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An autonomous implantable computer for neural recording and stimulation in unrestrained primates

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Abstract

To perform neurobiological experiments on freely behaving primates, we have developed a miniature battery-powered implantable computer capable of recording and stimulating through chronic electrodes in the cortex. The device has: (1) an analog front end with a four-pole bandpass filter (500 Hz–5 kHz), programmable gain and offset nulling; (2) an analog-to-digital converter to sample the data at 11.7 ksps; (3) a programmable microcontroller to discriminate spikes in real time and perform computations; (4) a stimulator to deliver biphasic current pulses of up to 100 μA with variable pulse width and frequency; (5) a 4 Mbit non-volatile memory to store biological data; (6) a 57.6 kbps infrared data link for wireless communications with a hand-held or desktop computer. The device is enclosed in a 5.5 cm × 5 cm × 3 cm titanium casing on the monkey's head along with a 3.3 V lithium battery and an array of cortical electrodes. In in vivo tests, the device was able to record stable cell discharge continuously for time periods of a week or more. After downloading the parameters for recording, stimulation, discrimination, and other computations, the device is capable of operating autonomously, delivering stimuli to one electrode triggered by spikes recorded at a separate site.

Keywords: Brain computer interface (BCI); Autonomous experimentation; Cortical neurons; Neural prosthesis

1. Introduction

The ability to record neural activity from awake, behaving animals has greatly advanced our understanding of the neural mechanisms mediating behavior. However, conventional microelectrode recording techniques typically require some degree of restraint, for example, head fixation, to obtain stable recordings. Animals must be trained to accept this restraint and the range of behaviors that can be studied is necessarily limited. Furthermore, results obtained under such restricted conditions may not reflect the full repertoire of brain activity that occurs during natural behaviors.

To collect data from freely moving animals, researchers have developed miniaturized, implantable electronic circuits for use with species ranging from insects (Fischer et al., 1996; Ando et al., 2002) to mammals (Obeid et al., 2004; Mojarradi et al., 2003; Lancaster et al., 1995; Grohrock et al., 1997; Lei et al., 2004). Many of these designs use radio-frequency (RF) transmission of raw or digitized physiological data to a remote computer for storage and analysis. However, the high power consumption of continuous RF transmission in these battery-powered systems limits the duration of the experiment to a few hours. Another limitation is the unidirectional RF link, which precludes animal–computer interactions such as the delivery of electrical or sensory stimuli contingent on the animal's behavior. Although a bidirectional link enables these closed-loop interactions, limited bandwidth introduces delays that impair real-time operation (Bossetti et al., 2004).

To overcome the high power consumption and long link delays of RF systems, as well as to explore the possibilities of fully autonomous animal–computer interfaces, we are

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developing low-power, self-contained, miniature computers called "neurochips" that are implantable into and onto animals (Diorio and Mavoori, 2003; Mavoori et al., 2004). Rather than fabricating the neurochips using full-custom very large scale integration (VLSI), we are using commercial off-the-shelf components for the benefits of reduced cost and development time. Our prototypes range in size from the smallest (1 cm × 1 cm) for insect flight studies to the largest (1.2 cm × 5.4 cm) for primate studies. The circuits and architecture of the neurochip can be adapted for neurobiology and field ecology research with other animals. These neurochips process and store data onboard rather than transmitting it in real time to a remote host. Additionally, our neurochips can locally analyze the electrophysiological signals, and respond to them in real time by delivering electrical stimuli back to the animal.

The field of neural prosthetics (Nicolelis, 2001; Donoghue, 2002) is another application for neurochips. Recent advances in implantable microelectrode arrays (Hoogerwerf and Wise, 1994; Nordhausen et al., 1996; Kralik et al., 2001) have enabled chronic recording of action potentials from individual cortical neurons. Neural signals extracted from these electrodes have been used to control computer cursors (Taylor et al., 2002; Serruya et al., 2002) and robotic arms (Chapin et al., 1999; Taylor et al., 2003; Carmena et al., 2003), and one day this technology may help restore mobility and independence to paralyzed patients. Low-power consumption, continuous and autonomous operation, and the ability of real-time closed-loop interaction with neural tissue will be important features of a practical neural prosthesis.

