Active Microelectronic Neurosensor Arrays for Implantable Brain Communication Interfaces

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Abstract—We have built a wireless implantable microelectronic device for transmitting cortical signals transcutaneously. The device is aimed at interfacing a cortical microelectrode array to an external computer for neural control applications. Our implantable microsystem enables 16-channel broadband neural recording in a nonhuman primate brain by converting these signals to a digital stream of infrared light pulses for transmission through the skin. The implantable unit employs a flexible polymer substrate onto which we have integrated ultra-low power amplification with analog multiplexing, an analog-to-digital converter, a low power digital controller chip, and infrared telemetry. The scalable 16-channel microsystem can employ any of several modalities of power supply, including radio frequency by induction, or infrared light via photovoltaic conversion. As of the time of this report, the implant has been tested as a subchronic unit in nonhuman primates ($\sim$1 month), yielding robust spike and broadband neural data on all available channels.

Index Terms—Brain–computer interface, neural interface, neural prosthesis.

I. INTRODUCTION

MODERN brain science is actively trying to "break the neural code" by many different tools. Truly understanding the brain will require sensing access across a vast range of spatial and temporal scales, including the ability to read neural signals from a select subset of single neural cells *in vivo*. One way to access a collection of single cells for deciphering their role in relation to motion or behavior is by means of using invasive arrays of microelectrodes that pick up the single cell electrical activity representing the local neural code. Their spatial and temporal resolution is high compared to extracranial imaging techniques (fMRI). Based on recent advances, there is now the prospect of direct electronic communication with the brain, motivated by compelling medical rationale. There are millions of individuals who suffer from serious neurological illnesses, whose quality of life is substantially compromised even if the brain itself is functional. Enabling such individuals to communicate directly from the brain to command assistive and therapeutic devices is of substantial societal and personal value. Here, we describe our approach and developmental status, in the quest of an implantable, wireless cortical recording modality which we have demonstrated in short term subchronic experiments in fully awake macaque monkeys ($\sim$30 days).

The paper is organized as follows. Section II motivates the work through an example of current research where a "passive" microelectrode neural sensor array is cabled through the skull and the skin to external electronics in human pilot trials. In Section III we outline one approach towards an implantable wireless neural sensor for cortical communication, focusing on the key engineering design and fabrication challenges and development pathways. Section IV describes the performance of a prototype of our current microelectronics system with the microelectronics mounted atop the head of a monkey (hence outside the skin envelope). Section V shows initial results of the fully implantable system in our current work in nonhuman primates.

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II. MOTIVATION: "THOUGHT-TO-ACTION" USING CORTICALLY IMPLANTED "PASSIVE" NEUROSENSOR ARRAYS

Within the mammalian brain, specific areas of the cortex can be identified where bursts of electrical signal impulses ($\sim$1 ms duration "spikes") arise due to electrochemical activity within single neural cells, and can be decoded to reveal correlation with the underlying commands for motor function, e.g., limb movement [1], [2]. Within the primary motor cortex (M1), an "arm-area" can be identified within a few mm precision that is responsible for issuing commands relaying arm motion, such as reaching for a target, to the spinal cord. Two-dimensional arrays of up to 100 needlelike, surgically implanted electrodes with interelectrode separation on the order of 100 μm have been employed in animal tests over the past decade to develop understanding of the neural code for motor tasks in nonhuman primates [3]–[5]. Recently, similar techniques have also been used to restore mechanically or anesthetically prohibited motor functions in monkeys by cortically controlling a robotic arm or a functional electrical stimulation (FES) device [7], [8].

The silicon-based, multielectrode arrays used as neural sensors in our work follow from the original design by Normann *et al.* [6] recording "spikes" best when their impedance in the ~ 1 KHz frequency domain is in the range of a few hundred kilohms. This empirical observation has governed the neural system electronics design to date. Once the digitized neural signals from a monkey are extracted, decoding algorithms and filters correlate the rates of spike activity recorded across the microelectrode array to the observed motion such as using a joystick or mouse to move a cursor on computer screen [7].

