Gamma_j^{new} = Z_j^{-1/2} (Z_j^{1/2} X_j X_j^T Z_j^{1/2})^{1/2} Z_j^{-1/2} \quad (10)$$

Solving this equation generates a two dimensional heat map of activity within the transverse cross section of the nerve. From this map, the set of pixels P_i with the highest source variance, Γ_j , are identified for each source and stored. This last step completes the training phase, and is repeated for each of i sources. To extract signals from test data, equations 8–10 are iteratively solved for a defined segment of time (here 100ms), and the output is the average of the Γ_j 's associated with each source, P_i ; this differentiates the proposed approach from previous work [12], [16], which learned a set of static weights (spatial filters) for signal extraction on test data. For the end goal of using this algorithm to extract command signals for a prosthetic device, the algorithm must provide estimates within a small time window, on the order of milliseconds. To reduce the computational complexity of signal extraction, two steps were taken. First, only pixels which were identified and stored in training are solved for Γ_j ; as each pixel is treated as a zero mean, Gaussian and independent signal, each pixel can be estimated without the knowledge of neighboring pixels, thereby greatly reducing processing time. The next improvement utilized the beamforming algorithm to initialize the source variance term Γ . Beamforming offers a reasonable source estimate, and thus reduces the number of iterations needed to obtain a solution.

Processing time

As mentioned, the proposed algorithm must operate in real time to prove functional. The memory requirements consist of the lead field matrix ($K \times P_i$), the beamforming transformation matrix ($P_i \times K$), the noise matrix Σ ($K \times K$), the vector of previously identified source pixels P_i , the recorded data, and the algorithm itself, consisting of Z , X and Γ . The algorithm requires a matrix inversion ($K \times K$ matrix) for each iteration, followed by the update of each pixel. Using the timing function in Matlab, each iteration took ~1–2ms, with a total of <10ms of total processing time for 4 iterations used in the data presented (Matlab R2012B, running on Intel Core i5 @ 2.5GHz). This processing time does not include the bandpass filtering step, which must occur before processing. The spatial filtering techniques discussed below, beamforming and BSFE, are virtually instantaneous (<1ms) as they involve a single matrix multiplication.

Benchtop setup

To generate representative test signals, the source must be precisely placed within the cuff in known locations. Fig. 1 shows the developed test platform. The center of the platform is a pedestal, which holds the FINE with thread (not shown), and the entire platform is submerged in 0.9% saline solution. Attached to this pedestal via a base are two corner pieces, which serve as the zero position for the moveable arm. This arm holds two small wires which form a dipole. A small segment on each wire is exposed, 2 mm apart (Fig. 1(b)), and current is passed between them to generate signals. The arm is attached to a micromanipulator (WPI M3301R), which allows the source to move within the cuff with high precision (100 μ m). This platform was printed on a Fortus 400mc, which offers a

resolution of $\sim 250\mu\text{m}$. The FINEs in this study were the same as those in a chronic study and were built in-house [18]. Briefly, they were 2 cm long tripolar cuffs with 16 Pt-Ir (90/10) recording contacts and four large reference contacts embedded in silicone with exposed gold faces on the outside to act as shielding (Fig. 3(a)).

Signal generation

The source signal was taken directly from a chronic neural recording of the sciatic nerve in a canine using a FINE during five seconds of treadmill locomotion, and is shown in Fig. 2(a); the procedure for this chronic experiment is described below. A custom LabVIEW program was developed to create an analog signal using a DAQ (NI USB-6251 BNC). An isolated analog stimulator (A-M Systems Model 2200) received this analog signal and generated a current output across the dipole. Signals were amplified using the same custom amplifier board as [15] and recorded with the AlphaOmega recording system (AlphaLab SnR). The noise seen in Fig. 2(b) represents the physical noise generated from the impedance of the electrode/saline interface, the inherent electronic noise, and ambient environmental noise. To adjust the SNR, the source current was varied from 0.25 to 2 microamps in steps of 250nA.

Source localization and recovery

To test the resolution of source localization, the dipole was moved throughout the transverse section of the FINE (within the x-y plane, see Fig. 4(a)) in 500 μm discrete steps while recording. From these single source recordings, the source localization algorithm created a heat map of activity which represents the estimated variance of each pixel. Each recording consisted of 5 seconds of activity localized using 100ms segments, resulting in 50 source estimates per trial. The nine pixels with the highest activity were identified and the calculated centroid was compared to the known location of the dipole. Radial errors were tabulated for 16 locations within the cuff.