In this article, we describe a version of our neurochip developed specifically for neuronal recording and stimulation in primates, although it is possible that similar circuitry could be also placed in a backpack and worn by smaller animals. The total implant is of a comparable size and weight to some telemetry systems used with rats (e.g. Xu et al., 2004). The primate neurochip includes front end analog signal processing to amplify and filter neural signals, an analog-to-digital converter (ADC), a microprocessor core for spike discrimination and governance of autonomous interactions, non-volatile data memory for storing raw waveforms and spike firing rates, a stimulator to deliver biphasic constant-current stimuli, and an infrared (IR) interface. The neurochip is powered by a lithium battery and the entire system is housed in a casing attached to the monkey's skull.

We have tested the operation of our neurochips in vivo over several weeks with two freely behaving macaques. The circuits successfully recorded neural activity from motor cortex with the animals (1) under sedation, (2) performing a trained task in a recording booth, and (3) moving freely about the home cage. We have routinely been able to track the firing rate of a single cell for over a week. In some experiments, action potentials discriminated from one cortical electrode were used to trigger stimuli delivered to a separate cortical site.

2. Implantation details

We have implanted neurochips in two male monkeys (*Macaca nemestrina*, weighing 6.5 kg and 4.3 kg). During an initial sterile surgery under gas anesthesia, the scalp was retracted and a mold of the skull was made with dental impression compound (Jeltrate, Dentsply International Inc.). A 5.5 cm × 5 cm × 3 cm titanium casing was machined to fit snugly over a plaster of Paris replica cast from this skull mold. In a second surgery, the casing was attached to the skull with titanium screws and dental acrylic. At the same time, an array of 12 microwire electrodes was implanted into the arm area of left primary motor cortex (M1). The electrodes were made from 50 μm diameter tungsten wire insulated with Teflon (A-M Systems Inc.) and crimped into a strip connector (Centi-Loc, ITT Canon). The end of each wire was cut flush with sharp scissors to give a tip impedance of around 0.5 MΩ at 1 kHz. A bare stainless steel wire wrapped around a skull screw provided the signal ground. The animals received post-operative antibiotics and analgesics, and adjusted to the head implant without visible signs of discomfort. All procedures were approved by the University of Washington Institutional Animal Care and Use Committee (IACUC).

Fig. 1 shows a diagram of the neurochip implant. The casing encloses the microwire implant, neurochip circuit boards and battery and has a transparent lid made of plexiglass to allow IR communications. The lid is removable to allow direct access to the circuits and to change the battery. The positioning of the electronics allows access to an area of skull measuring approximately 5 cm × 1 cm within the outer enclosure for positioning of microwire arrays and ground connectors. We have designed our system such that this area centers on left motor cortex but also allows access to premotor and somatosensory areas. Alternate arrangements could allow access to other cortical areas. The large spacing of the crimp connector we use in our arrays effectively limits the number of microwires that can fit within the enclosure. However, smaller connector systems should make it possible to place significantly more microwires within the enclosed space, covering multiple cortical areas. Short jumper wires connect the circuits to the microwire connector block and are used to select recording and stimulation electrodes. The circuit boards and battery weigh 26 g. The casing and lid weigh 30 g.

3. Neurochip architecture

Fig. 2(a) gives a functional overview of the neurochip. The neural signal from a chronically implanted microwire electrode is buffered, bandpass filtered 500 Hz–5 kHz by a four-pole multiple feedback Butterworth filter and amplified 1500× (Fig. 2(b)). This signal passes to one input of a Programmable System-on-a-Chip (PSoC CY8C27443 from Cypress Semiconductor). This chip incorporates a configurable array of analog modules which are used to implement a variable gain amplifier that allows additional amplification of