A contemporary version of such a brain recording platform, cabling the cortical neuroprobe from a subject's head to the signal acquisition and processing electronics, has been used in the first human pilot trials involving chronic implants in severely paralyzed patients [9]. This system (Braingate) employs a 10×10 element silicon-based array encased in dielectric silicone and has a 100-wire bundle that conducts the neural signals through the skull to external instrumentation. The human trials have yielded motor-task-related neural data for applications that enable communication activities such as reading email, typing messages, and opening and closing a prosthetic hand. One patient is presently able to operate a simple but effective communication interface more than three years after the microelectrode implant—an important milestone which shows 1) how the arm area of the motor cortex remains viable even in the absence of active use of physical limbs, and 2) that tissue/microelectrode interface has not been degraded beyond functional use over this time interval. Other assistive devices being tested under such "direct brain control" include a wheelchair and a robotic arm. These results underscore the motivation for our work to miniaturize and fully implant such brain–interface sensors by integrating microelectronic devices and wireless telemetry onto the sensor platforms.

III. IMPLANTABLE ACTIVE NEUROPROBE "MICROSYSTEM:" DESIGN AND FABRICATION REQUIREMENTS

Several groups worldwide are now working towards implantable wireless active microelectronic neural interfaces [10]–[16], with recent progress reflected by papers published in this issue. The concept of an implantable wireless platform, without any percutaneous skin-puncturing elements, demands the implementation of a heterogeneous, active microelectronics platform. At a minimum, the implanted "microsystem" requires *in situ* integration of ultra-low-power microelectronic ASICs with the cortical microelectrode neural probes, and must provide broadband telemetry and a means to deliver power wirelessly to the active implanted components. In our laboratory, a 16-channel version of a fully implantable microsystem, whose design and performance is summarized in the following sections, has been implemented and tested on the benchtop and used in initial animal tests. Our microsystem is a single-unit construct (Fig. 1) where analog and digital chips are integrated on a flexible substrate together with a low threshold, infrared semiconductor diode laser to transmit the digitized neural signals through the skin. Power and clocking are delivered to the system via inductive coupling [13], [15], [18], [19], but the system can also be configured to be powered optically using a high efficiency photovoltaic energy converter [12].
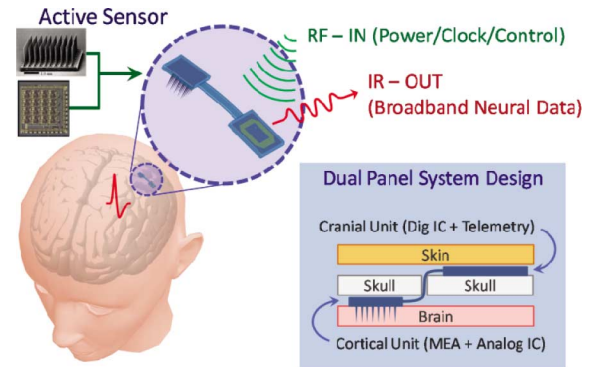

Fig. 1. Schematics of the "dual panel" brain implantable microsystem featuring an active brain sensor (microelectrode array integrated to amplifier IC) in the cortical unit, and hybrid A/D, control, and RF-IR(Infrared) telemetry in the cranial unit.

The present use of a 16-electrode sensor as a development model of our system reduces its complexity, fragility, and cost. This allows us to test telemetry and power transfer, package design, and surgical adaptability more thoroughly and quickly. However, all aspects of the system have been designed to be scalable in two senses. First, the amplifiers and A/D converter (ADC) systems scale nearly linearly in power with increasing numbers of electrodes. We have already established that our inductive coupling loop is capable of supplying the additional power and the preamplifiers (45 μW per electrode) are sufficiently low power that their thermal load on the cortex will still be acceptable. The infrared telemetry has so far demonstrated capacity for 32 channels *in vivo* and is scalable to 100 channels. The digital processing is adaptable in its current form to any number of channels as long as the clock rate, limited by the telemetry channel, is sufficient to carry the data.

The second sense of scalability refers to the ability to place two or more separate cortical sensors in the cortex so that as more channels are available, they can be used to acquire data from different brain areas simultaneously. (One example is to implant one array in the motor cortex and a second in the parietal cortex). This is possible because we separate the signal processing, power, and telemetry subsystems from the electrodes and their analog amplification and multiplexing. Channel addressing and ADC conversion have been designed to merge two sets of data into a single output stream at no increase in power, alteration in chip design, and no change in the number of wires to each array.

