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Inferring the Stability of LIFE through Brain-Machine Interfaces

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***Abstract*—We examine neural signals from Longitudinally implanted Intra-Fascicular Electrodes (LIFE) in a chronic, rabbit model. Translation-invariant wavelet de-noising methods are used to improve SNR. Then traditional template-based spike sorting is applied to discriminate single units. We investigate the effect of discriminating between identified units on Brain Machine Interface (BMI) decoding performance. We infer the stability of LIFE based on decoding performance with and without current BMI methods to counter-act electrode neural signal degradation.**

I. Introduction

BRAIN-machine interface (BMI) research has developed technologies which restore functional ability to patients suffering from motor neuropathies. The BMI develops a functional mapping between *neural signals* and an *external signal* (e.g. hand or cursor position) [1-4] to restore user communication and control. Ideally, a BMI could be used chronically without requiring algorithm or user retraining. However, two issues currently prevent development of robust, chronic BMIs: changes in statistics of neuronal modulations and neural signal sensing degradation.

Modulations in neural activity specifically refer to changes in spatio-temporal patterns of task-related spiking. Although there is disagreement on how long a neural signal is stationary [5, 6], changes on any time-scale disrupt the BMI's modeling because the BMI assumes a static neural activity to external signal mapping. Typically, BMIs use a retraining period before each use to overcome this issue.

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Neural signal sensing degradation refers to the loss in signal quality (decreasing SNR) over time in chronically implanted electrodes. This problem may stem from the electrode moving with respect to the neuron, electrode degradation, and/or glial scarring which encapsulates the electrode [4, 7]. BMI developers use the similar retraining approach to overcome this issue periodically re-sorting and reclassifying responding spikes (for review see [8]). The most current (possibly degraded) neural signals are re-sorted such that individual neurons can be discriminated with new templates. Besides being time intensive and requiring expert supervision [8], this approach ultimately cannot overcome the total loss of the neural signal. For this reason, electrodes are currently a weak-link in developing robust, invasive BMI for clinical applications [2, 3, 7, 9]

Longitudinal Intra Fascicular Electrodes (LIFE) have shown promising semi-chronic stability and relatively minimal encapsulation and nerve damage in animal and human subjects [7, 10]. LIFE penetrate the epineurum and perineum and are oriented approximately parallel to the nerve fiber (Fig. 1). LIFE may have multiple recording sites.

The issue of neural signal stability for LIFE is investigated in a rabbit model. However, instead of looking at structural or physiological changes, LIFE's *functional* stability is inferred. Specifically, the following functional question was addressed: Does electrode degradation and/or immune response to LIFE adversely affect BMI performance? A standard technique (re-spike sorting each session) is compared against re-using old sorts in a BMI. Re-sorting is mainly necessary to overcome neural signal sensing degradation; it is shown to be unnecessary using LIFE implanted for over four months. The issue of changes in neural activity is also addressed by combining all neurons with similar functional responses as in [11, 12]. This method yields significant improvements in BMI performance.

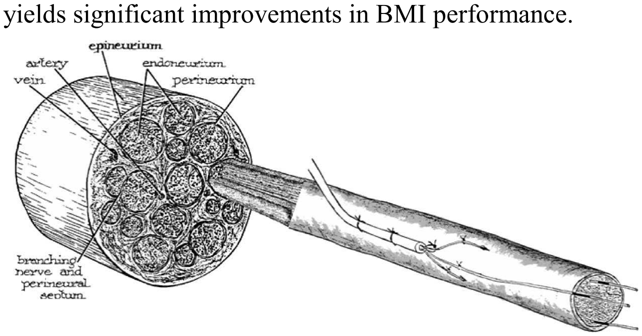

Fig. 1. Longitudinal Intra Fascicular Electrodes (LIFE) (from [1]).

II. METHODS

A. Surgical Technique & Neural Signal Acquisition

Two female New Zealand White rabbits were surgically implanted with two two-channel LIFE in either the Lateral Gastrocnemius/ Soleus or Medial Gastrocnemius nerves, surgical details are in [13]. A cuff electrode external to the nerve is used for reference. Neural signals from the LIFE are amplified with a custom built headstage amplifier [14]. Signals are then further amplified with an Axon Cyberamp and then recorded synchronously at 48 kHz. All analysis is performed offline after down-sampling the data to 12 kHz. (Prior studies have shown increasing sampling rate > 10 kHz does not further increase spike discriminability [15].)

