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Selective Recovery of Fascicular Peripheral Nerves

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Abstract

The peripheral nerves of an amputee's residual limb still carry the information required to provide the robust, natural control signals needed to command a dexterous prosthetic limb. However, these signals are mixed in the volume conductor of the body and extracting them is an unmet challenge. A beamforming algorithm was used to leverage the spatial separation of the fascicular sources, recovering mixed pseudo-spontaneous signals with normalized mean squared error of 0.14 ± 0.10 ($n=12$) in an animal model. The method was also applied to a human femoral nerve model using computer simulations and recovered all 5 fascicular-group signals simultaneously with $R^2=0.7 \pm 0.2$ at a signal-to-noise ratio of 0dB.

This technique accurately separated peripheral neural signals, potentially providing voluntary, natural, and robust command signals needed for advanced prosthetic limbs.

Keywords

Cuff Electrode; Beamforming; Flat Interface Nerve Electrode; Inverse Problem; Localization; Selective Neural Recording; Spatial Filters; Sinusoidal Stimulation; Pseudo-stochastic Stimulation

Introduction

Recent advances in the fields of electronics and robotics have made possible the design and manufacture of sophisticated anthropomorphic prosthetic arms and hands[1–3], each of which possess a large number of possible degrees of freedom. However, there are a limited number of ways for amputees to control such devices. Some use EMG signals from residual muscles, mechanical connections to the contralateral shoulder, or even a simple mode switch. None of these techniques provides a sufficient number of command signals to take advantage of all the degrees of freedom available in these devices.

In order to make full use of this technology, and advance the quality of life of amputees, it is necessary to develop a set of robust and natural command signals. Recently, Targeted Muscle Reinnervation (TMR)[5] has been shown to provide these types of signals, but the surgery required is very invasive, the systems require daily electrode placement and have significant cross-talk. Penetrating electrodes have also been employed, such as the Utah Slanted Electrode Array (USEA)[6] and the Longitudinal Intrafascicular Electrode (LIFE) [7]. Both of these devices have shown excellent signal to noise ratio and single-unit recording capability due primarily to penetrating the perineurium so that their contacts are placed very close to axons. Unfortunately, these results have not yet translated into robust,

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Author Contributions

All authors contributed extensively to the work presented in this paper.

long-term command signals and the stability of these penetrating devices has not been established.

Another potential approach is to place cuff electrodes around the nerve. These electrodes do not compromise the perineurium or the epineurium and have been shown to be both a safe and robust means of recording from the peripheral nervous system[8]. Moreover, they can be shaped, as in the Flat Interface Nerve Electrode (FINE), to increase the surface area of the nerve[9]. This technique allows more electrodes on the surface of the nerve and spreads the fascicles of the nerve apart to improve selectivity[10]. However, as they are much farther from the axons in the nerve, the signal to noise ratio is lower compared to penetrating devices, and they are only able to record field potential activity from a large number of units. This may be acceptable in the case of peripheral nerves as functional units of axons tend to be bundled within the same fascicles. This also suggests that recovering fascicular level activity may be sufficient to reconstruct a muscle command signal, and would make the system less sensitive to micro-motion and other perturbations. Several efforts have been made to use cuff electrodes to separate recorded signals into the functional components controlling each muscle, using statistical[11, 12], neural network[13] and inverse problem methods[14, 15]. While all of these techniques have shown some level of selectivity, none take advantage of an important piece of a priori knowledge: the geometry of the cuff itself. In Wodlinger and Durand[4], a novel method was presented based on Antenna Array techniques[16], where linear weights are used to focus the sensitivity of an array of recording electrodes to the broadband, near-field nerve signal. The simulation results showed that training the system on a homogeneous, rectangular epineurium and testing it on a finite element model of a human femoral nerve, localization of the fascicles was accurate to $180 \pm 170 \mu\text{m}$ and mixed signals from fascicles located more than 1.5mm apart were recovered with $R^2 > 0.8$ using a single-pixel filter (SPF) algorithm. Here, we extend that algorithm to reduce cross-talk between sources and show that the modified algorithm in an *in-vivo* rabbit preparation can separate and recover both evoked and pseudo-random ENG fascicular activity from rabbit sciatic nerve.

