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A Framework for the Discrimination of Neural Pathways Using Multi-Contact Nerve Cuff Electrodes

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***Abstract*— Monitoring the activity of specific neural pathways in a peripheral nerve is a task with numerous applications in implanted neuroprosthetic systems. Achieving selective recording using multi-contact nerve cuff electrodes is appealing because these devices are well suited for chronic use, but no viable general solution to the task of discriminating combinations of active pathways from extra-neural recordings has yet been proposed. Bioelectric source localization approaches have been suggested, but their effectiveness is limited by the accuracy of the nerve model used to solve the forward problem. We propose a model-free alternative to the pathway discrimination task, in which experimental data is used to estimate a solution to the forward problem. The method was evaluated using a 56-channel cuff placed on the rat sciatic nerve. 3 pathways were discriminated with a 94.2% success rate when individually active, whereas further improvements are needed in order to recover combinations of simultaneously active pathways.**

I. Introduction

A major bottleneck of current neuroprosthetic systems lies at the neural interface: the bi-directional transfer of information between the nervous system and an artificial device is limited, precluding the use of sophisticated closed-loop algorithms that could accurately reproduce the close sensorimotor integration of the central nervous system (CNS).

Improving interfaces with peripheral nerves would be particularly valuable to the development of better neuroprosthetic systems, with applications ranging from bladder control to grasping [1-3]. Peripheral nerve interfaces are less invasive than brain-computer interfaces, with the potential to be implanted using minimally invasive interventions. They innervate well delimited regions of the body, giving their electrical activity clear functional relevance. Lastly, they provide a window into the "inputs and outputs" of the CNS, and so are a valuable tool in understanding how the CNS processes information and generates motor commands.

Nerve cuff electrodes are a type of peripheral nerve interface attractive for its safety and relevance to long-term clinical use [4], but typically providing little information about the particular neural pathways responsible for the recorded whole-nerve activity. As more sophisticated nerve cuffs with multiple recording contacts are produced [5], the question arises of whether improved spatial sampling of the electric potentials at the surface of a peripheral nerve can lead to the monitoring of specific pathways within that nerve. We present a short review of previous approaches to selective recording using nerve cuffs, and illustrate how recent work by our group constitutes a flexible generalization of previous methods that provides a useful framework for the study of multi-pathway discrimination in peripheral nerves.

II. Review of Approaches To Selective Nerve Cuff Recording

Multi-contact nerve cuffs may discriminate pathways by taking advantage of the fact that an action potential (AP) traveling along a given fiber will produce different measurements at different contacts, depending on the distance to each contact and the conductivities of the tissues. Early attempts examined the recording differences in traditional cuffs (with eight to twelve contacts) when APs traveled in various fascicles or pathways [6-9]. Developing this approach, later studies quantified the extent to which sources between and within fascicles produced different measurement patterns, using flat interface nerve electrodes (FINEs) [10,11]. However, identification of the active fascicle from the measurements was not discussed, beyond matching measurements with known patterns. Extending a pattern-matching methodology to situations in which several pathways may be simultaneously active and have varying levels of activity soon becomes infeasible. Other attempts to separate the activity of different fascicles based on extraneural recordings have included the use of blind source separation [12] and linear regression [13]. Both of those studies were limited to discriminating the activity of two fascicles. An earlier attempt to localize activity in the nerve with an eight-contact cuff used a very simplified model of the nerve's electrical properties and therefore obtained only

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coarse mappings [6]. Selectivity studies have also been reported that focused on discriminating activity related to specific innervated muscles, rather than to specific fascicles [14].