The rationale for our choice of the particular spatial distribution of the passive (cortical) neural sensor, the active signal acquisition electronics, the digital control components, and the telemetry and power elements, is based on convergence of considerations of microelectronic device engineering, thermal loading, neurophysiology, anatomy, and surgical constraints. At one extreme of such possible layouts is a construct with all the microelectronic components physically integrated directly onto the multielectrode neural sensor. Such a monolithic "brain button" would be entirely located proximate to the brain, i.e., below the skull, and is currently being pursued elsewhere [14]. By contrast, our considerations have led to a "dual-panel" design with cortical and epicranial (subcutaneous) sections mounted on a common flexible polyimide substrate
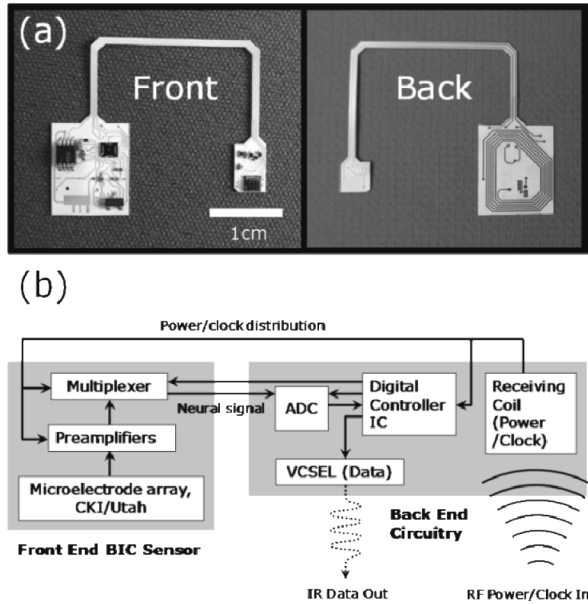
Fig. 2. (a) Photographic images showing an implantable 16-channel microsystem with a dual-panel liquid crystal polymer substrate. A spiral pattern of RF power receiving coil is clearly visible in the backside image. (b) Block diagram of the dual-panel microsystem showing neural signal and power/clock flows among various micro- and optoelectronic components.

(Kapton-fabricated by MicroConnex Inc.), as shown in Fig. 1. Distributing the microelectronics payload in this manner can have several advantages for future human applications.

The cortical "front-end" panel consists of the electrode array flip-chip bonded (using an epoxy dot technique described in [17]) to a monolithic low power CMOS integrated circuit (IC) with preamplifier array and analog multiplexer and a single bypass capacitor. Placing only the preamplifier-multiplexer chip directly onto the cortical microelectrode array ensures that we capture the full neural signals from the brain with minimum environmental interference while minimizing direct heating of the brain tissue. (Our criterion for $\Delta T < 0.6\,^{\circ}\text{C}$ rise is conservative versus typical thermal limit for medical implants).

A small flat ribbon cable, part of the common polymer substrate, with seven embedded gold wires for signal and power connects the cortical panel to the epicranial "back-end" panel. That panel, placed between the skull and the skin, holds the A/D converter and a digital control ASIC as well as the power and data transmission components. Most of the system power dissipation occurs in these components. Their placement can enable improved heat dissipation by surgically arranging "arterial plumbing," and allows ready access for infrared data detection and for radio-frequency (RF) inductive coupling. It isolates the neural array from any magnetic forces that may be used to align the RF and telemetry units. Finally, it keeps open future options for telemetry and power supply.

Fig. 2(b) shows an electronic block diagram of the present 16-channel system. Some of the key system requirements for the prototype units described below are 1) mW level power consumption, 2) ability to record both spikes and lower frequency field potentials, and 3) a safe packaging and encapsulation strategy for eventual chronic use in humans.

Front and back photographic images of a prototype microsystem are shown in Fig. 2(a), displaying components and interconnect wiring. (The cortical front-end shown contains several discrete components which have now been integrated into the preamplifier chip.) The "U-shape" for this construct was for testing in a specific nonhuman primate based on its anatomy. This was quantified by reconstructing the skull and the brain in a rapid-prototype plastic model from the monkey's MRI and X-ray CAT scan images. The surface-mount components on the epicranial section are fastened to their contacts with silver epoxy. The bare die of the digital controller IC is wire bonded using gold wiring. The gold spiral on the back of the epicranial section is the RF inductive pickup coil. The largest components are the ADC and the digital control ASIC. The analog-to-digital converter is an off-the-shelf, 12-bit, AD7495 (Analog Devices) packaged in a standard micro-SO8 package. The ADC operates at 34–40 Ksps per channel depending on the way power is supplied. This choice of a high sampling rate preserves all the subtle features of the spike waveforms so that useful information enabling distinction between single and multiunit activity recorded at a single electrode is available from such data.