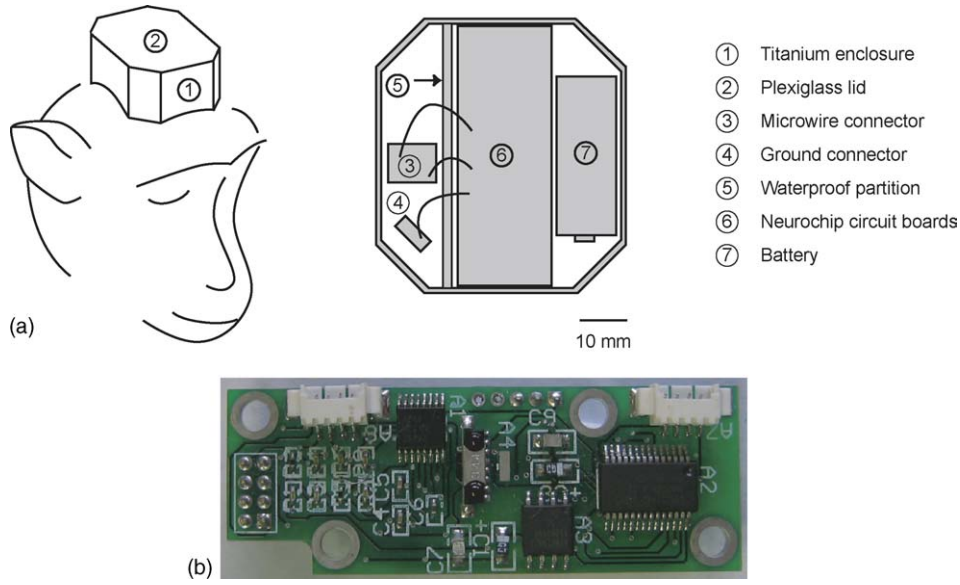


Fig. 1. (a) Components of the implant. All parts are enclosed in a titanium casing and mounted on the head. (b) Photograph of a neurochip circuit board. Actual size: 1.2 cm × 5.4 cm.

(1–48)×, followed by an 8-bit delta–sigma ADC sampling at 11.7 ksps (details of the internal PSoC settings required to implement these modules can be obtained by contacting the first author). Additionally, the PSoC includes an 8-bit microprocessor core which runs a spike discrimination algorithm. The algorithm, which identifies action potentials based on a threshold crossing and two adjustable time–amplitude windows, is detailed in Section 4.1. On detecting a spike, the microprocessor can initiate a stimulation control algorithm which instructs a stimulator to deliver precisely timed stimuli