To test source recovery, a mixed recording of two sources was generated. Instead of simultaneously stimulating two dipoles, the same recordings as above were utilized; two recordings with the dipoles in different locations were added together such that the signals overlapped for half of their duration, or 2.5 seconds, with 2.5 seconds of each source active alone (Fig. 5). The SNR of these signals as well as the distance between sources was varied, and three different algorithms were used to separate the two source signals. Outcome measures were the SNR, correlation coefficient (CC) and signal to interference ratio (SIR), and are defined more precisely in the results section.

EMG interference

The effect of external interference, such as muscle activity (EMG), on raw recordings and signal recovery was tested. The same paradigm as above was utilized, except that an interfering dipole was placed outside (above) the FINE. A series of sine waves of frequencies between 10Hz and 10kHz in logarithmic steps (1,2,5,10), each lasting 1 second, was injected at six locations, starting right above the FINE ($x=0$) and moving 2.5cm longitudinally away from the cuff in 0.5cm steps. Two different FINE configurations are compared – with and without gold shielding. Current ranging from 0.1–1mA was used for these sources. These recordings were then combined with the previous mixed signals to

measure each algorithm's ability to reject extrinsic noise. Each one second sine wave at each frequency was combined to create one second of multiple overlaid sine waves, resulting in a broad spectrum interference signal. This signal was then added to the two source recordings, with alternating one second bursts of activity (i.e. one second active, one second off). With this mixed two source and external interference recording, each algorithm was applied to recover the two internal source signals as the amount of external interference was varied. Three cases were tested: 1. No external noise in the training, 2. The same external noise in training and testing and 3. Different external noise used in training and testing (i.e. noise from one location used in training and from a different location in testing).

Chronic ENG recordings

Chronic electroneurogram (ENG) recordings from the sciatic nerves of canines were conducted; the methods have previously been published [15]. Canines were chosen due to their unique physiology in that the sciatic nerve is largely composed of two large fascicles instead of many smaller ones, simplifying the task of localizing neural activity. Briefly, FINEs were implanted on the sciatic nerve of canines just proximal to the bifurcation of the tibial and peroneal fascicles. These fascicles control plantarflexion and dorsiflexion of the lower limb. These motions in turn are predominately controlled by the gastrocnemius (GN) and tibialis anterior (TA) muscles, respectively; EMG signals from these muscles were simultaneously recorded, and compared to the extracted neural signals. Fig. 3 depicts the experimental procedure. Recordings were taken as the animal walked freely on a treadmill at a moderate pace.

The amount of information obtained from these recordings was also estimated. Under this paradigm, recovered signals are the received message and EMG is the expected message (ground truth). Both the EMG and recovered signals were discretized into 2–8 bins (corresponding to 1–3 bits per estimate). The DC offset was removed and the signals normalized prior to binning, such that each signal ranged from 0 to 1. Then the standard information rate calculation was employed [12] to calculate the bit rate (BR) on this single trial for each source using equation 11:

$$BR = R(\log_2 N + P \log_2 P + (1 - P) * \log_2 [(1 - P)/(N - 1)]) \quad (11)$$

where R is the classification rate (10 Hz), N is the number of bins or possible states, and P is the classification accuracy.

Results

Source can be localized within 1mm

To determine the accuracy of source localization, recordings from 16 different source locations within the cuff were processed. Examples of the recorded signals from 2 of the 16 channels are shown in Fig 2(b). Fig. 4(a) shows a heat map generated by a single source within the cuff, with red representing the highest activity and blue the lowest. Several different values of the recorded SNR were tested, ranging from near 0 to 6 dB, for a total of 12 trials at each location. The radial error for each estimated source location (red X) from

the known dipole location (circle) was tabulated and is shown in Fig. 4(b). The mean and standard deviation (SD) were 0.36 ± 0.2 mm. Within the tested range, there was only a small correlation between accuracy and SNR of the recorded signal (not shown). The errors were tested against the hypothesis that the mean error was less than 0.5 mm, which is roughly the size of a normal fascicle. The mean error was not significantly different from 0.5 mm, but was at 1 mm (Mann-Whitney U test, $p < 0.01$).