The ADC receives a clock and a start-of-conversion signal from the digital controller IC that also supplies the channel address to the amplifier circuit. The controller is a custom integrated circuit built in the AMIS 0.5-μm process through MOSIS and has been described in more detail elsewhere [20]. The controller has two other functions. First, it multiplexes the ADC data with a periodic synchronization code word that replaces the data from one channel. The external electronics that receive the neural data uses this unique code word to find the beginning of the serial data for the first channel. Second, the controller converts the multiplexed data into the drive current for a low-current, high-efficiency, vertical-cavity surface-emitting laser diode (VCSEL), which produces a peak optical output power of 2 mW for the optical telemetry. The VCSEL occupies less than 1 mm^2 of substrate area. The controller derives its clock from either the RF inductive power loop or from modulation on the dc power source depending on the supply mode. The controller IC contains a comparator that regenerates the digital clock from a small sinusoidal signal separated from the appropriate source in the power module. Total system power consumption is approximately 12 mW in the present version including all parts of the implanted system.

The present integrated preamplifier-multiplexer chips has some excess noise at low frequencies that limits their utility for local field potential (LFP) measurements. They exhibit an equivalent amplifier input noise of 7.3 μV$_{\text{rms}}$ in a 50 Hz to 7.5 KHz bandwidth. Typical the 3 dB design bandwidth for each amplifier is approximately 7.5 KHz with a representative gain of 43 dB. We have carefully analyzed the noise sources [20] and have developed a new design similar to that pioneered by Harrison *et al.* [21] but have not yet used it in implantable units. This new design is anticipated to have an equivalent noise voltage of 4.7 μV$_{\text{rms}}$ and 45 dB of gain (for design details see [20]). The power in both current and anticipated designs is about 45–50 μW per channel depending on the exact power supply voltage. These performance values are viewed as acceptable for a practical chronic implant.

The entire microsystem of Fig. 2(b) is presently encapsulated in polydimethylsiloxane (PDMS) for electrical isolation and mechanical flexibility. Surgical implant considerations require careful control of PDMS thickness to maintain flexibility in the tether and to prevent buildup over the electrode array. For images of the structure after encapsulation, see [12] and [19]. The main functions of the encapsulation are to ensure 1) that electrical leakage current to the adjacent tissue is less than 10 pA, and 2) ionic leakage from the tissue to the electronic components is inhibited. For chronic implant applications, this presents a formidable challenge for all researchers in the field of implantable neural prosthetics. We view our initial approach, using PDMS (NuSil R-2188), as a useful starting pathway at least to subchronic or short-term (1–3 months) *in vivo* animal testing.

To evaluate the performance of our "soft" encapsulation we have soak tested samples for six months in saline at $T = 52\,^{\circ}\text{C}$. The testing is done using a small test circuit board that is a simplified version of the complete implantable neurosensor. The test structure enables continuous monitoring of the resistance between interdigitated conductors on the substrate surface as well as leakage current through the encapsulation material. The leakage currents are a proxy for the presence of ions that might have leaked through the encapsulation material. The test structure includes elements with all the same morphological characteristics as those encountered on the real devices and includes a working ADC. In a test of 10 sample devices, the leakage current between bath and circuit was found to typically vary between 1 and 10 pA at 3 VDC with no significant change over time. The ADCs provided appropriate data for the duration of the test. In spite of these results, it is clear that chronic implants will require a more reliably impermeable barrier. We are presently exploring combinations of soft organic polymers with inorganic thin film multilayer barriers or heterogeneous mixtures, solid solutions of inorganic molecules in polymers. Candidate inorganic materials include SiC, SiO_x, or Si_3N_4.

IV. NEURAL MICROSYSTEM EVALUATION

Development and testing of a fully implantable neural microsystem is a multistage process, requiring rigorous performance evaluation and validation at each step. In this section, we report on our development pathway towards the final goal of a fully implantable (presently 16-channel) system via four steps: 1) evaluation at the benchtop level via immersion in physiologic saline solution (mimicking the conductivity of brain tissue) and "pseudospike" electrical current injection; 2) building a printed circuit board (PCB) version of the microsystem ("Neurocard") for external mounting atop a primate skull, to validate the system component performance by coupling this external unit to passive microelectrode array implants with skull-mounted connectors, 3) *in vivo* testing during acute surgery in rodents (rats, whose anatomical dimensions only permit the insertion of the cortical "front panel"), and finally 4) surgical techniques for microsystem implant into a monkey with wireless transcutaneous signal transmission, with online reliability and animal safety monitoring.