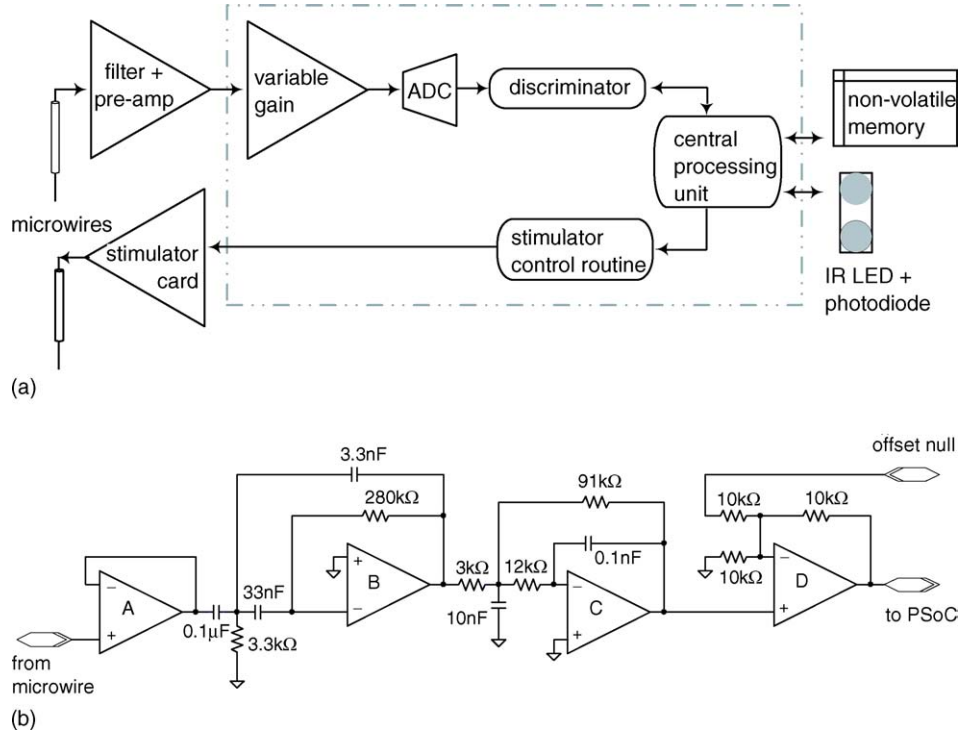
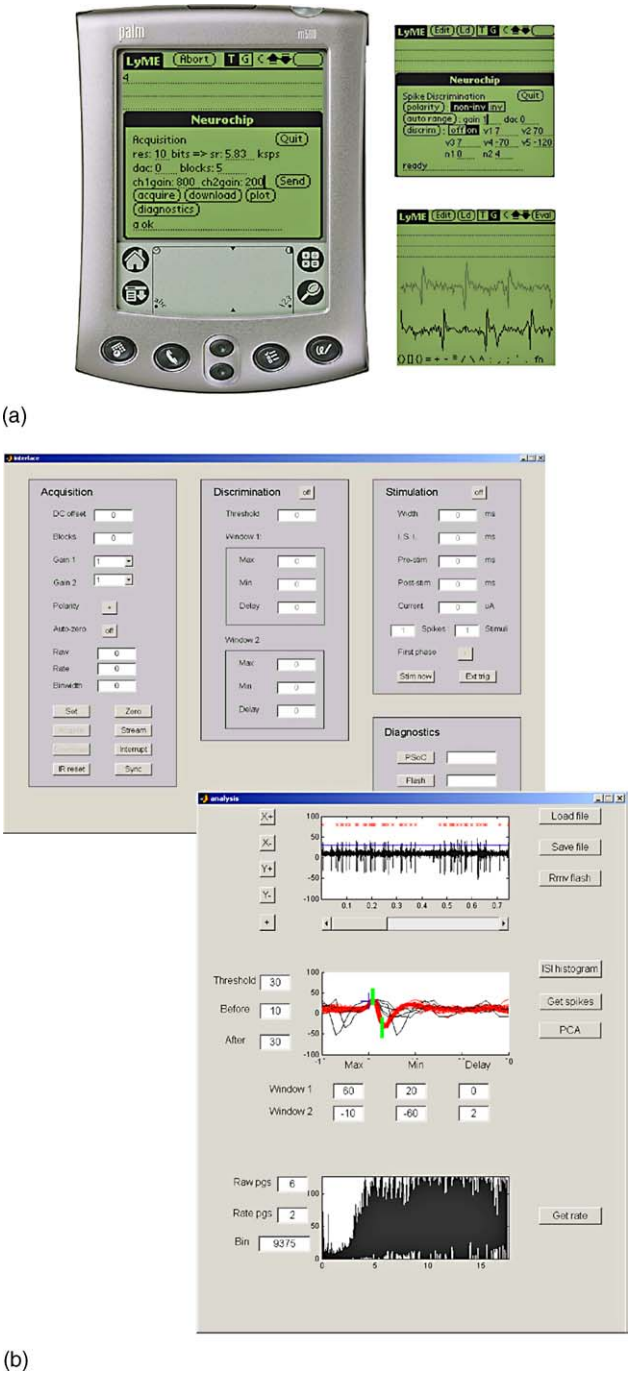


Fig. 2. (a) Architecture of our implantable neurochip. Blocks in the dotted rectangle are implemented in a CypressMicro Systems PSoC, which includes a configurable array of analog modules, an 8-bit microprocessor, and digital blocks to implement the functions shown here. Atmel DataFlash equipped with a serial interface is used for onboard storage. Sharp Microelectronics' IR LED and photodiode integrated module is used for wireless communications and has a range of 1 m along line-of-sight with a ±15° angular spread. (b) Circuit diagram of the filter, pre-amplifier and offset nulling circuit built with Texas Instruments TLV2625 opamps.

to the animal through another microwire. The experimenter can set the stimulus current, pulse width inter-stimulus interval, as well as the ratio of discriminated-spikes to delivered-stimuli.