III. Bioelectric Source Localization In Peripheral Nerves

A generalization of the approaches described in the previous paragraph is to formulate the task as a problem of bioelectric source localization. This framework makes it possible to account for distributions of multiple simultaneously active sources, as well as to apply regularization methods that can incorporate *a priori* information about the problem and help deal with noise in the measurements. We have recently investigated whether methods adapted from electroencephalography (EEG) source localization could fruitfully be applied to the peripheral nerve case [15, 16]. Simulations and experimental results indicated that a crucial condition for useful performance is to have an accurate model of the nerve with which to solve the forward problem. The forward problem consists of computing the measurements that would be produced by a source at a known location, and can be solved for example using finite element modeling. The influence of each source location on the measurements is encoded in a matrix known as the leadfield. An inaccurate leadfield is an obstacle to solving the inverse problem, which consists of recovering the source distribution from the measurements. Our work focused on a rat sciatic nerve (1 mm diameter) surrounded by a "matrix" design multi-contact spiral nerve cuff [5], and found that the source localization problem as traditionally formulated was too sensitive to modeling errors and noise to be reliable.

In a similar study, Wodlinger and Durand showed that, with a FINE placed on a large nerve, major fascicles can be successfully identified using a beamforming approach with knowledge only of the electrode geometry [17, 18]. These results are promising and highlight the influence of nerve size and electrode geometry on performance, however it is unclear what resolution could be achieved in vivo without a more accurate model of the nerve's anatomy, or in the case of combinations of several simultaneous sources.

Because these methods are derived from the EEG source localization literature, a summary of the differences between the EEG and peripheral nerve contexts is useful in interpreting the results described above (Table 1). Briefly, the EEG case can generally benefit from better signal to noise ratios and lower modeling errors. These observations are consistent with our findings in [15, 16]. The peripheral nerve case does, however, benefit from an experimental advantage: many neural pathways can be activated experimentally in a well controlled manner, using techniques ranging from direct electrical stimulation (e.g. intra-operatively) to cutaneous stimulation of innervated dermatomes. In contrast, it is very difficult to experimentally isolate particular brain regions while ensuring that activity in other regions is limited. In the next section, we describe how this feature of peripheral nerves can serves as the basis for a novel and flexible framework for spatially selective nerve cuff recordings.

TABLE I. Contrast of Factors Affecting EEG vs. Peripheral Nerve Source Localization

EEG	Peripheral Nerve
Larger region, more pronounced differences between recording sites (+)	Smaller region, less pronounced differences between recording sites (-)
Lower noise can be achieved by trial averaging (+)	High noise, more limited opportunity for averaging in neuroprosthetic applications (-)
Subject-specific brain models can be obtained via MRI and used to construct accurate leadfields (+)	Nerve-specific models cannot currently be obtained *in vivo* (-)
Difficult to isolate individual brain regions experimentally (-)	Feasible to isolate certain individual pathways experimentally (+)

IV. A Model-Free Approach to the Forward Problem

We have recently proposed an approach in which the solution of the forward problem is estimated using a training set of experimental single-pathway recordings, rather than a finite element model of the nerve [19]. In this way, difficulties due to model accuracy are alleviated by taking advantage of factors specific to peripheral nerves, namely the ability to experimentally isolate pathways. Furthermore, the problem remains formulated as an inverse problem of source localization, making it possible to: (1) deal with combinations of simultaneously active pathways with different intensities; (2) apply regularization methods to deal with noise levels and incorporate any available *a priori* information. The method is summarized here; more details can be found in [19].

A. Data Collection

Acute experiments were performed on five male Long-Evans rats (old breeders, 640 g to 850 g). All animal care and use procedures conformed to those outlined by the Canadian Council on Animal Care (CCAC). A "matrix" design polyimide spiral nerve cuff electrode [5] was placed on the sciatic nerve and used to record the nerve activity. The matrix cuff had a length of 23 mm, a diameter of 1 mm and 7 rings of 8 contacts, for a total of 56 contacts. To stimulate the nerve branches, three tripolar polyimide spiral nerve cuffs (8 mm long and 1 mm in diameter) were placed around the tibial, sural, and common peroneal nerves. By stimulating the tibial (T), peroneal (P), and sural (S) nerves nerves distally, we could control which of the fascicles was active at the level of the recording cuff. The measurements from the recording cuff were acquired using a SynAmps2 64-channel amplifier (Neuroscan Inc., USA), with a sampling rate of 20 kHz and a gain of 2010. The signals were band-pass filtered between 0.3 and 3 kHz. The reference for the recordings was a contact included in the

matrix cuff design and located just outside the cuff [5]. A needle electrode in the calf was used as the ground.

