Ultra-Long Term Stability of Single Units Using Chronically Implanted Multielectrode Arrays

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***Abstract*— Recordings from chronically implanted multielectrode arrays have become prevalent in both neuroscience and neural engineering experiments. To date, however, the extent to which populations of single-units remain stable over long periods of time has not been well characterized. In this study, neural activity was recorded from a Utah multielectrode array implanted in the primary motor cortex of a rhesus macaque during 18 recording sessions spanning nine months. We found that 67% of the units were stable through the first 15 days, 31% of units were stable through 47 days, 21% of units were stable through 106 days, and 8% of units were stable over 9 months. Thus not only were units stable over a timescale of several months, but units stable over 2 months were more likely to remain stable in the next 2 months.**

I. Introduction

Chronically implanted multielectrode arrays are commonly used in neurophysiological experiments because of their ability to record from a large number of units over a long period of time. However, it is useful to know whether a unit recorded on the same electrode on different days might actually be originating from the same neuron. Initial attempts to track neurons involved visually inspecting the waveform shape across days [1], by computing the correlation between average waveforms [2], or by comparing the clustering in principal component space [3]. However, relying purely on the waveform shape along might lead to false positives, since different neurons may have a similar average waveform. Subsequent attempts at tracking neurons used addition information besides the waveform, such as the 3-D location relative to a tetrode [4], the inter-spike interval histogram [5] or the correlation of neuronal firing with other stable neurons [6]. Fraser and Schwartz reported tracking stable units in rhesus macaque motor cortex for over 100 days [6].

Here, we use the method described in Dickey et al. to track neurons over a series of datasets recorded over a longer time scale of 265 days. The recordings occurred during an experiment in which a naïve monkey was introduced to brain-machine interface (BMI) control of a robotic arm and hand. Thus the identification of stable units over these datasets would allow the examination of learning effects during the initial exposure of BMI real-time control.

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II. Methods

A. Neural Recordings

All surgical and behavioral procedures involved in this study were approved by the University of Chicago Institutional Animal Care and Use Committee and conform to the principles outlines in the Guide for the Care and Use of Laboratory Animals.

Data used for this analysis were collected from a female rhesus macaque (*Macaca mulatta*) monkey that was implanted with a Utah 100-microelectrode array (Blackrock Microsystems, Salt Lake City, UT) in primary motor (MI) cortex. The macaque had been the recipient of a therapeutic amputation 5 years prior due to injury. The array used for this analysis was placed contralateral to the intact limb. The electrodes on the array were 1 mm in length. During a recording session, spike waveforms from up to 96 electrodes were amplified (gain of 5,000), filtered between 0.3Hz and 7.5 kHz, and recorded digitally (14-bit) at 30kHz per channel using a Cerebus acquisition system (Blackrock Microsystems). On the first experimental session, units were sorted online with a hoop-sorting algorithm, described in Santhanam et al. [7]. Potential spikes were first identified when the filtered voltage dropped below a user-defined threshold. These spikes were sorted by placing a lower and upper voltage threshold (the "hoop") at specific times relative to the initial threshold crossing. The same sorting rules were applied to the remainder of recording sessions, so that the number of sorted units remained constant over time. The recordings for this analysis were collected on 18 separate daily sessions over the course of nine months. The first session was recorded 11 months after implantation of the array.

B. Behavioral Task

The macaque performed the same behavioral task on all of the recording sessions. In this task, the macaque had to learn how to navigate two control dimensions of a robotic arm in order to perform a reach-to grasp task. The robot was composed of a 7 DOF WAM arm attached to a 4 DOF BarrettHand (Barret Technology, Inc.). Through the use of operant conditioning, the macaque learned to control the

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reaching motion towards and away from the base of the robot, as well as the grasping motion, opening or closing all three digits of the hand concurrently. A successful trial would involve reaching-to-grasp a sphere placed on a board in front of the robot, pulling it back, and finally dropping it.