A 57.6 kbps IR interface (GP2W0114YPS from Sharp Microelectronics) is used for wireless communication between the PSoC and a hand-held or desktop computer. Fig. 3 shows examples of user interface screens for each. As compared to an RF interface, an IR interface offers the advantages of a smaller footprint on the printed circuit board (PCB), and lower power consumption. The biological data is stored onboard in a 4 Mbit non-volatile memory (AT45DB041B from Atmel). The user can choose to store samples of raw digitized data, binned spike rate, or a mixture of both, during the course of an experiment. This flexibility allows efficient utilization of memory and battery power.



(a)

(b)

Fig. 3. User interfaces to neurochip: (a) a palm user interface developed in LyME (Calerga Sarl) and (b) a similar interface for a PC developed in Matlab (Mathworks Inc.). The interfaces facilitate transmission of parameters for recording, discrimination, stimulation and other computations to the neurochip and display uploaded data.

All the components described above are housed on a single PCB. A stimulator circuit is designed as a separate PCB that can be connected to the first one. The stimulator PCB has a DC–DC converter to boost the 3.3 V battery voltage to roughly 14 V. A current-limiting circuit allows delivery of biphasic current pulses of up to 100 μA to the biological tissue. The current pulse magnitude can be adjusted in steps of 2.6 μA. Once all the experimental parameters are downloaded into the neurochip via the IR interface, it can be set to perform the experimental sequence autonomously.

To maximize battery life, we have incorporated onboard power management into our algorithms. For example, on completing the experiment, the neurochip stays in a low-power standby mode awaiting IR commands to upload data or to initiate another experimental sequence. The power consumed is about 20 mW in standby mode and varies from 40 mW to 120 mW while recording, stimulating and discriminating actively. Unused modules are turned off to conserve power, and the microprocessor's clock speed is changed according to the computational needs and varies from 3 MHz to 12 MHz, yielding additional savings in power. In a typical configuration with a 2000 mAh lithium battery (AA-size weighing 17.6 g, Tadiran Batteries), the circuit operates for up to 60 h.

The current version of the neurochip lacks the processing power to handle multiple cortical channels simultaneously. However, we are currently working on extending the system by deploying multiple neurochips, each dedicated to a separate channel of data. These neurochips can communicate via an onboard network to exchange data, synchronize with each other and share computational resources.

4. Experiments and results

4.1. Neural recording

Fig. 4(a) shows a typical sample of raw data recorded from a microwire in the arm area of the primary motor cortex (M1) while the animal moved freely about his home cage. A gain of 12,000× was used for this recording. The background noise level (6 μV rms) is comparable to recordings from the same electrode with a conventional amplifier system (MCP-Plus, Alpha-Omega Engineering). Several action potentials can be seen to rise clearly above the background noise. In order to extract these discrete action potential events from the continuous data, we use a spike discrimination algorithm based on