The tibial, peroneal, and sural nerves were stimulated individually and in every combination. Compex Motion stimulators (Compex SA, Switzerland) were used to generate the pulses, which had estimated durations of 2-4 μs and amplitudes in the 0.7 to 3.8 mA range. These pulses were able to reliably produce action potentials in the nerve, as indicated by muscle twitches. 100 trials were conducted at 2 Hz for each combination. The amplifiers were not blanked during the stimulation due to equipment restrictions; the stimulation pulses did not overlap with the neural signal, and the amplifiers did not saturate, but they were susceptible to an impulse artifact with a time constant of approximately 0.5 ms and thus overlapping with the signal of interest. To compensate for this, the measurements were converted to a common-average reference, thereby eliminating the common artifact signals.

B. Construction of the Leadfield

Solving an inverse problem of bioelectric source localization requires a solution to the forward problem, which predicts influence of each source location on the boundary measurements. The relationship between the sources and the measurements can be expressed as shown in Eq. 1, where **d** is an Mx1 vector containing the recorded data from the M electrodes contacts, **j** is an Nx1 vector whose entries represent the magnitudes of the sources at each possible location, and **L** is the MxN leadfield matrix whose entry (i,j) represents the influence of a unit source j on the potential recorded at electrode i. □ is an Mx1 vector of additive noise. M is typically much smaller than N, making the problem ill-posed.

$$\mathbf{d} = \mathbf{L}\mathbf{j} + \epsilon \qquad (1)$$

The source localization problem is then to recover **j** based on the measurements and the estimate of **L**.

In the formulation adapted from EEG the sources are current dipoles distributed in a grid covering the endoneurium of the nerve; **L** contains one column for each grid point [16,17]. In our model-free approach, the leadfield consists instead of observed measurement vectors that are obtained from a training set of single-branch recordings, made possible by the fact that the branches can be isolated experimentally. Each leadfield column is a 56-element vector corresponding to an instantaneous spatial pattern of activity produced by an entire stimulated pathway. Each pathway will be associated with several vectors, because different patterns of activity will be produced as a compound action potential (CAP) travels in that pathway along the length of the recording cuff. The training set includes only observations of single-pathway activity, because the system should be able to identify combinations of pathways based only on knowledge of the single-pathway base cases. The main steps are summarized in Fig 1; a detailed description of the methods is available in [19].

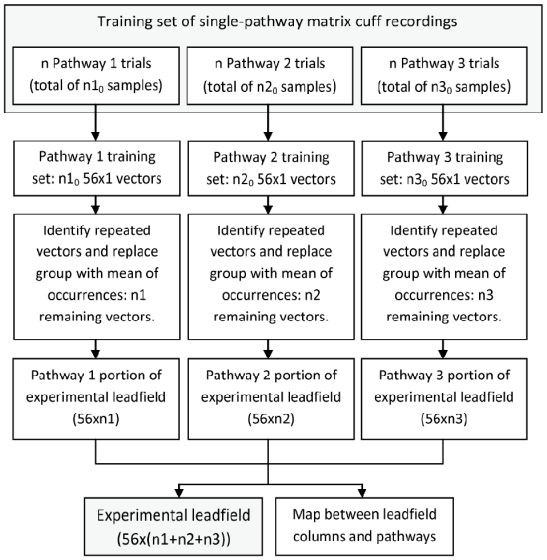

Fig 1: Flowchart illustrating the main steps of the model-free leadfield construction process. Reproduced from [19].