Using neurons identified using online spike sorting, distinct clusters of functionally connected groups of neurons were created for the purpose of controlling each control dimension. Decoders using the neural population activity of either group, binned at 50 milliseconds, were initialized in an unsupervised manner using spontaneous data [8]. Over the course of the study, the macaque learned this mapping such that she could coordinate movement along both dimensions in order to perform successful trials at an increasing rate.

C. Stability Analysis

The methodology outlined by Dickey et al. [5] was used to analyze the stability of single-units on the array over the course of nine months. For each sorted unit, we computed the average waveform and interspike interval histogram (ISIH). . Waveforms on two different datasets were compared by computing the Pearson's correlation coefficient to create a waveform score. The ISIHs were fit with a mixture of the three log-normal distributions, and the parameters of that fit were compared to create an ISIH score. The waveform and ISIH scores were then combined into a single score. A unit was classified as stable on a given day if this combined score fell below a fixed threshold.

III. RESULTS

Using stability criteria outlined earlier, units were classified as either stable or unstable with respect to the first recording session. For a unit to be considered stable over the course of the entire study, it was necessary for the unit to be considered stable in every one of the recording sessions.

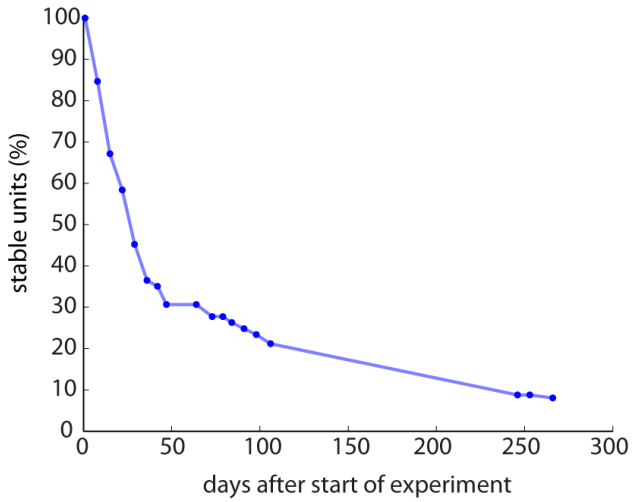

Fig.1 Survival curve of tracked units. The Y axis shows the percentage of stable units, relative to the 137 neurons sorted on day 0.

Similarly, for a unit to be considered stable through a particular day, it must have been stable on all of the previous recording sessions prior up to that day. The survival curve in Fig. 1 shows the percentage of stable units through a particular day for all of the recording sessions.

Fig. 1 illustrates that around 8% of neurons are stable over the entire nine months of the study. After 106 days have elapsed, over a fifth of the units are still stable. An inflection point can be observed around 50 days. Around 31% of the units are stable through day 47, while around 23% of the units are stable through day 98. Thus 75% of the units that are stable on day 47 survive the next 51 days. In contrast if we look at earlier recording sessions, about 58% of units are stable through day 22, while about 31% of units are stable through day 47. So only 53% of the units that are stable on day 22 survive the next 25 days.