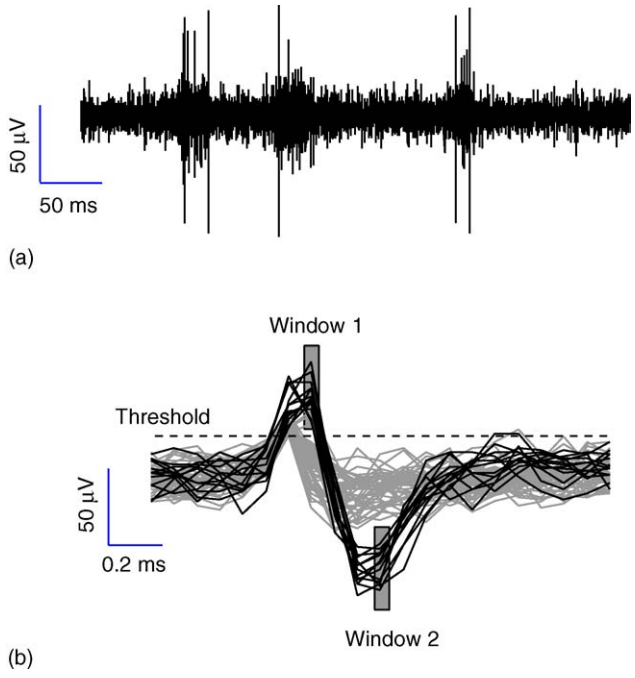


Fig. 4. (a) Sample of multi-unit spike activity recorded by the neurochip from M1 while the animal moved about the home cage. (b) Operation of the time–amplitude window discriminator. Waveforms crossing the trigger level are overlaid. The accepted waveforms (dark) are those that pass through the two user-positioned time–amplitude windows (gray boxes).

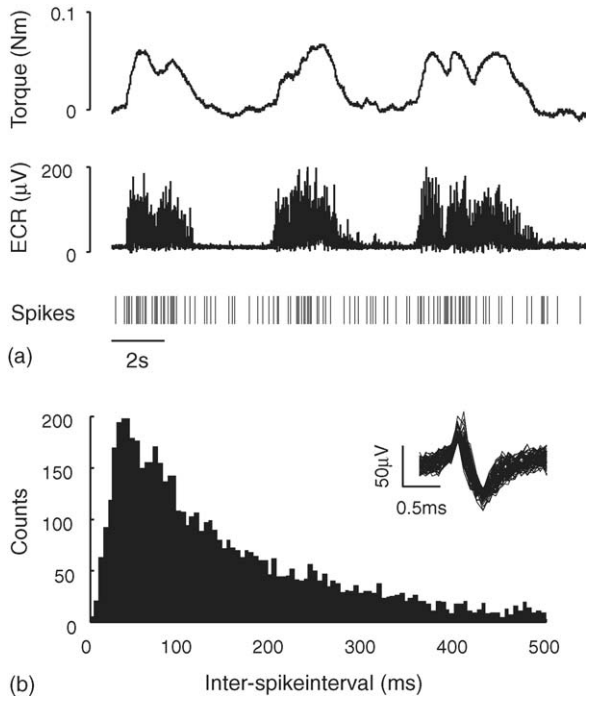


Fig. 5. (a) Sample torque, rectified EMG from *extensor carpi radialis* muscle and spike data obtained while the monkey performed a trained task in a recording booth. IR pulses signaling the occurrence of spikes were recorded simultaneously with behavioral data. (b) Inter-spike interval histogram. The absence of intervals less than 2 ms and a consistent spike waveform (inset) suggest that these action potentials came from a single, well-isolated neuron.

a threshold crossing and two time–amplitude windows (Fig. 4(b)). The spike discriminator is triggered whenever the digitized sample crosses the user-defined threshold (shown as a dashed horizontal line). In Fig. 4(b), successive spike waveforms have been overlaid and aligned to this trigger crossing. Each spike event is accepted if the waveform subsequently passes through two windows (shown as gray boxes). The vertical extent of each of these windows, as well as the time latency following the trigger event can be individually adjusted by the user and relayed to the neurochip via the IR link. In Fig. 4(b), these windows have been chosen to discriminate the larger action potentials in this record. These waveforms are shown in black, while the spikes that were excluded by this algorithm are shown in gray. In general, we find that two discrimination windows suffice to isolate large single-units from our data records, although the program could be extended to include additional windows or a more sophisticated spike sorter, within limits of the computational capabilities of the microprocessor.

