

## INTRODUCTION

Until recently, neurobiologists have used computers for simulation, data collection, and data analysis, but not to interact directly with nerve tissue in live, behaving animals. Although digital computers and nerve tissue both use voltage waveforms to transmit and process information, engineers and neurobiologists have yet to cohesively link the electronic signaling of digital computers with the electronic signaling of nerve tissue in freely behaving animals.

Recent advances in microelectromechanical systems (MEMS), CMOS electronics, and embedded computer systems will finally let us link computer circuitry to neural cells in live animals and, in particular, to reidentifiable cells with specific, known neural functions. The key components of such a brain-computer system include neural probes, analog electronics, and a miniature microcomputer. Researchers developing neural probes such as sub-micron MEMS probes, microclamps, microprobe arrays, and similar structures can now penetrate and make electrical contact with nerve cells without causing significant or long-term damage to probes or cells.

Researchers developing analog electronics such as low-power amplifiers and analog-to-digital converters can now integrate these devices with microcontrollers on a single low-power CMOS die. Further, researchers developing embedded computer systems can now incorporate all the core circuitry of a modern computer on a single silicon chip that can run on miniscule power from a tiny watch battery. In short, engineers have all the pieces they need to build truly autonomous implantable computer systems.

Until now, high signal-to-noise recording as well as digital processing of real-time neuronal signals have been possible only in constrained laboratory experiments. By combining MEMS probes with analog electronics and modern CMOS computing into self-contained, implantable microsystems, implantable computers will free neuroscientists from the lab bench.

## **INTEGRATING SILICON AND NEUROBIOLOGY**

Neurons and neuronal networks decide, remember, modulate, and control an animal's every sensation, thought, movement, and act. The intimate details of this network, including the dynamic properties of individual neurons and neuron populations, give a nervous system the power to control a wide array of behavioral functions.

The goal of understanding these details motivates many workers in modern neurobiology. To make significant progress, these neurobiologists need methods for recording the activity of single neurons or neuron assemblies, for long timescales, at high fidelity, in animals that can interact freely with their sensory world and express normal behavioral responses.

## CONVENTIONAL TECHNIQUES

Neurobiologists examine the activities of brain cells tied to sensory inputs, integrative processes, and motor outputs to understand the neural basis of animal behavior and intelligence. They also probe the components of neuronal control circuitry to understand the plasticity and dynamics of control. They want to know more about neuronal dynamics and networks, about synaptic interactions between neurons, and about the inextricable links between environmental stimuli and neuronal signaling, behavior, and control.

To explore the details of this biological circuitry, neurobiologists use two classes of electrodes to record and stimulate electrical signals in tissue

- intracellular micropipettes to impale or patch-clamp single cells for interrogation of the cell's internal workings, and
- extracellular wires or micromachined probes for interrogating multisite patterns of extra-cellular neural signaling or electrical activity in muscles.

Neurobiologists use amplifiers and signal generators to stimulate and record to and from neurons through these electrodes, and signal-processing systems to analyze the results. They have used these techniques for decades to accumulate a wealth of understanding about the nervous system. Unfortunately, to date, most of these experiments have been performed on slices of brain tissue or on restrained and immobilized animals, primarily because the electronic instruments required to run the experiments occupy the better part of a lab bench.

This situation leaves neurobiologists with a nagging question: Are they measuring the animal's normal brain signals or something far different? Further, neurobiologists want to understand how animal brains respond and react to environmental stimuli. The only way to truly answer these questions is to measure a brain's neural signaling while the animal roams freely in its natural environment.

## SALIENT OBJECTIVES

The solution to these problems lies in making the test equipment so small that a scientist can implant it into or onto the animal, using materials and implantation techniques that hurt neither computer nor animal. Recent developments in MEMS, semi conductor electronics, embedded systems, bio compatible materials, and electronic packaging finally allow neuroscientists and engineers to begin packaging entire neurobiology experiments into hardware and firmware that occupy less space than a human fingernail.