Fig. 3. (a) RF input power/clock transmission with coil separation of ∼3 mm (Top Trace); Pulse-coded optical output datastream representing part of a neural event (Bottom Trace), and (b) Comparison of system performance using pseudospike recording test in saline bath. 100–500 μV signals are injected into the saline bath and recorded by hybrid RF-IR power/telemetry wireless system (right) and a system with electrically wired telemetry and power links as a reference (left).

A. Benchtop Testing

We characterized the performance of a prototype 16-channel fully integrated system in benchtop tests (15 active and one synchronization channel). The unpopulated side of the substrate for the epicranial panel of the microsystem has an integrated six-turn metal strip spiral coil, with an outer diameter of 1 cm [as shown in Fig. 2(a)], serving as an RF power receiver for inductive coupling. The RF frequency (the clock frequency) is 13.56 MHz, driven by a programmable RF signal generator through an external coil with dimensions matching the integrated coil. The multichannel amplifier outputs are multiplexed, digitized and converted into pulse code modulated (NRZ-PCM) infrared light pulses by the digital controller IC and VCSEL. Transcutaneously transmitted infrared (IR) pulses are received in free space by a silicon PIN photodiode (S6967, Hamamatsu Inc.), which converts the PCM light signal to a digital stream of electrical pulses for real-time reconstruction and storage. Signal acquisition and storage is done on an IBM-compatible PC though a custom digital interface board.

The performance of one representative channel is shown in Fig. 3(b), where a bipolar transient voltage has been applied between a $Ag/AgCl_2$ bath electrode and the reference electrode of a microsystem immersed in physiological saline. Clear bipolar
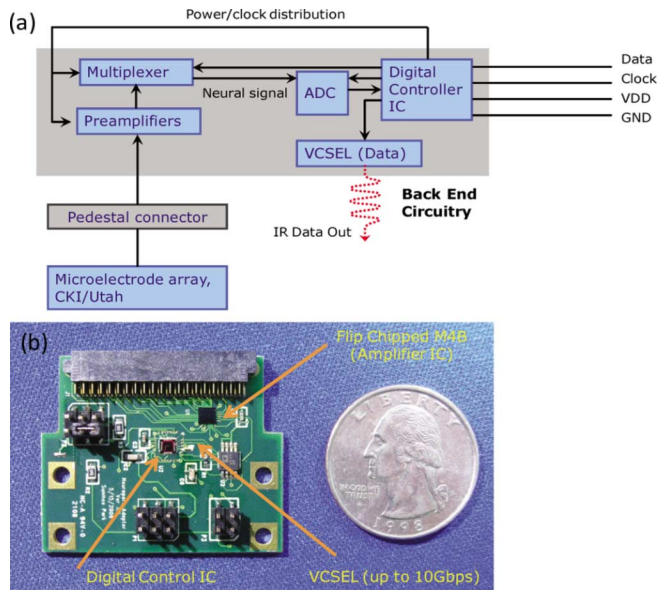
Fig. 4. (a) A block diagram of the "Brown NeuroCard," which is a compact neural recording system on PCB substrate with a Neuroport adapter connecting to the input terminals. (b) Potographic image of the Brown NeuroCard showing various micro- and optoelectronic components on a small PCB substrate.
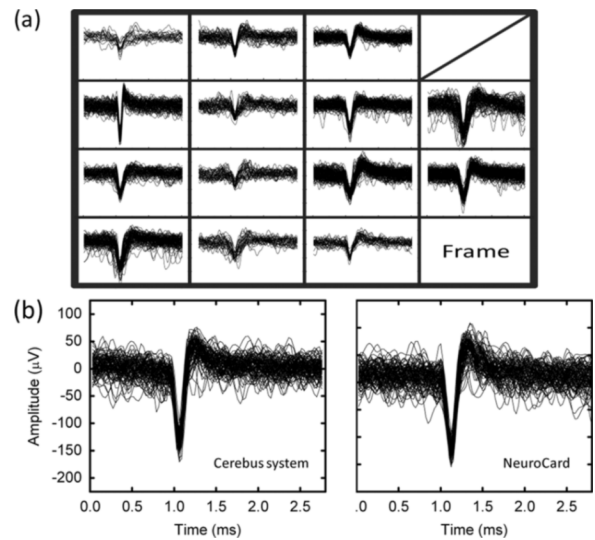

