

Design and Fabrication of a Flexible Substrate Microelectrode Array for Brain Machine Interfaces

Erin Patrick, Matthew Ordonez, Nicolas Alba, Justin C. Sanchez, and Toshikazu Nishida

Abstract— We report a neural microelectrode array design that leverages the recording properties of conventional microwire electrode arrays with the additional features of precise control of the electrode geometries. Using microfabrication techniques, a neural probe array is fabricated that possesses a flexible polyimide-based cable. The performance of the design was tested with electrochemical impedance spectroscopy and *in vivo* studies. The gold-plated electrode site has an impedance value of 0.9 M Ω at 1 kHz. Acute neural recording provided high neuronal yields, peak-to-peak amplitudes (as high as 100 μ V), and signal-to-noise ratios (27dB).

I. INTRODUCTION

TECHNOLOGICAL advances in microelectrode neural probes have great potential to benefit patients with neurological diseases and injuries because they allow for direct interfacing and intervention with neurons of the nervous system [1]. The idea is to bypass damaged tissues by using engineered interfaces (brain machine interfaces (BMI)) for communication and control. The interface design involves chronically collecting neural activity directly from the cortex of the brain, interpreting its information, and delivering therapy via an electronic interface. Such devices have the potential to allow paralyzed individuals to communicate with the external world via computer control or direct control of prosthetic limbs and wheelchairs.

For motor control neural interfaces, the functionally representative modulation of activity in cortical columns (i.e. hand, arm, etc. of the homunculus) is the signal of interest. In the rat, cortical columns consist of a dense network of cells with estimates of 100,000 cells per cubic millimeter with pyramidal cells appearing 89% of the time [2]. Two major types of fixed probes commonly used to record from such cells are: (1) conventional wire microelectrodes assembled from insulated tungsten wires and (2) micromachined electrodes fabricated using integrated circuit microfabrication technologies.

Wire microelectrodes have been extensively used for acute and chronic applications of neural recording [3]-[5]

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and have provided the precise firing information of single neurons from cortical and subcortical structures. Typical microwire electrodes consist of bundles of 50 μ m diameter insulated tungsten wire with either blunt or sharp electropolished tips. For BMI's, the ultimate application of a fully implantable device warrants the need for integration between the amplifiers and electrode arrays. Traditional microwire arrays may not be prepared for this functional integration.

The limitations of mechanically assembled wire electrode arrays can be overcome by using microfabrication and micromachining techniques employed in integrated circuits [6]-[9]. Moreover, integration of signal processing circuitry onto the substrate of the probe is possible. The recording sites typically consist of exposed metal pads located on rigid shanks that are connected via interconnect traces to output leads or to signal processing circuitry on a monolithic substrate. Some place multiple recording sites along the length of the shank to allow for interrogating cells at varying depths in the neural tissue [7], [9]. An electrode design known as the Utah probe [10], [11] uses micromachined square arrays of 100 single contact electrodes bonded to a demultiplexer connector with local amplification.

Rigid substrate micromachined probes described above may introduce chronic tissue damage due to mechanical forces encountered from strain transferred from the mount to the probes floating in neural tissue [12]. As one way to mitigate this challenge, Ref. [13] designed a flexible substrate microelectrode array, where thin metal electrode sites and subsequent wiring are enclosed between polymers. This flexible electrode array adds needed strain relief yet cannot be inserted into the brain matter directly. An incision must be created first in order for the electrode to be implanted. Ref. [14] incorporates rigid probes with planar electrode sites on the probe shank hybrid-packaged to a flexible cable that connects electrodes to output ports. This design may be inserted directly into neural tissue, keeping damage to a minimum, and provides greater reliability of the probe assembly.

In this paper, we report a neural microelectrode array design that leverages the recording properties of conventional microwire electrode arrays with the additional features of precise control of the electrode geometries and flexible micromachined ribbon cable integrated with the rigid probes. The goal is to produce electrode arrays that have high neuronal yield, are highly customizable in terms of geometry/layout, minimize tissue damage, and are easy to mass fabricate. The detailed design is described and characterization results on the lab bench and *in vivo* are given. Performance characteristics include impedance, noise floor, and *in vivo* measurement of action potentials.