Materials and Methods

Beamforming and Source-based Filters

Described more completely in Wodlinger and Durand[4], Beamforming involves the generation of a number of spatial filters from *a priori* knowledge of the cuff geometry. These filters can then be used to map the instantaneous voltage on each contact of a recording electrode to an image of the activity within the nerve cross-section. This image makes it possible to localize sources, and differences in spatial location make it possible to recover the voltage signals from each source. The full algorithm is broken into three steps. First, a finite element model of a large saline bath with the cuff to be implanted containing a homogeneous, rectangular estimate of the epineurium is created. This model is used to calculate the lead-field matrix representing the sensitivity of each contact to each pixel in the nerve cross-section. This lead-field matrix is used to calculate the Transformation matrix described below which integrates the *a priori* knowledge of the cuff geometry and estimated epineurium conductivity. Second, after the cuff has been implanted, functionally distinct sources are localized by activating single fascicles or functional groups. The recorded responses during this activity are multiplied by the transformation matrix (training phase) to localize the signal within the nerve cross-section. Depending on the signal to noise ratio, a short 100ms segment has been shown to be sufficient. Once the sources have been localized, the spatial filters associated with each source are calculated. In Wodlinger and Durand[4], these filters were based on the locations of single pixels (Single Pixel Filters or SPF). Here, source-based filters (SBF) are designed to select signals from the full spatial extent of a particular source, while rejecting signals from interfering sources.

Transformation Matrix—First, a lead-field matrix (S) is generated[17] using a finite element model of the cuff electrode including a homogeneous, rectangular epineurium (Figure 1A). The lead-field matrix provides the sensitivity of each contact on the electrode to each pixel in the nerve cross-section and is used with Equation 1 to calculate the least-squares optimal filter (t) for each pixel (i), where δ is the Kronecker delta. These filters are normalized using Equation 2, and then concatenated into a transformation matrix which can be multiplied by the contact voltages to give an instant-by-instant estimate of the activity at each pixel in the cross-section.

$$S t_i = \delta_i \quad (1)$$

$$t_i = \frac{t_i}{\|S t_i\|} \quad (2)$$

Localization of sources—The second step in the signal recovery is determining the location of the source in the cuff in order to optimize the filter spatial filter, t . 130Hz current-controlled sinusoidal stimulation was used to elicit compound action potentials (CAPs) on each branch in separate trials which were then averaged over 30 seconds of iterations to improve the SNR. The mean squared power was calculated on each channel over the duration of the CAP and the transformation matrix was applied to the resulting 16×1 vector producing an estimate of the location of the source within the nerve cross-section. Similarly, averaging the power on each channel over 30 seconds of recording during 5kHz sinusoidal stimulation was found to produce nearly identical location estimates. Figure S1 shows the results of three localization experiments on three separate nerves. In each case, the top 10% of the beamforming activity map for the tibial and peroneal sources are shown (tibial in red, peroneal in green). The accuracy of the source localization has been previously studied using computer simulations and is $180 \pm 170 \mu\text{m}$ [4]. To obtain experimental verification, the images for each source are superimposed on histological nerve cross sections (Methylene Blue stain) showing the fascicles and a scale illustration of the cuff and contact positions. In all three cases, the position of the nerve is not exactly known but is roughly superimposed on the cuff. The separation between the sources and relevant fascicle groups are consistent with the location of the source. Further quantification of these data is not possible since neither the position of the cuff relative to the fascicles, nor the exact origin of the signals within their respective fascicular groups, is exactly known.

Source-Based Filter (SBF) Generation—The transformation matrix contains ideal filters for each pixel in the nerve cross-section and in previous simulation experiments the filters corresponding to the source locations were used directly to recover the signals (the “single pixel filter” or SPF technique)[4]. However, this matrix does not account for the finite spatial extent of the source or the locations of interfering sources.