Fig. 5. (a) A typical multichannel (15 channels) neural recording acquired with the Brown Neurocard from a behaving Rhesus monkey with a passive microelectrode array implanted in the primary motor cortex (M1). Each subplot represents a 500 μV range and 3.5 msec interval and contains superimposed action potentials from continuous recording for about 5 s. (b) Successive recordings were performed in a single session (within 2 h) with Cerebus recording system (left panel) and Brown Neurocard (right panel), yielding very similar results in both spike shapes and spiking rates. All the waveforms shown here are band-pass-filtered at 0.3–7.5 kHz. Channel 4 did not exhibit clear spike activity.

spike waveforms are reconstructed from the PCM optical data stream. The waveforms acquired from the IR wireless system [right traces in Fig. 3(b)] show identical gain to those from a wired system [left traces in Fig. 3(b)], demonstrating the practical utility of IR optical telemetry and RF inductive power delivery schemes.

B. Testing in Primates—Active Microsystem Electronics Exterior to the Skull

Implanting passive microelectrode arrays into nonhuman primates is relatively routine; however, integrated constructs such as the one described here require a different set of surgical parameters to be "mastered" by neurosurgeons. One key issue is to ensure that microelectrodes reach their required target area and depth (latter with submillimeter precision), while carrying the additional electronic payload and a mechanically different tether and associated force loads.

A practical approach to decouple the evaluation of microsystem electronic performance from surgical, anatomical and neurophysiological implant complications is to move the active electronics to an external platform and use input from existing implanted passive arrays. Such an approach has been adapted recently for neuroscientific studies in freely moving monkeys [16]. We have pursued this strategy and developed a small printed circuit board (PCB) bearing all the active microelectronics of Fig. 2. This PCB (3×3.7 cm) rigidly connects to a skull-mounted pedestal connector, and can be used in conjunction with standard passive implants in monkeys. The neural signals extracted from the board (by wire or wirelessly via IR) can then be directly compared in quality to those acquired from the same animal using a standard commercial (rack-mounted) neural signal acquisition system. Fig. 4 shows (a) a block diagram of the test system and (b) a photographic image of the "Brown Neurocard."

Fig. 5(a) shows a snap shot of the multichannel recordings from a head restrained monkey. Comparison of the extracted spike waveforms acquired with the Brown Neurocard test system versus those collected with the commercial Cerebus neural signal acquisition and processing system, composed of a skull mounted preamplifier unit and a rack-mounted electronics module, is shown in Fig. 5(b).

Comparison of the signal-to-noise ratio of data acquired through the two systems shows similar performance. Fig. 5(b) demonstrates the isolation of a single neural spike waveform with high temporal fidelity with either system. This *in vivo* monkey experiment conveniently checks our microsystem as a neural recording platform, since the completely implantable microsystem and Neurocard test system are identical except for substrate materials.