Researchers call these bioembedded systems **neurochips**. Scientists from the University of Washington, Caltech, and Case Western Reserve University have teamed to build these miniaturized implantable experimental setups to explore the neural basis of behavior.

This research effort has developed or is in the process of developing the following:

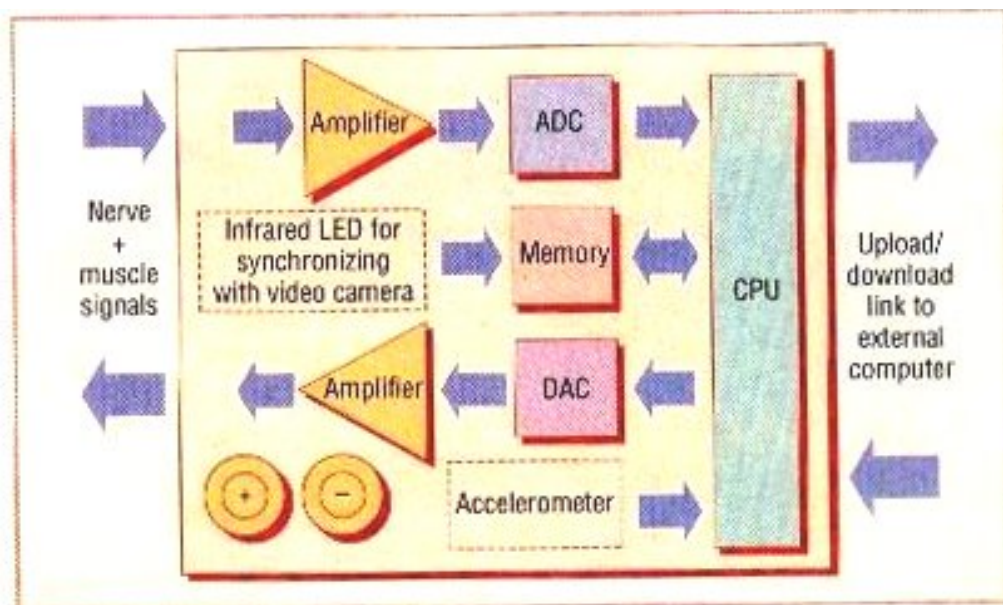
- miniaturized silicon MEMS probes for recording from the insides of nerve cells;
- biocompatible coatings that protect these probes from protein fouling;
- a stand-alone implantable microcomputer that records from and stimulates neurons, sensory pathways, or motor control pathways in an intact animal, using intracellular probes, extra-cellular probes, or wire electrodes;
- neurophysiological preparations and techniques for implanting microchips and wire electrodes or MEMS probes into or onto animals in a way that does not damage the probes or tissue;

- firmware that performs real-time biology experiments with implanted computers, using analytical models of the underlying biology; and
- software to study and interpret the experimental results, eventually leading to reverse-engineered studies of animal behavior.

As the “Neuroscience Application Examples” sidebar shows, the first neurochip experiments use sea slugs and moths in artificial environments, but broad interest has already arisen for using implantable computers in many other animals.

## DESIGNER NEUROCHIPS

Like their benchtop experimental counterparts, neurochips use amplifiers to boost low-voltage biological signals, analog-to-digital converters (ADCs) to digitize these signals, microcomputers to process the signals, onboard memory to store the signals, digital-to-analog converters (DACs) to stimulate nerves, and software to control the overall experiment.



*Figure 1. Neurochip functional block diagram solid line show required components, dashed lines show some optional components*

Figure 1 shows a neurochip's basic elements. The key requirements are that the neurochip be small and lightweight enough to fit inside or onto the animal, have adequate signal fidelity for interacting with the millivolt-level signals characteristic of nerve tissue, and have sufficient processing power to perform experiments of real scientific value.