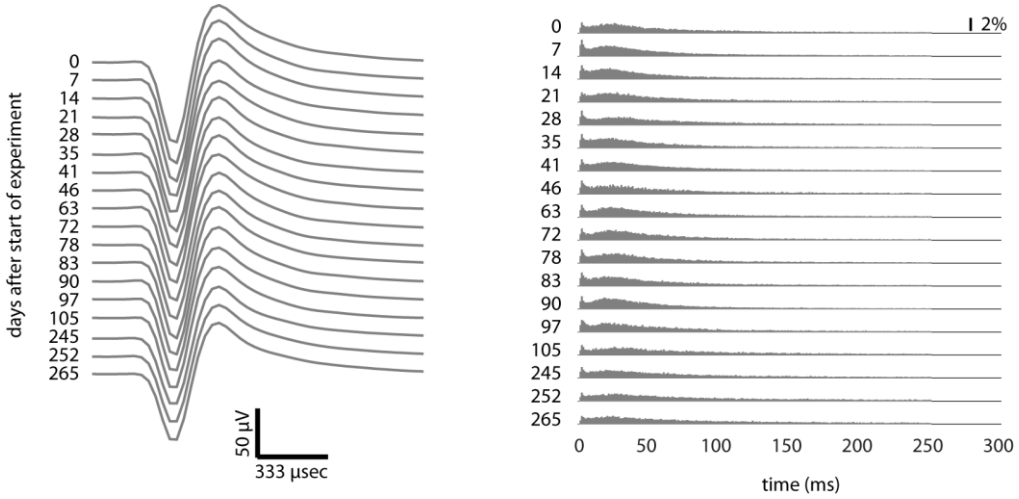

Fig.2. (Left) Waveforms and (Right) Interspike interval histograms for a stable unit over 265 days

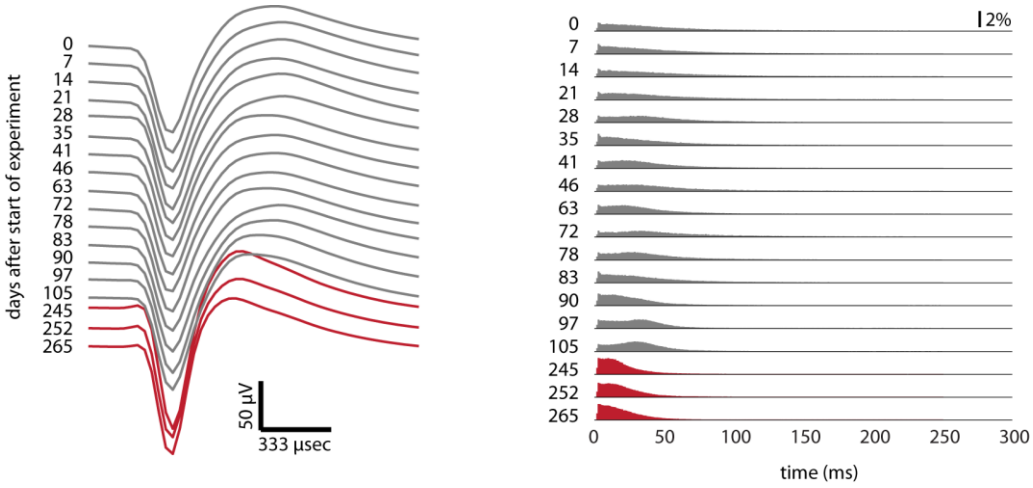

Fig.3. (Left) Waveforms and (Right) Interspike interval histograms for an unstable unit over the course of the study. Note the change in both waveform and ISIH between day 104 and 245

TABLE I. STABILITY SCORES

Unit Stability Scores		
# Days	***Stable Unit (Fig.2)***	***Unstable Unit (Fig.3L)***
7	-6.57	-6.03
14	-10.88	-12.49
21	-21.19	-3.64
28	-4.42	-11.05
35	-3.26	7.56
41	-6.20	-0.59
46	-6.60	-11.45
63	-0.97	0.43
72	-2.96	1.14
78	-3.35	2.79
83	-3.13	0.37
90	-2.75	1.33
97	-2.19	-13.16
105	-2.15	-6.86
245	-5.07	17.10
252	-3.21	21.80
265	-4.23	19.38

An example of a stable unit is provided in Fig. 2. The similarity in waveforms across all eighteen of the recording sessions over nine of months of recording is quite apparent. The same is true for the interspike interval histograms; the characteristic bimodal distribution (a Type II neuron as described in Chen & Fetz [9]) can be seen in each session. In contrast, Fig. 3 provides a clear example of a unit that changes the properties of both the waveform and the ISIH between the 15th and 16th dataset. This is when there was a 5 month gap in recording, and it appears that the first neuron was replaced with a completely different neuron. This unit was classified as stable through the 15th dataset on day 106, but not thereafter. Other unstable units change properties in both the waveform and the ISIH multiple times; in one example, the first change occurs between the first data of recording and seven days later, the second is, again, between the 15th and 16th dataset. Table 1 provides the scores for the stability of each unit shown (Fig. 2, Fig. 3) when compared with the first day of recording. The threshold for stability was below a score of 11.67 as defined by Dickey et al. [5].