B. Experimental Paradigm

The neural data was collected in an experimental paradigm designed to study afferent (sensory) signals. The rabbits were anesthetized and placed into device which rigidly held their upper leg and knee static. Connected to their foot was a servo-controlled motor which moved the foot (flexing the ankle joint) at 28.6^o/sec. The rabbit's electroneurographic (ENG) signal was recorded for a series of approximately ten flexion-extension cycles. These cycles consisted of flexing the ankle joint for 1s (moving 28.6^o), holding the new position for 2 s, extending the ankle for 1 s, and holding at the initial position for 2 s [14]. Cycles typically produced identical temporal ankle positions; these cycles were included in the functional analysis. We analyzed the ENG signals from 1 – 4 months after surgery (recorded at 1 month intervals) and assume transient response due to implantation stabilized before that period.

C. Neural Signal Pre-processing

The ENG signal has low SNR and various pre-processing steps have been applied to extract action potentials [15, 16]. However, based on a recent, comparative analysis [13] of discrimination afferent signals, wavelet de-noising (WD) with template-based spike sorting provided the best results.

Wavelet de-noising is a technique to remove signal noise by first identifying the noise in an orthogonal time-frequency domain, applying a threshold to remove noise, and then transforming the de-noised signal back to the original domain. Specifically we use the translation-invariant wavelet transform [17] with discrete wavelet transforms (Symlet 7 mother wavelet) as was done in [13].

D. Spike Sorting

Next, potential *single units* in the de-noised signal were identified. Standard template-matching based spike-sorting methods are used to detect and discriminate between units in the ENG [15, 16]. The spike-sorting parameters are given in [13]; however, we used a stricter error maximum (10%) in template creation and fixed template width (2.0 ms) based on the LIFE recordings in this experiment. The unit templates were created for each recording session.

All discriminated single units were checked for biological plausibility: templates were restricted to < 2.0 ms and all unit's inter-spike intervals were restricted > 1 ms (the absolute refractory period of most neurons [8]). These checks add confidence that the units could represent an neuron and that two neurons were not being classified as one unit [8]. The procedure created 11-15 units for each electrode, which is approximately the estimated number of classifiable units reported by [16]. Unit firings are summed within non-overlapping 100 ms bins to estimate firing rates.

E. Single Unit Responses

Peri-event spike histograms (PESH) show the average unit activity during the flexion-extension cycle. We show the five units with the highest firing rates in Fig. 2a for a LIFE in the initial session. The PESH illustrates that most discriminated units had a similar response: increasing firing to a maximum value during flexion and a steady but lower firing rate while the ankle was held flexed. Unit firing generally decreased to nearly zero for the other two segments of the cycle. This response (along with the implant location) suggests that all discriminated units could be muscle stretch receptors [18]. All of the discriminated units were combined into a non-neuron discriminated signal (NND) [12], where the NND signal was the average of all units with the same response [11]. Figure 2b shows the ankle position signal superimposed over the PESH of the NND signal.

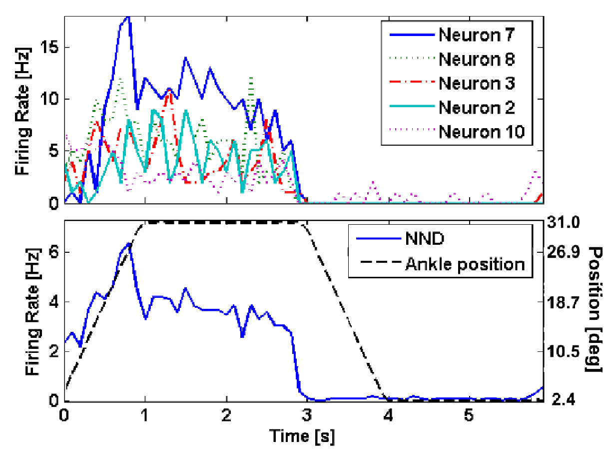

Fig. 2. (a) PESH the five units with the highest firing rates. (b) NND PESH and ankle position. Ankle flexion is 0s to 1s, extension is 3s to 4s.