II. MICROELECTRODE DESIGN

An optimal electrode design for BMI chronic *in vivo* recording requires

1. small profile probes that generate the least amount of tissue damage during insertion and chronic recording.
2. structurally robust probes that do not buckle during insertion into tissue.
3. low probe impedance that is stable during chronic recording.
4. recording sites selective to single neuron action potentials.
5. adaptability to on-chip processing circuitry.

Using conventional micromachining techniques, we design small-profile metal traces enclosed between flexible polyimide insulation, making a cable, as seen in Figure 1. The actual probes extend from the cable 2 mm and include $20 \times 50 \mu\text{m}$ electrode sites on the tips. The electrode area is chosen for sufficient compromise between signal selectivity and noise performance [15]. The corresponding probe dimensions assure adequate structural integrity according to calculation using Euler-Bernoulli beam theory. The metal traces and corresponding bond sites can be made to any size specification and spacing distance via photolithography. Therefore, custom application specific integrated circuits (ASIC) for signal amplification and spike detection may be packaged on the flexible substrate using flip-chip bonding techniques in future designs.

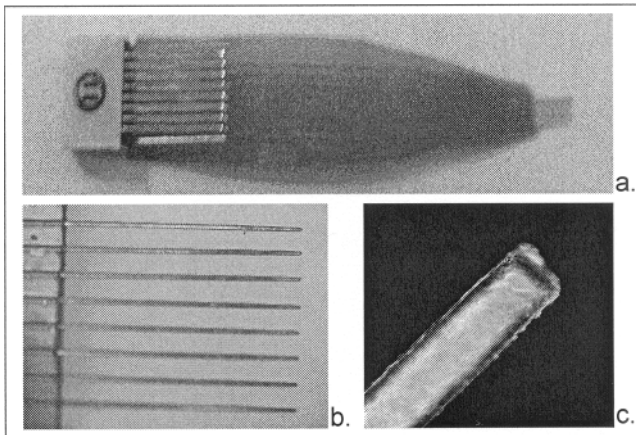


Figure 1. a. Flexible substrate microelectrode array with Omnetics connector. b. Microelectrode array. c. Probe tip showing insulation along shank and gold plating on tip.

A. Material Selection

Polyimide, chosen as the cable material for its flexibility and good dielectric properties, is widely used in the medical field as a neural implant material with negligible tissue response [16], [17]. Parylene-C, chosen for the probe insulation material, has also been successfully used as insulating material on chronically implanted microelectrodes [19]-[21]. Nickel is chosen as the rigid probe material due to its ability to be electroplated easily. However, [22] cautions that nickel implants can instigate allergic response in some individuals. Therefore, gold is electroplated on the exposed nickel electrode sites to increase its biocompatibility.

B. Process Flow

All processing is performed on the surface of a 100 mm diameter silicon wafer covered with Kapton tape (which provides adequate adhesion for the subsequent polyimide layers). The polyimide bottom insulation layer (PI 2611, HD Microsystems) is spin deposited and cured to a final thickness of $20 \mu\text{m}$. Sputtered nickel, 100 \AA , is patterned to define the probe, wiring, and bond pad dimensions. Then nickel is electrodeposited on the nickel seed to an average thickness of $20 \mu\text{m}$ via a 10 mA direct current for 4 hours in a nickel sulfamate bath (Nickel S, Technic Inc.). Adhesion promoter (VM9611, HD Microsystems) is next applied followed by three spin coatings of the PI 2611 to achieve the final $20 \mu\text{m}$ top layer of insulation. Aluminum (1000 \AA) is patterned as a hard mask for the subsequent oxygen plasma etch. The etching process includes an O_2 reactive ion etch (RIE) that removes the polyimide from the top of the bond pads and the probe tips. The remaining polyimide under the probe tips is isotropically etched in a plasma barrel asher. Then the probe-cable assembly is removed from the substrate wafer and primed for parylene-C deposition with a silane adhesion promoter (Acros Organics). The parylene-C vapor deposition step insulates the shank of the metal probes to a thickness of 2-4 μm . Then the probe ends are manually cut with a blade to expose bare metal for the electrode sites. Finally, the probes are immersed in an electroless gold plating solution (TechniMGold AT, 600, Technic Inc.) that covers the electrode sites as well as the bond pad sites with $0.1 \mu\text{m}$ of gold. An Omnetics connector is then fixed to the bond pads with silver epoxy.