Because the spike discrimination algorithm runs in real time, accepted spike events can be relayed immediately via IR for remote recording with simultaneous behavioral data. Fig. 5 shows results from an experiment in which the monkey, seated in a recording booth, performed a trained task that involved controlling a cursor with torques generated about the wrist. The neurochip was configured to emit an IR pulse for every detected spike. A remote computer equipped with an IR receiver recorded the pulses along with the wrist torque as measured by a force transducer attached to the manipulandum. Because the neurochip is optically isolated from the recording system, additional physiological signals (in this case electromyograms) can be collected simultaneously with conventional rack amplifiers without ground loop interference. The spike activity shows a clear correlation to the muscle activity. The absence of short inter-spike intervals (Fig. 5(b)) suggests that in this case the neurochip discriminated action potentials from a single neuron with a refractory period. Raw spike waveforms were subsequently uploaded from the neurochip to verify the quality of discrimination (Fig. 5(b), inset).

Wireless IR communications require a direct line of sight to the monkey's head. This does not pose a hard limitation even for experiments during fully free behavior, as the neurophysiological data is stored onboard and uploaded at a convenient time even while the monkey is in the cage. The onboard spike discriminator allows the neurochip to compile and record spike firing rates over user-specified time bins, offering significant data compression for long experimental sessions. With the neurochip configured to store firing rates calculated over 1-s bins, interspersed every 9 min with 140 ms of raw data, the 4 Mbit memory can store up to 36 h of continuous data. For extended experimental runs, our typical procedure involves transferring the animal daily from the home cage to a training chair to upload data, replace the

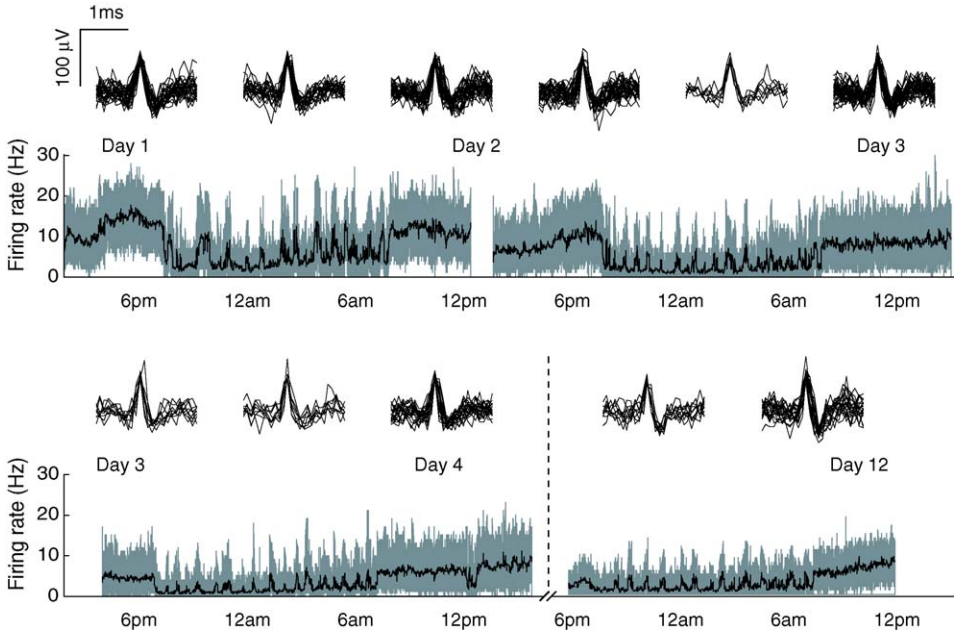


Fig. 6. Summary of firing rate of an isolated neuron during a 12-day period. The dark line indicates the mean firing rate over consecutive minutes; gray shading shows the maximum and minimum rates obtained from the 1-s bins within this minute. Note the distinct activity pattern during the night with rhythmical bursts of activity that may reflect natural sleep cycles. Plotted above the trace are sample waveforms extracted from the interspersed raw data recording.

battery and record with the trained task. Using this protocol we have often been able to track the firing rate of a single cell continuously for periods of a week or more. Fig. 6 plots variations in firing rate of an M1 cell over a 12-day period while the animal moved freely about his home cage. Note the lower rate and rhythmic fluctuations in firing rate during the night. These have been consistent features in our overnight recordings and it is interesting to note the similarity with the time-course of electroencephalogram patterns during undisturbed sleep (Klerman et al., 2000).