To improve the recovery, new filters are generated to take into account information about the position and the spatial extent of the sources. The filters from each pixel are weighted by the value of the source image at that pixel and averaged. This method places more emphasis on locations where the source is stronger, and provides some spatial averaging to reduce noise.

The following two equations are applied iteratively to estimate the appropriate filter, $f_i^{\{1 \times n\}}$ for source i based on the estimated source location image $S_i^{\{m \times 1\}}$ where n is the number of

contacts, m is the number of pixels, and $M^{(m \times n)}$ is the transformation matrix. Note that the quantity $(M f_i^T)^T S_j$ in equation 4 represents the level of interference due to source j picked up by the filter for source i . Interference is then reduced by making use of the known locations of the other sources. Through this iterative process the filter sensitivity to regions where interference is high is decreased. Iterations are terminated when a threshold is reached, or the previous iteration was ineffective at improving the signal to interference ratio.

$$f_i^n \rightarrow f_i^{n+1} = S_i^T M \quad (3)$$

$$S_i^n \rightarrow S_i^{n+1} = S_i - \sum_{(j|j \neq i)} (M f_i^T)^T S_j (S_j - S_i) \quad (4)$$

Data Collection

Five New Zealand White Rabbits were used for this study. Anesthesia was induced with 20–50 mg/kg IM ketamine and 5 mg/kg IV diazepam and maintained with 60 mg/kg IV alpha-chloralose (followed by one quarter dose every 2 hours or as needed) and .02 mg/kg IM buprenex every 9 hours. All protocols were approved by the Case Western Reserve University IACUC. Recordings were made from a novel 16-channel tripolar Flat Interface Nerve Electrode (FINE) placed on the sciatic trunk near the popliteal fossa. The signals were AC coupled, amplified, multiplexed and low-pass filtered at 5kHz by an RHA1016 preamplifier chip (Intan Technologies, Utah). A National Instruments data acquisition card was used to perform A-to-D conversion and sampling at 15 kHz/channel. Tripolar stimulating FINE cuffs were placed on the Tibial and Peroneal branches of the Sciatic, distal to the recording cuff. Stimulation was applied to one or both of the cuffs using 130Hz, 5kHz, or 10kHz sinusoids. Signals were post-processed using an 800Hz – 3kHz band-pass digital filter to ensure removal of any remaining EMG or stimulation artifacts. A schematic of the setup is shown in Figure 1b. These stimulation paradigms allow both high-SNR synchronized activity and lower-SNR pseudo-spontaneous activity to be generated and used for several offline experiments. The methods used to generate the test signals, the beamforming algorithm applied to them, and the metrics for analysis are all described below.

Fascicular Signal Generation

Synchronous Evoked Activity: Traditional pulse-evoked Compound Action Potentials (CAPs) contain very large stimulation artifacts. Since anatomical constraints made moving the stimulating and recording cuffs farther apart difficult, we applied 130Hz sinusoidal stimulation which was found to generate CAP-like synchronized neural activity with an easily filtered artifact.

Pseudo-random neural activity: Traditional methods of eliciting more realistic activity (i.e. sensory stimulation) were found to be difficult to control and ill-suited for the task of generating consistent, repeatable, and finely controlled neural signals. Similar to techniques for more physiological cochlear implant stimulation[18], 5 or 10 kHz sinusoids were used to elicit pseudo-spontaneous activity at a variety of amplitudes. The timing and amplitude of this activity could be controlled by modulating the amplitude of the stimulation waveform. Unlike the synchronous activity described above, this activity was meant to reproduce naturally observed neural responses, for instance from sensory activity.

See the supplementary section for examples of signals evoked by each type of stimulation.