Signal recovery from dipole sources

The proposed HBSE algorithm as well as BSFE and beamforming (Beam) were applied to the mixed recordings. Examples of recovered signals from two sources separated by 2 mm are shown in Fig 5(a) (current source shown in Fig. 2(a)). The results obtained from the three algorithms were compared with the following metrics: recovered signal SNR, the correlation coefficient (CC), and the SIR. The SNR was calculated between segments when a single source was active versus the baseline activity (i/iv for source 1, Fig. 5(b)). The CC was calculated across the entire signal period (i–iv). The SIR is measured between segments when a single source is active versus the pure interference recording (i/iii for source 1); by this definition, the SIR measures interference from sources within the cuff. Fig. 5(c) shows the envelope of the source and extracted signals using HBSE. Fig. 6 shows the results obtained with all three algorithms. For all algorithms, recovery metrics improved with increasing inter-dipole distance, shown on the x-axis. The HBSE algorithm significantly improved the SNR (Wilcoxon rank sum test, $p < 0.01$), with mean SNR of recovered signals 7.4 ± 3 dB vs ~ 3 dB for beamforming and BSFE; SNR of beamforming and BSFE were not statistically different. Similarly the SIR of HBSE was significantly higher than the other two, with 8.1 ± 4 vs 3.2 ± 1 and 1.6 ± 1 dB. BSFE was statistically better than beamforming in this category. HBSE outperformed beamforming in CC, with a mean of 0.9 ± 0.1 vs 0.75 ± 0.15 , and only slightly improved upon the CC compared to BSFE, achieving statistical significance below 2 mm inter-dipole distance (Wilcoxon rank sum, $p < 0.05$). The higher variance in the HBSE metrics, specifically for the SNR and SIR, is because the input-output relation between these metrics has a slope greater than one, i.e. increasing the SNR of the input signal causes a proportionally larger increase in the output signal SNR (data not shown).

EMG interference and rejection

The effect of external sources on the raw recordings from the cuff was investigated, specifically to test the efficacy of gold shielding in reducing external interference. Fig. 7(a) shows an example interference recording, in which the external dipole was positioned directly (~ 1 cm) over the cuff opening. Fig. 7(b) shows an example of the average recorded RMS values of the signal as the dipole is moved from above the center of the cuff ($x=0$) to 25 mm away, parallel to the nerve fiber path. The responses to both a standard cuff (i.e. without shielding) and shielded cuff are shown. The recorded interference signal reaches a maximum at 10 mm with a decline in amplitude as the signal moves further away from the cuff. Fig. 7(c) shows the lumped results from 8 trials in three cuffs. Two standard cuffs were used, while only one gold shielded electrode was used due to limited supply of electrode materials. On average the gold shielding reduced the recorded interfering signal by 80%, with the greatest reduction occurring at 5 and 10 mm. One interesting trend is the frequency

response of the two cuffs. The pass-band filter for the raw data was set from 10Hz–10kHz. The example shown in Fig. 7(a) shows a band rejection response with frequencies from 100–500Hz. The non-shielded cuffs showed a different frequency response, resembling a high pass filter favoring frequencies above 1 kHz (not shown). This trend was repeatable, and could not be attributed to differences in source signal strength. The cause for this effect is unknown.

These same recordings were used to test each algorithm's ability to reject external noise/signals. One second of extrinsic noise was alternately added to the two source setup (Fig. 5(a–b)) to create two internal sources (i.e. neural) and one external source (i.e. EMG). An example is shown in Fig. 8(a). Fig. 8(b) displays the correlation coefficients as a percentage of the zero-interference CC between the internal sources and the extracted signals for each algorithm in the presence of varying amounts (100uA to 1mA) of external interference. The reported SIR (in dB) represents the ratio of the recorded internal signal over the recorded external signal. All algorithms show improved correlation coefficients as SIR is increased, approaching 0% above 8dB. The three subplots of Fig. 8(b) correspond to three different experimental paradigms. In the first case there is no external signal in the baseline/training phase. In the second case the same external signal is present between training and testing, while in the third a slightly different external signal is present between training and testing. HBSE demonstrated improved performance (i.e. lower reduction in CC) over the beamforming algorithm in all three scenarios (Wilcoxon rank sum test, $p < 0.01$) for SIR below 6dB. For cases one and three, HBSE demonstrated better performance than the BSFE (Wilcoxon rank sum test, $p < 0.05$) for SIR below 6dB, with $-40 \pm 39\%$ and $-13 \pm 24\%$ reduction vs $-58 \pm 33\%$ and $-40 \pm 37\%$. For case 2, HBSE only achieved statistically better CC for SIR below -6 dB (Wilcoxon rank sum, $p < 0.05$).