III. RESULTS

A. Electrical Characterization

a. Impedance

Electrochemical impedance spectroscopy was performed on a neural probe array in 0.9% NaCl at room temperature using a potentiostat (Solatron 1286) and frequency analyzer (Solatron 1250). A silver/silver chloride reference electrode and platinum counter electrode were used. Measurements were taken over a frequency range of 5 Hz to 10 kHz at open circuit potential with a sinusoidal perturbation voltage of 10 mV. All data shown is consistent with the Kramers-Kronig relation as prescribed by [23]. An impedance of $0.9 \pm 0.02 \text{ M}\Omega$ is obtained for a single probe at 1 kHz.

Regression of the impedance data was performed to obtain an equivalent circuit describing the physical nature of the electrode/electrolyte interface. The most appropriate circuit that physically explains the interface consists of R_e (electrolyte resistance) in series with a parallel combination of R_t (charge transfer resistance), and $Q_{dl} = j(2\pi f)^\alpha C_{dl}$ (double layer constant phase element). The regressed parameters are given in Figure 2.

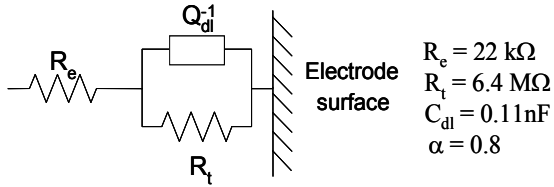


Figure 2. Equivalent circuit for electrode/electrolyte interface.

b. Noise Floor

Thermal noise from the real part of the electrode/electrolyte interface impedance is assumed to be the dominant noise source [24]. The resulting noise voltage can be given as follows

$$V_n(rms) = \sqrt{4kT \int_{\omega_{low}}^{\omega_{high}} \left(R_e + \frac{R_t}{1 + (\omega^\alpha C_{dl} R_t)^2} \right) d\omega}, \quad (1)$$

where ω_{high} and ω_{low} are the high and low pass-band frequencies of the amplifier [24]. The theoretical rms noise voltage of the designed neural probe is 2 μ V based on the regressed equivalent components and frequency range of 100 Hz to 6 kHz.

B. In vivo testing

a. Surgical Implantation

Adult male 250 g Sprague-Dauley rats were used to test the recording performance of the flexible electrode arrays. All procedures have been approved by the University of Florida IACUC Board and were performed in the University of Florida McKnight Brain Institute. Prior to surgery, the rats were anesthetized and the surgical site was thoroughly sterilized. The top of the skull was then exposed by a midsagittal incision from between the eyes and the landmarks bregma and lambda were located on the skull [25]. The microwire array was implanted to a depth of 1.66 mm into the forelimb region of the primary motor cortex. The electrodes were stereotaxically moved to the appropriate site and lowered to the appropriate depth using a micropositioner (1 mm per hour) to minimize distress to the brain tissue (FHC, Bowdoinham, ME). The array was then

grounded using a 1/16" diameter stainless steel screw. A low profile Omnetics connector was used to attach the recording wire.

b. Surgical Recording

Extra-cellular potentials recorded at 12,207 Hz during surgery were analyzed and spike sorted using Spike2 (CED, U.K.) software package. Recordings were analyzed over a period of 130 seconds at a cortical depth of 1.66 mm. To detect and sort neural activity within each channel, an automated waveform matching system within Spike2 was used to construct templates using threshold detection.