C. Acute In Vivo Testing in Rats

Once system component performance has been satisfactorily validated, the crucial next steps are to evaluate the microsystem in real biological and surgical operating room environments, and to develop appropriate insertion techniques for implant surgery. Using rodents as an animal test-bed is a key step prior to any trials in nonhuman primates. We have implanted just the analog "front-end" of our microsystem in the somatosensory cortex of anesthetized rats (anatomical size constraints), and recorded well-characterized spontaneous neural activity over a period of several hours. These *in vivo* trials have enabled us to verify our packaged microsystem functionality, and allowed us to investigate both surgical insertion techniques and control of environmental spurious noise [19]. Male Sprague-Dawley rats were used in this *in vivo* proof-of-concept demonstration. The anesthesia was induced by the barbiturate and short-acting hypnotic Pentobarbitol. The initial dose was 80 mg/kg with additional
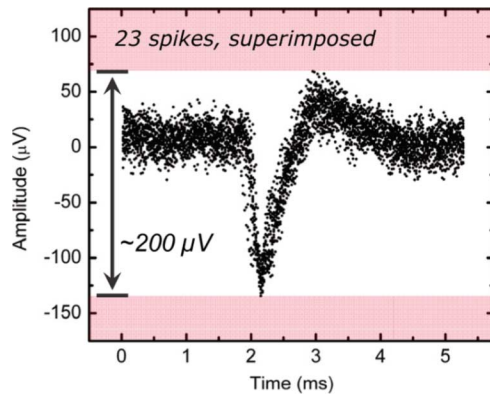
Fig. 6. *In vivo* recording of neural activity by the 4 × 4 element integrated active neural probe from motor cortex of an anesthetized rat, showing 23 consecutive spikes superimposed in a 5 ms window [18].
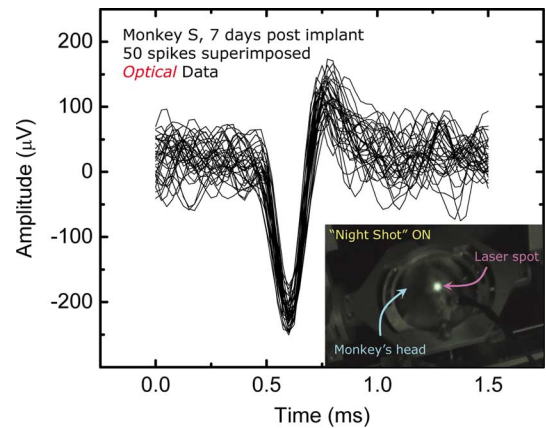

Fig. 7. Cortical action potentials recorded from a fully implanted neural microsystem in a rhesus monkey. Pulse code modulated IR optical signal of neural data was transmitted to an external photoreceiver through skin (inset: an IR sensitive "night vision" photograph showing a bright spot on the monkey's head where the IR laser is located under the skin). 48 spike waveforms are detected for 15 s, and superimposed in a single plot after offline filtering. The data was taken seven days after implant surgery.

doses of 30 mg/kg when necessary. During the recording session, the depth of anesthesia was controlled by monitoring tail-pinch response, corneal reflex, and respiration rate. The monolithic front-end recording device was implanted using a pneumatic impulse inserter that was programmed to place the electrode tips about 1 mm below the surface of the brain near or within layer IV of the cortex.

The signals were processed through the entire microsystem and external support electronics. The output generated an audio-visual display. Fine adjustment in depth of microelectrode penetration into the cortex was made by a micromanipulator while audio-visually monitoring neural activity. Action potential spikes, with characteristic amplitudes of 200 μV and durations of 1 ms, were detected and recorded simultaneously from 15 electrodes as shown in Fig. 6. The neural activity correlated well with sensory stimulation on whiskers and posterior skin, with a higher rate of burst activity being evoked by such stimuli. The results were verified by a control experiment using a passive single-wire electrode. This *in vivo* animal experiment established another evaluation goal, namely that the system can perform satisfactorily as a cortical implant.

D. Steps Towards Chronic Implant in Primates

The present status of our work underway is summarized in Fig. 7 showing an example of ongoing experiments where the full microsystem of Fig. 2 is being implanted into the head of macaque monkeys. The night vision camera shows the spot at which the IR laser beam exits through the skin. This implant also includes an accompanying electrical feedthrough for *in situ* comparison between the wireless (IR) and wired telemetry. The implant was placed in a monkey subchronically (for a period of ∼30 days), and analyzed postexplant for functionality and performance. The inset on Fig. 7 shows neural pseudospike waveforms recorded on a single channel of the explanted microsystem, and verifies that there was no change in system performance through the duration of the implant as well the handling during the actual implant and explant surgeries. This durability is another initial indicator of the resilience of the packaging. Work is underway to correlate the neural signals to specific task related behaviors.

All animal procedures in Sections IV-B–IVD were conducted conforming to the National Research Council's *Guide for the*

Use and Care of Laboratory Animals(1996), and according to protocols approved by Institutional Animal Care and Use Committee (IACUC) at Brown University.

V. Summary

We have presented our progress through several stages, from saline bath to *in vivo* models, on a multitiered process in the development of fully-implantable cortical neural prostheses, presently implanted in monkeys. Researchers in this field still face several common challenges, including biocompatibility and reliability for eventual human patient applications. Our technical explorations towards extracting neurologically significant data from the human brain is one contribution at beginning stages of what is likely to be an exciting decade in neural prosthetic research.

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