Chronic neural recording

To determine the ability of the new algorithm to extract signals during a chronic trial, we recorded the activity on the sciatic nerve of a mongrel hound walking on a treadmill, illustrated in Fig. 3. One trial from this experiment was analyzed with all three algorithms. Fig. 9(a) shows 10s of raw neural recording from two channels, while 9(b) and 9(c) show the extracted signals for each algorithm alongside the corresponding EMG signal. All algorithms were trained with data from the first 20 seconds of the recording, which included baseline and neural activity. Isolated source activity for training was extracted by locating segments during the gait in which only one muscle was active. Testing was then performed on the data from 20–40 seconds, and the SNR, CC and SIR were calculated for each source/algorithm (Fig. 10). HBSE outperforms the other algorithms in extracting these signals, roughly doubling the recovered signal's SNR with 9.8 ± 3 compared to $\sim 4 \pm 2$ and the SIR from 4.6 ± 3 vs $\sim 2 \pm 1.5$ for the other two algorithms, while also obtaining higher correlation coefficients, 0.68 ± 0.3 vs $\sim 0.45 \pm 0.3$, for both sources.

Information rate

The information transfer rate (ITR) was calculated for each source (Fig. 11). Fig. 11(a) shows the ITR for each source/algorithm for several binning levels. HBSE achieves roughly 5 bits per second (bps) for both sources and across most bin levels, while the BSFE achieves

approximately 3 and 1 bps and the beamforming roughly 1 bps for each source. Fig. 11(b) shows the histogram of the EMG signals for this trial. The GN EMG signal exhibits a fairly uniform distribution, with only the highest levels showing a marked decrease in frequency. The TA EMG signal, however, has a highly non-uniform distribution as it is relatively inactive for ~80% of the gait.

Discussion

Physical setup

The physical setup presented in this paper represents a combination of *in silico* and *in vivo* experiments. A similar setup has been used to recreate single fiber action potentials and investigate EMG interference with nerve cuffs [19], [20]. The main improvement upon this method is the use of the micromanipulator to allow precise placement of user defined sources, similar to *in silico* experiments. The physical nature of the recording allows the full implant system, including FINE, amplifiers and signal acquisition unit to be tested, which is an advantage of acute *in vivo* experiments. The main drawback from this approach is the inherent isotropy of the saline medium. Nerves are anisotropic, with significantly lower conductance in the transverse direction compared to the longitudinal section. Perhaps more importantly, the perineurium surrounding the active fibers serves as a large impedance barrier between these fibers and the outside contacts. The results from this setup therefore represent the idealized scenario, as the lead field matrix L used to model activity assumes a homogenous medium and thus better fits the saline data than a nerve.

Source localization resolution

The ability to localize and resolve signals in distinct locations within the cuff is an important factor in signal extraction with these algorithms, as it provides a theoretical lower bound on the separation of spatially distinct sources. With the goal of extracting signals at the fascicular level, we want to discriminate signals separated by 500 μm , as most fascicles in the upper limb nerves of humans are roughly 500 μm [21]. The results in Fig. 4 demonstrate that the FINE should be able to reliably discriminate between sources that are at least 1 mm apart. An acute study analyzing source localization error with beamforming in acute rabbit experiments [12] reported lower errors, 0.14 ± 0.1 vs 0.36 ± 0.2 here, although this study recorded compound action potentials and thus had significantly higher SNR. Another study using a different source localization algorithm, sLORETA [22], reported $\sim 0.15 \pm 0.1$ mm error, although this study investigated source localization *in silico* in the smaller rat sciatic nerve and so the results are not directly comparable. It is possible that different source localization algorithms from EEG literature, such as sLORETA or FOCUSS, could improve upon this accuracy, although such a head-to-head comparison is beyond the scope of this work.

Previous simulation work [23] has demonstrated that sources closer than 2mm become increasingly difficult to separate with decreasing distance, while further separation has little to no effect on signal recovery. The localization error in this work revealed a similar trend within this critical region of 0.5–2 mm, further supporting the idea that sources greater than 1mm apart are identifiable while closer sources are increasingly difficult to isolate. Using a

more realistic lead field may improve upon this limitation, as recent EEG work suggests [11]. Using ultrasound, it may also be possible to obtain an image of the nerve during surgery which could be used to create a patient-specific lead field [24].