Since the stability criterion relies on scores from based on the similarity of both the waveforms and the interspike interval histograms, units can fail to be classified as stable if they exhibit similarity in one feature but not the other. For example, a can show stability in its interspike interval histograms throughout the recording sessions, but can fail to maintain a consistent waveform.

IV. DISCUSSION

The most telling result of this study is that we were able to identify a subset of neurons that were stable over the course of nine months. The stability criterion that we adopted is especially conservative, so it is likely that we are systematically underestimating unit stability. It could be that 8% is a more conservative estimate due to the fact that we saw units drop out for a couple of recording sessions, only to return for the remainder of the experiment. Anecdotally, it seems that an electrode can become noisy for a single recording session, perhaps because of mechanical disruption of the contact between the Utah array and the connector, or between the connector and the headstage. This would lead to a unit as being classified as unstable, even if the noise were to disappear the next day and the unit to return. One way to address this in future work is to allow a unit to drop out for a handful of sessions, as long as the unit reappears and is still classified as stable afterwards. This will require careful consideration of the false positive rate, given the multiple comparisons across units and days.

Recording every day instead of every week would give us a survival curve to a greater degree of precision. This presents the similar issue of determining how many datasets a neuron can "miss" and still be classified as stable. Additionally, it was not possible to have the same elapsed

time between datasets. We might expect of the probability of a stable unit disappearing during an interval to increase as a function of recording sessions in the interval—i.e. the true negative rate within an interval will depend on how often you are sampling within that interval. In this collection of datasets, five months elapsed between the 15th and 16th recording sessions as opposed to the otherwise weekly or biweekly recording sessions. Around 21% of units were stable through the 15th recording session, whereas only about 8% were stable through the 16th recording session.

This analysis was also completely dependent on the online spike sorting from the first recording session In the future, we intend to use the online spike sorting from an earlier or later dataset so that we can measure how sensitive the survival curve is to the online sorting on a particular day. In addition, neural data from the first recording session can be sorted offline; this sort could then to be applied to all of the datasets in lieu of the online sort to measure how sensitive the survival curve is to online vs offline spike sorting.

On a similar note, instead of measuring how sensitive the survival curve is to spike sorting, we could look at sensitivity to the stability threshold that was fixed as a value based on a previous stability study [5]. In fact, rather than discretely classifying the units as a "stable" or "not stable" for each day, we could use the continuous stability score to determine the exact day a unit switched from stable to unstable.

Our motivation for applying the stability analysis to this particular collection of datasets was to allow us to investigate the effects of learning to control a BMI on stable neurons. In the learning study described here, the animal was able to not only learn, but improve her ability to coordinate and control different dimensions of a robotic arm in a reach-to-grasp task despite what would appear to be instabilities in her neuronal units. She was able to modify and maintain function of these clusters of neurons, despite changing properties of individual neurons. These experiments can speak to how populations of neurons in primary motor cortex can impact overall behavioral function in a robust fashion, in the presence of dynamic changes at the single-unit level – the type of plasticity that has long been implicated in motor learning experiments [10] .

In addition, this kind of tracking could be of broader use to the science and engineering communities at large. The ability to pool neurons across different recording sessions for data analysis purposes, or to identify stable units that can be consistently used for brain machine interfaces without having to retrain decoders could be beneficial. Consequently, development of an algorithm that could analyze the stability of units online, taking into account their known properties and history, could prove very useful in a BMI-context [11].

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