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Expert-like performance of an autonomous spike tracking algorithm in isolating and maintaining single units in the macaque cortex

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ABSTRACT

Isolating action potentials of a single neuron (unit) is essential for intra-cortical neurophysiological recordings. Yet, during extracellular recordings in semi-chronic awake preparations, the relationship between neuronal soma and the recording electrode is typically not stationary. Neuronal waveforms often change in shape, and in the absence of counter-measures, merge with the background noise. To avoid this, experimenters can repeatedly re-adjust electrode positions to maintain the shapes of isolated spikes. In recordings with a larger number of electrodes, this process becomes extremely difficult. We report the performance of an automated algorithm that tracks neurons to obtain well isolated spiking, and autonomously adjusts electrode position to maintain good isolation. We tested the performance of this algorithm in isolating units with multiple individually adjustable micro-electrodes in a cortical surface area of macaque monkeys. We compared the performance in terms of signal quality and signal stability against passive placement of microelectrodes and against the performance of three human experts. The results show that our SpikeTrack2 algorithm achieves significantly better signal quality compared to passive placement. It is as least as good as humans in initially finding and isolating units, and better as the average and at least as good as the most proficient of three human experimenters in maintaining signal quality and signal stability. The autonomous tracking performance, the scalability of the system to large numbers of individual channels, and the possibility to objectify single unit recording criteria makes SpikeTrack2 a highly valuable tool for all multi-channel recording systems with individually adjustable electrodes.

1. Introduction

A fundamental challenge for intra-cortical neurophysiological recordings is isolating action potentials of a single neuron (unit) from background noise and signals of other neurons, and maintaining such well isolated units for the length of the recording (Adrian, 1926; Green, 1958). Each neuron in the vicinity of a recording electrode's tip produces a unique extracellular waveform (spike) when it fires an action potential. Due to the complex morphology of neurons, the shape of this waveform strongly depends on the position of the electrode relative to the cell body and dendritic arbor (Gold et al., 2009). To collect spikes from a single neuron, one has to make sure that its spikes are well separated from noise and clearly distinguishable from spikes generated by other neurons (Hill et al., 2011).

Unwanted residual movements of the electrode tip relative to the neural tissue, however, lead to inherently unstable signals (Snider and Bonds, 1998; Santhanam et al., 2007). One common source of such tissue movement, for example, is the slow recovery of the neural tissue from dimpling caused by driving in the microelectrodes in semi-chronic preparations, which can last over many minutes (Baker et al., 1999). Also, mechanical perturbations by movements of the animal in awake preparations, especially with larger animals like monkeys, can cause non-stationarities. To avoid the loss of the signal of interest, the experimenter has to repeatedly re-position the recording electrode during the course of the experiment in an attempt to maintain a stable signal (spike tracking).

Manual spike tracking is feasible with proper training and experience when recording only with a single or a few individual

Abbreviations: SNR, Signal-to-noise ratio; MD, Mahalanobis distance; P2P, Peak-to-peak amplitude; PMd, Dorsal premotor cortex; FSM, Finite state machine; PCA, Principal component analysis; MHTC, Multiple hypothesis tracker.

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microelectrodes. Manual tracking of multiple electrodes becomes challenging, and even impractical as the number of microelectrodes increases (Baker et al., 1999), since the experimenter can only pay attention to very few channels simultaneously. Moreover, manual tracking is time consuming in two ways. First, it requires the continuous attention of the experimenter in any potentially non-stationary recording situation, independent of the number of tracked channels. Second, the time needed for the initial channel-by-channel isolation of units scales with the number of channels, unless automatized and run in parallel on multiple channels. This means, manual tracking creates a time burden and impractical attentional load on the experimenter, which eventually prevents the use of semi-chronic micro-drives with high channel counts in awake animal preparations. An automated algorithm that performs with human-like accuracy in isolating and maintaining single units by autonomously adjusting moveable electrodes on multiple channels in parallel can overcome these limitations.

Many research questions require the simultaneous recording of a large number of individual neurons from various brain areas, for example, the analysis of large-scale inter-areal correlation patterns (Abeles and Gerstein, 1988; Riehle et al., 1997; Gabriel and Eckhorn, 2003; Smith and Kohn, 2008; Pesaran, 2010; Cohen and Kohn, 2011; Rosenbaum et al., 2011), the propagation of neural synchrony (neural avalanches) in cell assemblies (Plenz and Thiagarajan, 2007), or the development of brain machine interfaces (Chapin et al., 1999; Nicolelis, 2001; Donoghue, 2002; Helms Tillery et al., 2003; Mussa-Ivaldi and Miller, 2003; Nicolelis et al., 2003; Scherberger et al., 2003; Musallam et al., 2004; Schwartz, 2004; Schwartz et al., 2006; Ganguly and Carmena, 2009; Hatsopoulos and Donoghue, 2009; Scherberger, 2009; Bansal et al., 2011). So far, mostly chronic multi-channel recording devices with fixed geometry are used for this purpose (Schwartz et al., 2006), in which individual electrodes cannot be re-adjusted to optimize neuronal isolation over time. Even though more stable on the short time scale of an individual daily recording session, the chronically implanted electrodes signal quality deteriorates on a larger time scale, typically leading to non-stationary signals across days (Schwartz et al., 2006; Ganguly and Carmena, 2009; Heliot et al., 2010) and increasing multi-unit contamination of single unit discharges over the course of weeks and month. Moreover, the neural tissue often reacts adversely to cause tissue damage and neuronal loss around the implant, which cannot be circumvented with immovable electrodes (Szarowski, 2003; Biran et al., 2005).