F. Testing LIFE's Functional Stability

The single unit firing rates were processed in a BMI to test the functional stability of LIFE. We assume re-sorting the ENG data effectively overcomes neural signal degradation. Furthermore, we assume neural signal degradation should adversely affect BMI performance. Therefore, we inferred the neural signal degradation based on BMI performance with and without re-spike sorting, i. e. if performance is significantly worse then the neural signal has been degraded.

We also tested our assumption that combining single units into a NND signal will create a more stable signal; hence. improve BMI performance. We compared the NND inputs (all units averaged together) with neural discriminated (ND) inputs (all units considered unique) for the BMI. We test one linear and one non-linear BMI to construct the mapping between the NND or ND signals and ankle position. The Wiener Filter (WF) was used for the linear BMI because it provides a reliable benchmark in BMI research and an 'optimal' linear mapping for the given input-output signals [19]. A single-layer perceptron (SLP) with a hyperbolic tangent nonlinearity is used for the non-linear BMI [19] to exploit a non-linear relationship between the input and ankle position. The input signal (whether NND or ND) was embedded in time using a gamma (K = 2, μ = 0.4) structure [20] to preserve 500 ms of prior firing (μ optimized based on one session). Although there were more training samples available for BMIs using NND input, there were sufficient samples for BMIs using ND inputs to avoid over-fitting [19].

All BMI were trained using the *leave-one-out* method where one flexion-extension cycle is left-out for testing and the remaining cycles were used for training. Multiple BMI were trained such that every possible flexion-extension cycle was used for testing. BMI performance in all test segments was used to determine statistical significance (α = 0.05 for all tests). Average test segment performance is reported.

To infer neural signal degradation, one set of BMI were trained with input (NND or ND) data that was re-spike sorted (new unit templates created) in the training session. The other set of BMI were trained with input data where unit templates were created in the initial session and kept static.

III. Results

All networks were evaluated using two common BMI performance metrics: mean squared error (MSE) and maximum error. There were two electrodes per LIFE for each rabbit (four electrodes total); however, one electrode had mechanical connection problems and was excluded from the analysis. All combinations of BMI type (WF or SLP), input type (NND or ND), and template creation (re-sorted or static) were tested for this analysis (8 BMI per electrode). The two electrodes from the same LIFE were not grouped together because BMI performance was not significantly better than using each electrode separately (2-sample Kolmogorov-Smirnov (K-S) test).

The first comparison did not address stability; instead, it tested the assumption that NND input data can be used instead of ND. We compared the performance in both BMI types with static templates (alternatively re-sorted templates could have been used). Fig. 3 shows this comparison for a representative LIFE. For all three LIFE, the SLP with NND input data provided significantly better (2-sample K-S test) performance than any other BMI-input combination for both MSE and maximum error (see Fig. 3). Additionally, 2-sample K-S tests showed significant differences in each BMI type's performance with NND vs. ND inputs. The WF with NND inputs performed *significantly worse* than a WF with ND inputs. However, the SLP with NND inputs performed *significantly better* than a SLP with ND inputs. The significance applied to both performance metrics. This performance discrepancy may be due to the nonlinear functions ability to exploit mixed neural modulations while the WF requires the spatio-temporal correlations in ND.

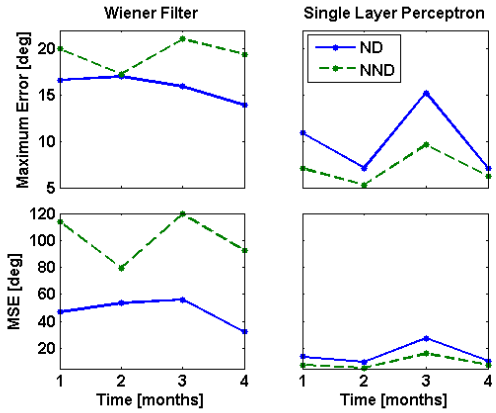

Fig. 3 Leave-one-out testing for one LIFE (representative of other two). ND (solid) and NND inputs (dashed) for the WF (left column) and SLP (right column) are compared in terms of maximum error (top row) and MSE (bottom row). All results are expressed in degrees.