Algorithm comparison on source recovery

While source localization remains a key component of all investigated algorithms, the most important metric for comparing algorithms is the ability to extract signals of interest. The metrics for comparing signal extraction in this study were SNR, SIR and CC. SNR represents the ability of the algorithm to reject intrinsic noise in the recording, SIR the ability to reject other active sources and CC the ability to extract the true signal (i.e. without distortion). Fig. 6 shows the improvements in signal recovery with the HBSE algorithm. One major advantage of HBSE is the ability to reject intrinsic noise. When no source is active, a pure spatial filter averages the inherent noise of the recordings, creating a noise floor. With this model based approach, no such limitation is placed; the signal can approach zero when the source is estimated to be inactive, which is demonstrated by the large increase in SNR. Similar to the BSFE algorithm, this algorithm rejects noise from known interfering source locations, and thus maintains a high SIR. For low SNR input signals, HBSE also outperforms the other algorithms with respect to correlation coefficients. As the SNR is increased, however, this effect dwindles and in fact reverses (data not shown). This effect is largely because the model based approach estimates the variance of a purely zero-mean Gaussian signal. While neural recordings from cuffs tend to represent Gaussian signals, this assumption is likely not perfect and so an upper limit exists on how precise this algorithm will recover signals. Given the reliance on estimating variances, HBSE must work on relatively large data segments (50–100ms), and thus fine resolution in the temporal domain is not possible. In the trivial case of recovering a compound action potential, for example, this algorithm will perform poorly relative to spatial filtering methods. The HBSE modeling method takes significantly longer to analyze a segment of data, on the order of milliseconds against the relatively instantaneous solution from spatial filter matrix multiplication, but achieves overall improved extraction metrics. The increased processing time/complexity places increased restraints on the necessary hardware to implement this algorithm in real time, although the time increase (~10ms) is not prohibitive in terms of functional delay for prostheses [25].

Effect of gold shielding

The results in Fig. 7 clearly demonstrate improved external source rejection using gold shielding. The recorded potentials match a previous study [26], in that the interfering signal is largest directly above the cuff opening and decreases to zero within a few cm. The reduction is greatest when the external source is just above the cuff. This result agrees with an *in silico* study which also showed an approximately 80% reduction in external interference with shielding [27], [28]. The absolute magnitude of the recorded signal is relatively meaningless in this setup, as the non-homogeneities in a realistic situation would affect the amount of recorded interference; this magnitude would likely decrease relative to that shown here, as the presence of a nerve should shunt current around the cuff. The relative reduction in interference, however, remains valid. One shortcoming was the low number of electrodes used (2 standard and 1 shielded) due to a shortage of materials for FINEs. Further

reductions in EMG may be achieved with improved shielding coverage. One approach not tested would imbed a fine gold mesh throughout the entire cuff instead of just the two largest faces (Fig. 3(a)). Other well studied peripheral nerve interfaces, such as the LIFE and USEA, have also demonstrated the utility of shielding for recording [29], [30]. Together these findings suggest that shielding should be an integral component of any chronic peripheral nerve recording interface.

EMG rejection by algorithm

The proposed algorithm demonstrates an improved ability to reject external sources as compared to BSFE and beamforming (Fig. 8(b)). The three cases investigated represent three levels of *a priori* knowledge about the external interference. The first case assumes zero knowledge, and represents the intrinsic ability of the algorithm to reject external interference. The second case assumes perfect knowledge of this noise and represents the ideal case. The third case represents the more realistic case in which this noise is known but not perfectly represented in training; it is difficult or impossible to record all possible types of EMG contamination since EMG is a dynamically changing signal (due to fatigue, length changes, etc.). HBSE shows an inherent ability to reject this external noise not present in the training set due to its model-based nature. Extrinsic sources cannot be sparsely modeled as point sources within the cuff, and thus HBSE naturally tends to ignore these signals by allowing the residual of the cost function to increase; fig. 8(a) demonstrates this feature. Fixed spatial filters, such as those used by BSFE and beamforming, have no such mechanism. If the interfering sources were constant and known, as in case 2, a spatial filter can be constructed to reject it, as evidenced by Fig. 8(b). As previously stated, though, EMG interference cannot be fully characterized. Only a fixed interference, such as stimulation artifact, can be accurately characterized and thus properly accounted for with spatial filtering techniques.