Analysis Metrics

Correlation Coefficient—The correlation coefficient was used as a metric of similarity between signals in order to be consistent with previous work[4, 12, 13]. In particular, recordings of single-branch activity were filtered using the Source-Based Filter (SBF) technique, and correlated with multiple-branch activity filtered using the same SBFs in order to determine how well the filters rejected interfering activity. Correlation coefficients were calculated as in equation 5

$$R(x, y) = \frac{\text{cov}(x, y)}{\sqrt{\text{cov}(x)\text{cov}(y)}} \quad (5)$$

Best *a posteriori* Single Channel—In order to compare these high-contact density techniques with more traditional techniques, the channels most highly correlated with each recovered single-source signal were selected after each trial. These correlation coefficients, which take into account interference as well as SNR, were compared with the correlation coefficients produced by the beamforming algorithm.

Calculation of Information Transfer Rate—In order to determine the feasibility of using this system for controlling a prosthetic limb, a standard bit-rate calculation was performed. The signals from each source were treated independently, and the range of amplitudes recorded was broken down into a set of classes. A linear discriminant analysis was performed to determine the accuracy with which these data could be classified according to the strength of stimulation (and so expected level of neural activity over the 10 or more stimulation levels tested in each case) 10% of the data was used for training and the remaining 90% for testing. Equation 6[19] was used to calculate the throughput or bit-rate where TP is the throughput in bits-per-second, R is the classification rate (in this case fixed at 10 classifications/second or 100ms bins), N is the number of classes, and P is the classification accuracy.

$$TP = R (\log_2 N + P \log_2 P + (1 - P) \log_2 (\frac{1-P}{N-1})) \quad (6)$$

Results

Both short bursts of synchronous reflex-like neural activity and tonic pseudo-random neural activity were evoked on the branches of the sciatic nerve using distal tripolar stimulating electrodes. Antidromic activity was recorded using a 16-channel Flat Interface Nerve Electrode (FINE) placed proximally on the main sciatic trunk. These 16-channel recordings contain mixed activity from both tibial and peroneal branches and were processed off-line to recover the activity originating in each branch. Details of the experimental setup, stimulation techniques, and separation algorithm are presented in the Methods section. All numerical results are presented as mean $\pm$ standard deviation.

Recovery of Synchronous Evoked Activity

The tibial and peroneal branches of the Sciatic Nerve in Rabbit were each stimulated with a 130Hz sinusoidal stimulus independently to generate 30s 16-channel reference signals recorded from the sciatic nerve which were then mixed off-line. These references allow

quantitative analysis of the signal separation and recovery, and due to the linearity of the volume conductor no generality is lost recording the signals separately and then mixing them offline. The stimulation artifact was removed with the 800–3000Hz bandpass filter. These two 16-channel signals were normalized to eliminate the confounding effect of sensitivity differences in the recordings before being added to create a mixed 2-branch signal. The tibial and peroneal filters were calculated using the Single Branch Filter (SBF) beamforming algorithm (equations 3–4, Methods section) based on trials excluded from the test set, then applied to the data. An example of the actual and recovered signals from the sources is shown in Figure 2b,c.

The original recordings contained only single-branch activity and therefore could be used as a reference to gauge separation quality calculated using the correlation coefficient between the output of the filter on the single-branch signal and the output of the filter on the mixed 2-branch signal. For comparison, the correlation was also calculated between each of the 16 channels in the combined signal and the output of the filter on the single-branch signal. Figure 3 shows the correlation coefficients obtained for both the SBF algorithm along with the correlation coefficient obtained from the “best” contact, defined as the single contact with the highest correlation to the filtered single-branch recording. Also included for comparison are the correlation coefficients obtained using the Single Pixel Filter (SPF) algorithm from Wodlinger and Durand[4]. The results from seven nerves (14 branches) show that the signals recovered by the source-based filter beamforming algorithm were highly correlated with the single-branch recordings, $R^2=0.81\pm0.08$ ($n=14$). This represents an improvement of $30\pm14\%$ over the best single channels in the mixed recording and $22\pm11\%$ better than the single pixel filter algorithm. Note that while the SBF results (light bar) are always better than the best single channel (dark bar), the SPF algorithm (grey circles) shows much higher variation, in one case slightly better than the SBF algorithm, and in three others worse than the best single channel. See the supplemental section for full numerical results, including experiments investigating the effect of reducing the number of contacts on the electrode.