The trials were divided into a training set and a testing set, for each of the three single-pathway case (T, P, S). In the case of the multi-pathway combinations (TP, TS, PS, TPS), all trials belong to the testing set. In each single-pathway case, the trials were divided into 5 groups, and the performance measured using 5-fold cross-validation. The multi-pathway performance was evaluated 5 times, using a different training set each time but always the same testing set (all trials).

For each single-pathway case, the set of distinct measurement vectors that occur within the training set was identified. Each new vector was compared to all previously observed vectors to determine whether it was a new pattern or one that had already been recorded [19]. For each trial, the measurement vectors used were from a time interval delimited by the peaks of the action potential recordings at the first and last contacts, plus 0.1 ms before and after this interval. A collection of vectors is built using these time instants from all the training set trials corresponding to a given stimulated nerve (Fig. 1).

C. Identification of Pathway Combinations

As long as there are more columns than rows in the leadfield, the problem remains underdetermined, and the process for solving the inverse problems remains similar to the process when using a model-based leadfield. We used Tikhonov regularization with a weighted minimum-norm method (WMN) [20]. Given that the solution is expected to be sparse (only a small number of pathways are expected to be active at once), we apply the FOCUSS algorithm [21] to the initial WNN solution. The regularization parameters are chosen using the L-curve method [22].

V. Results

Fig. 2 shows the mean of the three activity indices for each pathway combination and each rat (the activity index is

a summary of the values of all the variables corresponding to a given branch, over the time interval of a trial; see [19] for the details regarding the computation of the activity indices). In the single-pathway cases the algorithm was successful in identifying the stimulated pathway as the most active. Selecting the pathway with the highest activity index led to correct identification in 94.2% of single-pathway case. In the multi-pathway cases, the algorithm was less successful in identifying the active pathways. Although a few cases were close to being accurate, inactive pathway activities estimates were still high, and on the whole the method was not reliable: based on Fig. 2, the activity indices were thresholded at 0.2, leading to the correct combination of pathways being identified in 25.3% of multi-pathway cases.

VI. Discussion

A number of factors will affect the selectivity of nerve cuff recordings, include cuff geometry, number and location of contacts, nerve anatomy, and signal to noise ratio. In the context of an inverse problem of source localization, the selected regularization methods and *a priori* information incorporated will also play a significant role in the performance. Future work must therefore focus on understanding how these different factors can be controlled to achieve maximum selectivity and achieve effective monitoring in multi-pathway situations. It is also necessary to examine performance when natural neural activity is used rather than direct stimulation, which was used here to enable us to precisely control which pathways were active in a given trial. The contribution of this study is to provide a method for recovering a source distribution from extra-neural recordings that is flexible and designed specifically for peripheral nerves, and can be used to systematically

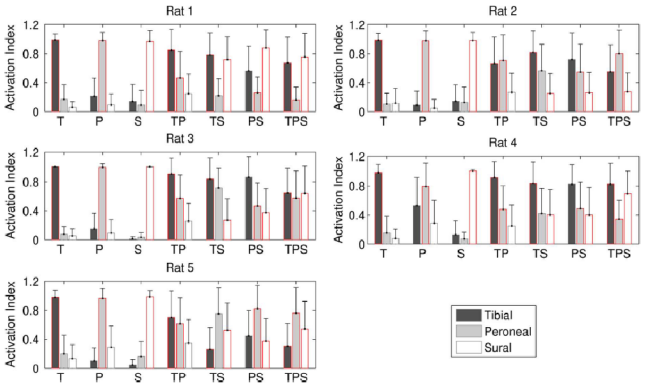

Fig 2: Means of the activity indices for the three pathways, for each rat and pathway combination. T: Tibial,P: Peroneal, S: Sural. The nerves being stimulated are outlined in red. Reproduced from [19].

investigate the factors listed above in order to maximize nerve cuff selectivity.

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