Chronic ENG recording example

Several recent studies attempted to predict the EMG signal of muscles from neural recordings. Researchers [31], [32] have shown that neural spike recordings and field potentials from the motor cortex of primates can predict muscle activity of the forearms. More recently a USEA in a human was used to predict the activity of the fingers of a phantom limb [33]. In this study, we aimed to show that extraneural peripheral nerve recordings could also predict muscle activity of multiple muscles in a freely moving animal. Fig. 9 demonstrates for the first time that it is possible, using the proposed algorithm and FINE.

All three algorithms appear to recover the GN signals well, although only the proposed algorithm recovers the TA signal well. As noted previously, HBSE appears to outperform the others when the target signal is very small. The TA muscle is smaller and produces more modest force compared to the GN, and thus should produce a smaller neural signal; this may explain why HBSE appears to have improved signal recovery.

The information rate calculation provides a more universal performance metric and agrees well with the correlation results, in that HBSE demonstrates an improvement over both

algorithms for both sources, particularly the TA signal. It is important to note, however, that this standard information calculation assumes various priors which aren't met with this setup [34]. The largest violation is that the distribution of messages (EMG) is not uniform, particularly for the TA signal. This error can be corrected for by employing non-evenly spaced bins, which create bins that have the same number of messages. This analysis was done (not shown), and had a small effect on the results for GN but a significantly negative effect on the TA for all algorithms; this effect was because the lower bins were largely determined by noise, as the TA was largely inactive. The errors for this setup are also not uniformly distributed; a given message is more likely to erroneously fall into the bins immediately adjacent to the target bin rather than being equally likely to fall into any bin. The results for the GN signal though largely hold, and further demonstrate that the HBSE could be used to extract dynamic, proportional signals from a nerve as opposed to 1 bit per second with the beamforming algorithm, which has previously been used to classify gait in a binary fashion (which corresponds to roughly 1 bit per second).

It is interesting to note that these two motor signals correlate with EMG so well given the presence of sensory activity, specifically proprioception and mechanoreceptors. Motor fibers are large, producing a correspondingly large signal, and fire relatively synchronously, which is critical to produce detectable signals with a nerve cuff and may explain this high degree of correlation. Although large sensory fibers exist, they may not fire to the degree of synchrony as these motor fibers. A study specifically measuring proprioception in canines [35], which consists of large sensory fibers which intuitively should fire synchronously, reported modest ENG (<10uV PP) despite utilizing large ankle excursions (~100 degrees). The recorded activity in this study was larger (~20–30uV PP) with smaller ankle excursions, supporting the hypothesis that the recorded activity is predominantly motor. A more comprehensive study with smaller cuffs/implants on downstream nerves would be required to resolve this issue.

Translation to humans

Implementation in humans would require a brief training set to prepare the algorithm. Depending on the nerve(s) implanted, the user would be required to imagine a series of movements, such as elbow flexion/extension, wrist flexion/extension, etc., each consisting of roughly 5 seconds. The algorithm is unsupervised beyond this point, and thus frequent retraining over time would be possible without the need of a technician. The signal extraction window, 100 ms, is comparable to that used in myoelectric devices and represents a reasonable delay for functional use [25]. The largest hurdle lies in the difference in anatomy; targeted human nerves have many more fascicles, and thus the algorithm may have to associate a given movement with more than one fascicle. Research suggests that functionally related fascicles course together in the nerve [21], thus as long as these functional groups are well separated in space the algorithm should be able to extract such sources. An *in silico* study investigating this problem has already been performed on the femoral nerve [23], demonstrating the ability to translate this technology to more anatomically complex nerves.

Summary/Conclusion

The results from the benchtop setup as well as the preliminary results from the chronic neural recording data show that extraneural cuff electrodes can be used to extract neural signals from electrodes placed around an intact, multi-fascicled nerve and predict muscle activations. Such predictions could then be translated into command signals for a powered prosthetic limb, allowing for natural and dynamic control. Such signals could also be used to recover signals from the organs innervated by the vagus nerve. Future work will involve using the proposed algorithm on more chronic neural recordings from dogs, investigating the stability of training and signal extraction.

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Fig. 1.