The results show that even *a posteriori* when the true single-branch signal is known, it is not possible to select a channel that is a better estimate than the beamforming filter. This is true even though the beamformer is calculated without knowledge of the reference signal.

Recovery of Pseudo-random Evoked Activity

Pseudo-random desynchronized activity was evoked using 5 and 10kHz sinusoidal stimulation as described in the Methods and Supplemental sections. Desynchronized neural activity generally has much lower signal amplitude[20, 21] than synchronous neural activity making it impractical for direct recovery as done for higher amplitudes signals. Instead, averaging was applied in 100ms windows before applying the source-based filters. Note that despite this change, the filters themselves are unaffected. Signals for the two branches were mixed in the volume conductor directly, rather than offline, as stimulation was applied in overlapping windows to the Tibial and Peroneal branches. These tests consisted of approximately 5 seconds each of baseline, followed by Peroneal stimulation, stimulation on both branches, Tibial-only stimulation, and a final 5 seconds of baseline.

This test was repeated on 12 trials in 4 different animals and one typical example is shown in Figure 4. The upper frame (A) shows the mean of all 16 channels in the rectified and 100ms bin-integrated recording. The mean of the 16 channels is used for clarity, since the 16 raw channels are difficult to visualize. The lower two frames (B,C) show the outputs of the Tibial and Peroneal source-based filters on the rectified and 100ms bin-integrated recording. The black bars in the upper frame correspond to the stimulation intervals, with the Peroneal stimulated first. The cross talk between the two branches was $17\pm13\%$, and the RMS error in

the signal $14 \pm 10\%$ of signal mean, calculated during periods when only one of the two branches was active ($N=12$). Note that the SBF algorithm does not significantly increase the RMS error in the recovery, but provides a significant improvement in cross-talk. This is reflected in the reconstructions in B and C which provide a useful estimate of the mixed signal in A, demonstrating how such a system could be applied to recover mixed neural control signals.

Information Transfer Rate

Pseudo-random evoked activity from each fascicular group was separated as described above using the SBF algorithm. An LDA classifier was then trained on 10% of the data to classify the signal into 10 power-level bins based on stimulation current level. Equation 6 was applied to determine the effective rate of information transfer using 100ms windows of neural data. Overall, 4 ± 2 bits-per-second from each fascicular group was achieved.

Discussion

The volitional signals that controlled an amputee's missing limb are still present in the peripheral nervous system, and with appropriate neural interface and recovery algorithm they may be used for natural, robust control of a prosthetic limb. Lack of a robust recovery algorithm has left these signals an untapped resource, however the Source-Based Filter algorithm allows neural signals originating in various functionally-grouped fascicles to be recovered with little cross-talk.

The Source-Based Filter technique presented here was able to separate synchronized high-SNR signals with $30 \pm 14\%$ higher accuracy (R^2) than any single contact on the nerve cuff electrode. This accuracy was also on average $22 \pm 11\%$ higher than the accuracy of the SPF algorithm described in Wodlinger and Durand[4]. The reduction in accuracy caused by lowering the number of recording contacts was quantified and the density proposed previously[4] found to be critical to the algorithm's function (Supplemental Results). This accuracy represents the algorithm's performance on large reflex-like signals (SNR 15 to 31dB).