4.2. Neural stimulation

Trains of intracortical microstimuli delivered to area M1 can elicit a motor response (Asanuma and Rosén, 1972). To verify the operation of our implantable stimulator, we delivered a train of 13 biphasic pulses at 300 Hz (50 μA, 0.2 ms each phase) to a microwire in M1 while recording electromyogram (EMG) from *extensor digitorum communis* muscle. Fig. 7(a) shows the response to this stimulation, demonstrating that the battery-powered stimulator is capable of delivering cortical stimuli of an intensity strong enough to elicit motor activity.

We have used the neurochip to deliver stimuli to one microwire electrode triggered by spikes discriminated on another, producing an artificial connection between two sites. Fig. 7(b) shows overlaid spike waveforms and corresponding artifacts from stimulating at 40 μA. The artifact is brief, allowing normal spike discrimination to resume within 2.5 ms of stimulation. In this experiment, a 0.5 ms delay was pro-

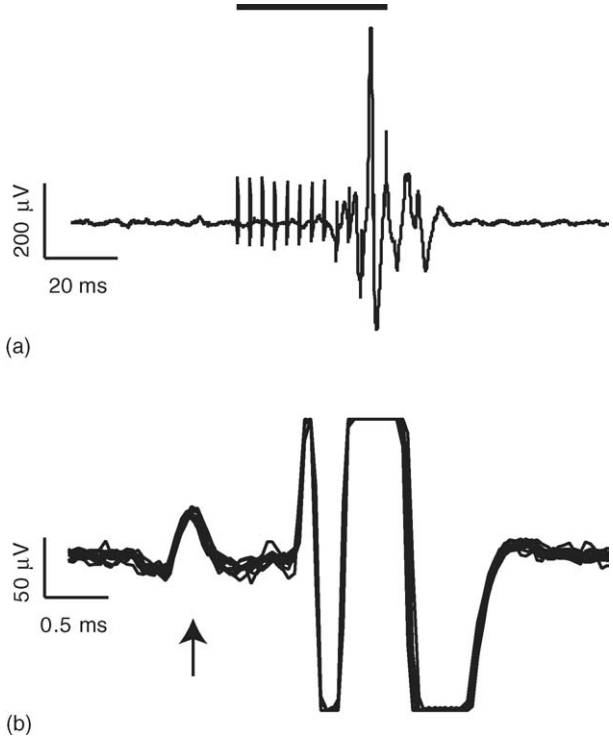


Fig. 7. Examples of stimuli delivered using the onboard stimulation circuitry. (a) Response recorded in the *extensor digitorum communis* muscle following a train of 13 stimuli delivered to the motor cortex. The dark bar over the stimulus artifacts indicates the duration of the stimulus train. (b) Stimulation of one microwire (40 μA) triggered by spikes discriminated on an adjacent microwire (indicated by arrow). A 1.5 ms stimulus artifact is observed on the recording electrode.

grammed between spike detection and the stimulus onset, although in general, no such delay is necessary. Spike discrimination occurs in real time and the stimulus can be delivered immediately once the neural signal has satisfied detection criteria. Since the neurochip implant operates autonomously, these artificial connections can be operational for several days while the monkey is free to move about the home cage.

5. Conclusion

We have designed and built an implantable neurochip for long-term recording and stimulation experiments in primates. Our system is lightweight and compact and could be adapted for smaller animals. The neurochip operates autonomously in conjunction with chronically implanted cortical electrodes. An onboard spike discriminator isolates action potentials from a single neuron, and the neurochip can store both raw waveform data and binned spike rates. The stimulator is capable of delivering biphasic, constant-current stimuli sufficient to elicit an overt motor response. The neurochip's power consumption is low, allowing continuous operation on a single battery for up to 60 h. With battery changes, we have tracked an individual cell continuously for up to 12 days. We have successfully tested this implant in vivo, collecting data while monkeys performed a trained task in a recording booth and during fully free behavior. We are currently investigating the consequences of chronic operation of the implant and the ability of monkeys to incorporate the feedback connections into normal motor behavior.

Acknowledgments

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