Therefore, implantable arrays with movable electrodes for the purpose of long-term neuronal recordings have been a focus of development (Fee and Leonardo, 2001; Cham et al., 2005; Jackson and Fetz, 2007; Yamamoto and Wilson, 2008). Especially in the last few years there have been several groups involved in the development of adjustable micro-drives with higher and higher number of electrodes (Gray et al., 2007; Gray and Goodell, 2010; Galashan et al., 2011). Most of these micro-drives depend on human experimenters for re-positioning. As with the semi-chronic recordings, an automated spike tracking algorithm would make such adjustable chronic multi-channel implants even more attractive and practical.

To address this need, we report the testing of an automatic spike tracking algorithm (SpikeTrack2). The algorithm continuously monitors neural activity from multiple channels in real time and readjusts multiple electrodes to allow unsupervised collection of well isolated spikes over long recording sessions. The currently tested version is the latest improvement to an algorithm developed by Burdick and colleagues (Andersen et al., 2004; Cham et al., 2005; Nenadic and Burdick, 2006; Wolf and Burdick, 2009a; Wolf et al., 2009). In principle, the algorithm can be applied to any motorized, moveable electrode array. Currently, it is implemented for use with the 5-channel Eckhorn drive (Thomas Recording GmbH, Giessen, Germany), the NAN 16-channel drive (Plexon Inc, Dallas, TX), as well as the FHC 4 and 8-channel electrode drives (FHC Inc, Bowdoin, ME). Technical details about the SpikeTrack2 algorithm have been published before (Hebert et al., 2011) as conference proceedings. Here we tested the performance of this algorithm in isolating and maintaining single units during extracellular recordings from the cerebral cortex of an awake, behaving rhesus monkey. Most importantly, we systematically compare the performance of the algorithm against human experts to test whether it could become a viable replacement to experimenters.

2. Materials and methods

First we compared the performance of SpikeTrack2 to passive electrode placement in improving signal quality over the course of approx. 30 min. Signal quality in this manuscript is defined by the quality of isolation, i.e., the discriminability of single units from each other and background noise. Second, we used longer recording sessions up to 3 h to compare the performance of SpikeTrack2 against three human experts. We compared signal quality and signal stability against humans when maintaining isolated units over time. Signal stability in this manuscript is defined as being proportional to the time for which an isolated single unit could be reliably maintained. Finally we compared the extent and frequency of adjustments made by the algorithm against those made by human experimenters.

2.1. Animal preparation

Two male rhesus monkeys (*Macaca mulatta*) were implanted with custom-fit titanium head-posts and MRI-compatible recording chambers (3di, Jena, Germany) over the dorsal premotor cortex (PMd). All surgical procedures were conducted under general anesthesia and complied with German laws governing animal care and experimentation.

2.2. Neural recordings

Neural data from PMd was obtained using a 5-channel Eckhorn Microdrive (Thomas Recording, Giessen, Germany). Glass-coated, tungsten-iridium electrodes with impedances ranging from 1 to 2 MΩ were lowered through epi-dural stainless steel guide tubes into the cortex, until spiking activity was encountered.

Data were collected using a Plexon recording system (Plexon Inc, Dallas, TX). Briefly, signals were amplified 6000–16,000× (20× Thomas Recording pre-amplification, 300-800X Plexon amplification) and bandpass-filtered (154 Hz to 8.8 kHz). Following this, two types of neural data were collected. Putative single unit spike waveforms (as just from online spike sorting) and part of the background noise were digitized at 40 kHz for the duration of 800 μs and time-stamped whenever crossing a simple manual-set voltage threshold (spiking data). In parallel, time-continuous data digitized at 20 kHz was collected (broad-band data) for some of the experiments.

For the first set of experiments, we were interested in how well automatic tracking with SpikeTrack2 can maintain stable signal quality, or even improve it over time. As a control experiment, we tested for comparison if signal quality under equivalent conditions would improve on its own, without making any attempt to track individual neurons (passive placement). We recorded sessions of 30 min duration using either SpikeTrack2 or passive placement of electrodes in the brain. Prior to each recording session, electrodes were driven into neural tissue and allowed to settle for 30 min, and at least one neuron was isolated on each channel by an experienced experimenter. Spiking activity was monitored while advancing the electrode, both acoustically over loudspeakers and visually via a digital oscilloscope (Tektronix Inc, Beaverton, OR), as well as via