High-frequency sinusoidal stimulation was used to elicit pseudo-spontaneous activity similar to natural tonic neural activity at a variety of signal levels (SNR <0 to 13dB). Signal to noise ratios were calculated using the peak-to-peak amplitudes of the signal, not signal power. This activity is stochastic with a bell-shaped histogram, similar to spontaneous activity, and has similar magnitude and power spectrum. Further, it can be easily controlled in amplitude, duration, and source by adjusting stimulation parameters, making it a good model for recording spontaneous neural activity. The SBF algorithm was applied to recordings during this high-frequency stimulation and the accuracy of the proportional signals was far lower (generally less than $R^2=0.5$). Averaging was performed to improve the effective signal to noise ratio. 100ms was chosen for the averaging window as this value has been shown to be acceptable for the control of prosthetic limbs[22]. Acting on this moving average of the data, the algorithm demonstrated separation with cross-talk of $17 \pm 13\%$. RMS error in the reconstruction was $14 \pm 10\%$ of signal mean. Examining only the information content of the signals from each source, the FINE and SBF algorithm were able to extract 4 ± 2 bits-per-second from each fascicular group.

In order to assess the capability of this algorithm to recover human neural signals, a computer simulation with a realistic human femoral nerve finite element model and 5 simultaneously active fascicle-groups (in 10 total fascicles) was tested with overall recovery accuracy of $R^2=0.7$ ($0.44 - 0.95$) (see Supplementary Results). These fascicle-groups were chosen based on muscle-innervations, so that this example corresponds to 5 simultaneously

active muscle activation signals. These results suggest that this technique may be sufficient to control high degree of freedom prosthetic limbs, naturally and robustly.

Future work will focus on the use of adaptive algorithms to reduce the cross-talk and improve noise-rejection. At the same time, the system will be adapted for long-term implantation in chronic animal preparation and tested in patients with upper extremities amputation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

A 16-channel quasi-tripolar FINE (A) is placed on the main sciatic trunk, and two tripolar stimulating cuffs are placed on the peroneal and tibial branches, distally (B). Stimulation is provided through isolated voltage-to-current stimulators and recording done using an Intan RHA1016 preamplifier. The flow chart in (C) demonstrates how this type of system may be trained and applied in the case of control for a prosthetic limb.

Figure 2.

Separation of Peroneal and Tibial components from combined signal using Beamforming filters. (A) The mean of all 16-channels (for clarity) for a signal created by adding a normalized recording during tibial stimulation with a normalized recording during peroneal stimulation. The beamformers were applied to this signal to generate an estimate for each branch, shown in the C,E (Recovered signal). The equivalent single-branch signals (calculated by applying the filters to the single-branch recordings directly) are shown for comparison in B, D. Aside from some cross-talk in E, the separation is nearly complete. (F) Histology from this experiment overlaid with the location estimates of the Tibial and Peroneal sources and placed approximately within a schematic of the cuff electrode. Histology confirms that the fascicles overlaid by the beamforming location estimate correspond to the correct branches of the nerve.

Figure 3.

Cross-correlation of the recovered single-branch signals with the recovered mixed-branch signals (light) and the best single channels in the mixed-branch recording (dark). The R^2 for each of the 16 channels compared to each recovered single-branch signal was calculated and the highest value is shown here compared to the value from the beamforming estimate. Note that despite the fact that the best channel was calculated *a posteriori* and the beamforming filters *a priori*, the beamformer still outperforms by $30 \pm 14\%$. Grey circles represent the performance of the beamforming approach in Wodlinger and Durand[4], without the source-based filter selection algorithm described in this work. The beamforming algorithm accuracy was $R^2 = 0.81 \pm 0.08$ ($n=14$).

Figure 4.

Overlapping stimulation of the Peroneal and Tibial branches. (A) The mean of all 16 channels in the rectified, integrated recording. Black bars indicate stimulation periods for the Peroneal (left) and Tibial (right) branches. (B) Output after applying Tibial beamforming filter to the rectified, integrated signal. (C) Output after applying Peroneal beamforming filter to the rectified, integrated signal. (D) Root mean squared error and (E) crosstalk between the Recovered and Mean of All Channels signals over the single-branch portions of the signal (12 trials on 4 nerves), for recovered signals using the SBF, and SPF algorithms, as well as the best single channels (see Methods and Supplementary Results). In D,E, the boxes represent the 25th to 75th percentiles, the red lines denote the median, and the whiskers extend to the extrema of the data not considered outliers.