Benchtop setup for generating realistic neural signals. A) Physical setup. The cuff is fixed to a custom made platform, which consists of a base, a pedestal which holds the FINE in place (middle) and two flanking corner pieces which serve as the zero position for the dipole arm. The dipole arm is attached to a μ manipulator at the top, and has two wires attached to it which form a dipole within the cuff (shown in B). Lead wires and gold shielding of FINE omitted (See online version for color).

Fig. 2.

Generating μV level signals. A) Signal output (current) from analog isolator. Waveform taken from chronic recording of the sciatic nerve and generated by an isolated current stimulator, controlled via a custom LabVIEW program. B) Two single channel recordings from one trial (see Fig. 4 for contact locations). Amplitude differences in the channel array are used by the algorithm to reconstruct source locations.

Fig. 3. Chronic recording experimental design. A) Example of implanted FINE, with 16 channels arranged longitudinally across the cuff, with gold shielding attached and exposed on the exterior of the cuff [28]. B) Example of previous FINE (no shielding) on sciatic nerve, just proximal to bifurcation of tibial and peroneal fascicles. C) After implant, canines were trained to walk on a treadmill while ENG and EMG recordings were taken (percutaneous connector/wires to amplifier not shown).

Fig. 4.

Localization resolution. A) Example of localization map from 100ms of data, with estimated source location (X), known dipole location (O) and radial error (white bar). B) Histogram of localization error performed in 16 locations with 12 trials at each location.

Fig. 5. Generating mixed recordings and recovering signals with HBSE. A) Two signals are independently placed at different locations with varying inter-dipole distances (white bar). B) Signals are combined to form a two source setup, in which source 1 is active, then both simultaneously, and then only source 2, followed by baseline (denoted by i–iv, respectively). C) Example of recovered signals (solid) against the original source (dashed).

Fig. 6. Comparison of algorithms. Bars show mean $\pm$ SD. The x-axis represents the distance between two active dipoles; all metrics showed a slight improvement as this distance increased. HBSE significantly outperforms the other two algorithms in terms of SNR and SIR, with more moderate increases in correlation coefficient.

Fig. 7.

Interference rejection with gold shielding. A) Example recording from EMG interference setup. One second of sine waves with frequencies ranging from 10 to 10kHz at 1 mA are injected into the dipole at various distances from the cuff. B) Example of interference signal RMS at locations ranging from 0 (above cuff center) to 2.5 cm away from the cuff, parallel to the nerve (mean $\pm$ SD). Dipole was located 1cm above the cuff. C) Lumped percent reduction in interference signal across all trials as a function of distance from the cuff center (mean $\pm$ SD).

Fig. 8.

Interference rejection by algorithms. A) Example of mixed two source and external interference recording. The solid red and blue lines represent the original single source recordings, while the solid black line represents the addition of these two signals along with the alternating 1s interfering EMG. The dashed red and blue lines show the recovered signals using HBSE. B) Performance of algorithms in recovering signals in the presence of external interference (labeled EMG). The three cases shown represent different levels of knowledge with 1. No EMG in the training phase, 2. The exact same interfering signal in training and testing and 3. Slightly different EMG in the training and testing (i.e. EMG from 1cm away from the cuff present during training and EMG from 2cm away present during testing).

Fig. 9.

Example chronic ENG. A) Raw data recorded from the sciatic nerve of a freely walking animal. Recordings from two contacts on opposite sides of cuff shown. Data is filtered from 0.7–5kHz. B) and C) Extracted signals from chronic ENG recording. B shows the extracted signals against the corresponding tibialis anterior (TA) EMG while C shows the medial gastrocnemius (GN) EMG and the corresponding extracted signals from each algorithm.

Fig. 10.

Extracted metrics for each algorithm on the example chronic ENG recording from the sciatic nerve. Proposed algorithm HBSE outperforms other algorithms in all three categories, similar to benchtop experiments. The largest improvements are seen in SNR and SIR, as well as the CC for the TA signal.

Fig. 11.

Information from recovered signals. A) Information calculation in bits/second for each algorithm and each source. Classification is performed by discretizing the EMG and recovered signals into N bins (here, 2–8 evenly spaced bins corresponding to 1–3 bits per symbol). HBSE achieves approximately 5 bits/second, with a slight downward trend as the number of levels is increased, achieving significantly higher rates for the peroneal/TA than the other algorithms. B) Histogram of the normalized recorded EMG signals. The GN EMG shows a roughly evenly distributed signal, while the TA EMG shows a highly lopsided distribution favoring inactivity.