Once a set of waveform templates were generated for a data stream, all templates (noise) that did not match characteristic neural depolarization behavior were removed. The remaining waveform templates were sorted according to amplitude and shape, and any waveform templates that were significantly similar to each other were combined into a single template. Clustering of waveform variance within templates was verified through principal component analysis (PCA). Each waveform template was statistically unique and representative of a distinct neuron within the channel.

Once neuron waveforms were isolated and sorted, peak to peak amplitude was evaluated by computing the average waveform of all spikes within the neuron template and measuring the potential difference from the apex of the repolarization peak to the apex of the depolarization peak. The noise floor of each channel was evaluated by computing the root mean square value of a 5 second period of noise. Using these two values, the signal to noise ratio for each neuron template was calculated. To ensure proper reporting, all spike waveform templates that possessed peak to peak amplitude of magnitude below three times the value of the noise floor were considered too close to the noise to be reliably and consistently distinguished and were removed from the study. Values of neural yield, noise floor, amplitude, and SNR are reported for each channel within Table 1.

TABLE 1
NEURONAL YIELD FOR EIGHT CHANNEL MICROELECTRODE ARRAY

Electrode	1	2	3	4	5	6	7	8
Yield (neurons)	2	2	2	3	6	5	3	4
Noise Floor (μ V, RMS)	4.1	5.0	5.3	4.4	5.2	3.8	3.7	4.3
Neuron Amplitude (μ V, PtP)	20.1	23.3	32.6	26.1	114.7	90.4	31.4	45.1
	13.2	15.5	24.7	18.3	56.8	52.3	13.4	29.7
				14.2	34.6	35.7	11.7	21.0
					21.3	21.0		16.0
					18.8	13.8		
SNR (dB)	13.8	13.4	15.8	15.5	26.9	27.6	18.6	20.4
	10.2	9.9	13.4	12.4	20.8	22.8	11.2	16.8
				10.2	16.5	19.5	10.0	13.8
					12.2	14.8		11.4
					11.2	11.2		
				10.5				

Action potential amplitudes as large as 115 μV and as small as 13 μV are discriminated by the electrode and recording system. The average RMS noise floor is 4 μV . Figure 3 shows recorded data from electrode number 6.

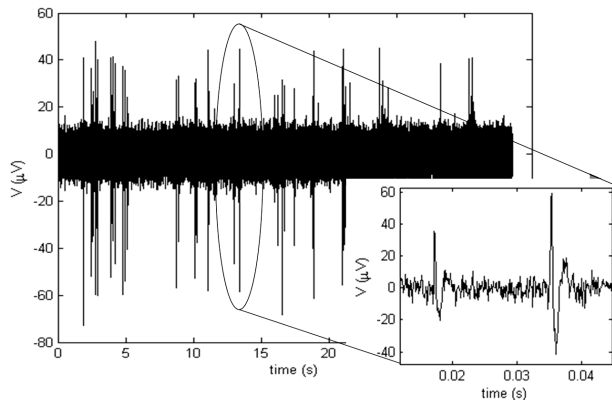


Figure 3. Data from neural recording in the rat motor cortex at a depth of 1.66mm during implantation surgery. Inset shows two distinct neurons recorded by single probe.

IV. CONCLUSION

A flexible substrate microelectrode array has been designed using microfabrication techniques and tested *in vivo*. Acute electrophysiological recordings show excellent yield of recordable neurons and signal to noise ratios from 10 to 27 dB. The neural probe array consists of eight probes with gold-plated electrode sites ($1000 \mu\text{m}^2$) on the tip that protrude from a flexible cable. The benefits of the microfabrication design allows for tailoring the electrode geometry for neuronal structures of interest. Moreover, high channel count arrays can be constructed by layering the proposed design. The flexible cable additionally provides strain relief from the fixed external connection and can be used to minimize tissue damage in chronic applications. Additional studies on the reliability of the electrode array as a chronic recording device is needed to confirm the biocompatibility of the electrode material. However, due to the adaptability of the fabrication process, other metals such as platinum may be readily incorporated.

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