The SLP results raise the question of whether spike sorting is necessary at all in this experiment. We compare an SLP with all sections of de-noised signal greater than three standard deviations marked as units vs. an SLP with sorted units (both networks used NND). The performance was *not significantly different* for all LIFE in both performance metrics (2 sample K-S test). This result suggests that spike sorting after WD may be unnecessary when using NND SLP and merits future investigation.

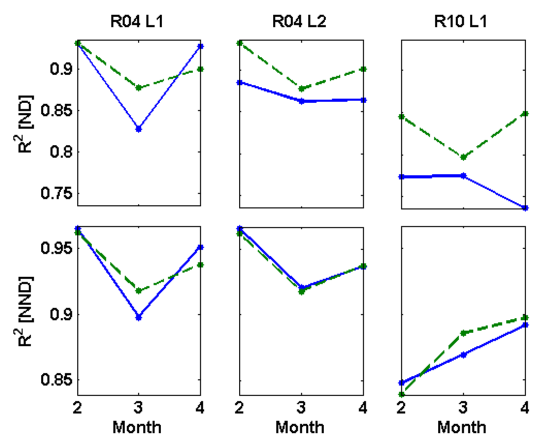

Fig. 4 SLP R^2 performance. Neural signal processing with static (solid) and re-calculated (dashed) performance is presented for each LIFE (each column) for both ND (top row) and NND inputs (bottom row).

The final comparison was designed to infer LIFE stability independent of BMI and input types. We compare performance of all BMI-input combinations with static templates vs. the same combinations with re-sorted templates. Fig. 4 compares the correlation coefficient (R^2) between SLP output and ankle position for ND and NND inputs. R^2 was used to simplify the figure but it is also a common BMI performance metric. For all three LIFE and all

BMI-input combinations (12 total comparisons) performance with static templates was *not significantly different* than using re-sorted templates (2-sample K-S test). The significance applied to both the MSE and maximum error performance metrics and also the R^2 metric.

IV. Discussion

We have designed three experiments in these chronic recordings. The first examined an assumption (based on the PESH) that all discriminated units had the same functional response. NND inputs performed significantly better than ND inputs for non-linear BMI. However, NND inputs performance significantly worse than ND inputs for linear BMI. Fig. 3 showed that changing the input to the SLP produced a correlated (R^2 of NND and ND performance = 0.97) difference in performance, possibly due to the reduced number of BMI parameters. However, the difference WF performance was not correlated (R^2 = 0.26), suggesting the WF exploited the spatio-temporal correlations in the ND to find a better mapping to the ankle position. It also could mean that SLP training should be improved to better learn correlations in ND data. However, multiple SLP were trained for each test to avoid dependencies on initial conditions and the training parameters were optimized based on cross-validation in a representative LIFE [19].

The second experiment was not an initial focus of our work but was added based on the NND results from the first experiment. While it is certainly exciting to consider processing neural data without spike sorting, there are potential confounds. It is possible that WD removes all noise in neural signal. This requires that the power spectrum of external noise (including electromagnetic and EMG) is outside of 700 – 6 kHz or the amplitude is less than ENG (1-10μV). Additionally, all signals recorded on the electrode may be stretch receptors but certain candidates were not marked as a template because of low firing rates. This requires all recorded signals to be generated from the same neural population. These are two strong assumptions that must be carefully examined before discarding spike sorting. Finally, spike sorting and PESH can discriminate functional groups of neurons which has been useful for BMI [11, 12].

The final experiment was designed to infer the functional stability of LIFE in this rabbit model. We assumed that re-creating spike-sorting templates each session is only necessary to counter-act neural signal degradation due to immune response and/ or electrode degradation. We find that BMI performance is not significantly (2 sample K-S test) different for three different electrodes (in two different rabbits) when templates were not re-sorted. We infer from this result that the LIFE were functionally stable for the duration of this 4 month recording. Although the BMI were only used for relative comparisons and not absolute performance, it is important to note that the BMIs in this study had an advantage of mapping neural signal to repeatable (over trials) signal. Typically an afferent-based BMI would require signals from muscle agonist-antagonist pairs to map both flexion and extension of a joint. However, these BMI exploited information in the gamma taps (time embedding) to predict the ankle position during extension where neural activity was negligible (see Fig. 2). If extension was not repeatable, the BMI reconstruction would suffer.

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