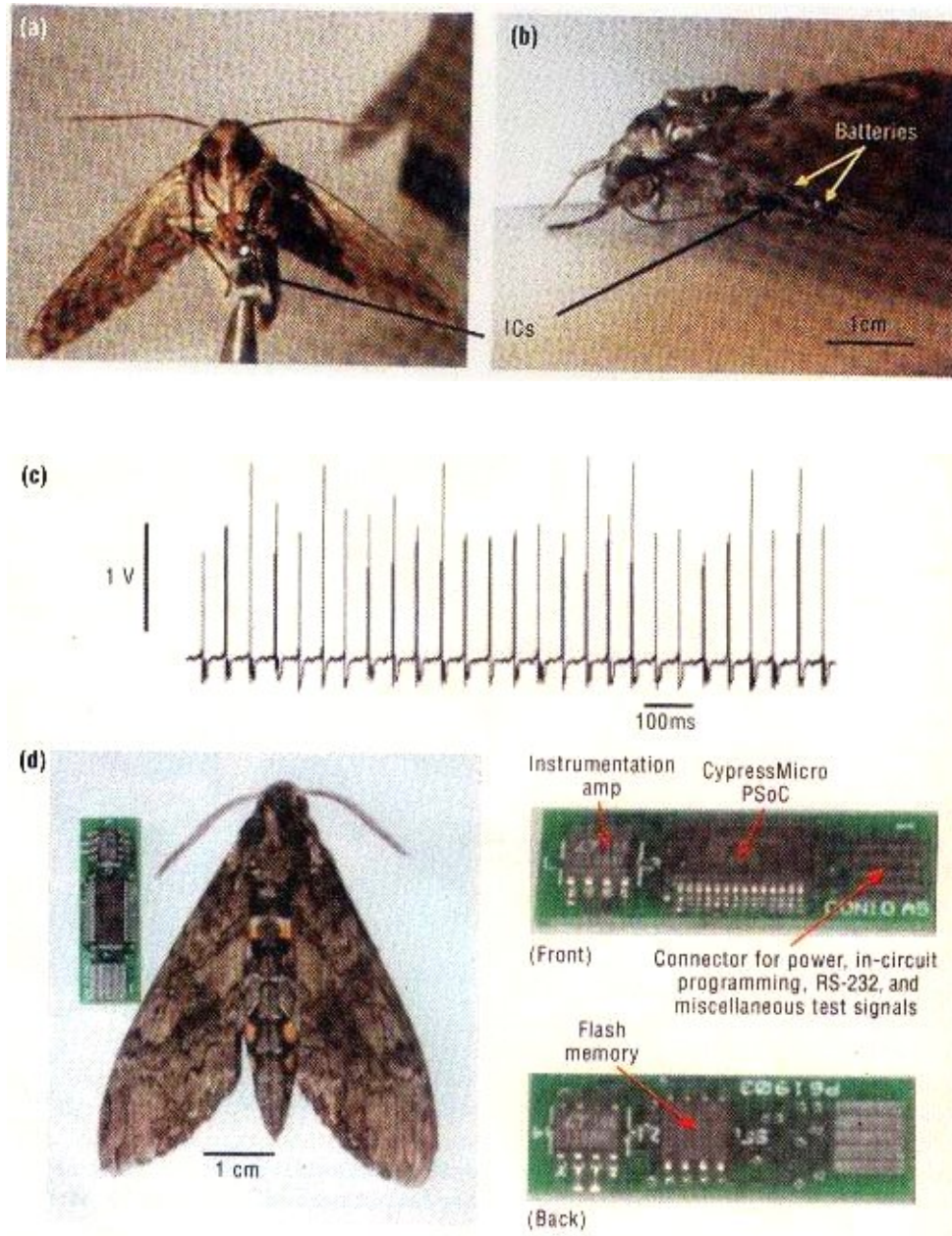


Figure 2. Prototype neurochips. (a,b) A first-generation neurochip comprising differential amplifiers and batteries on a micro PCB attached to the Manduca sexta's thorax. The animal's exoskeleton provides a simple attach point without biocompatibility issues. Manually implanted bipolar recording electrodes connect to recording sites. (c) A tethered in-flight recording from the thoracic flight musculature. (d) A second-generation neurochip prototype records from two nerve or muscle fiber sites, storing the signals in onboard nonvolatile memory.

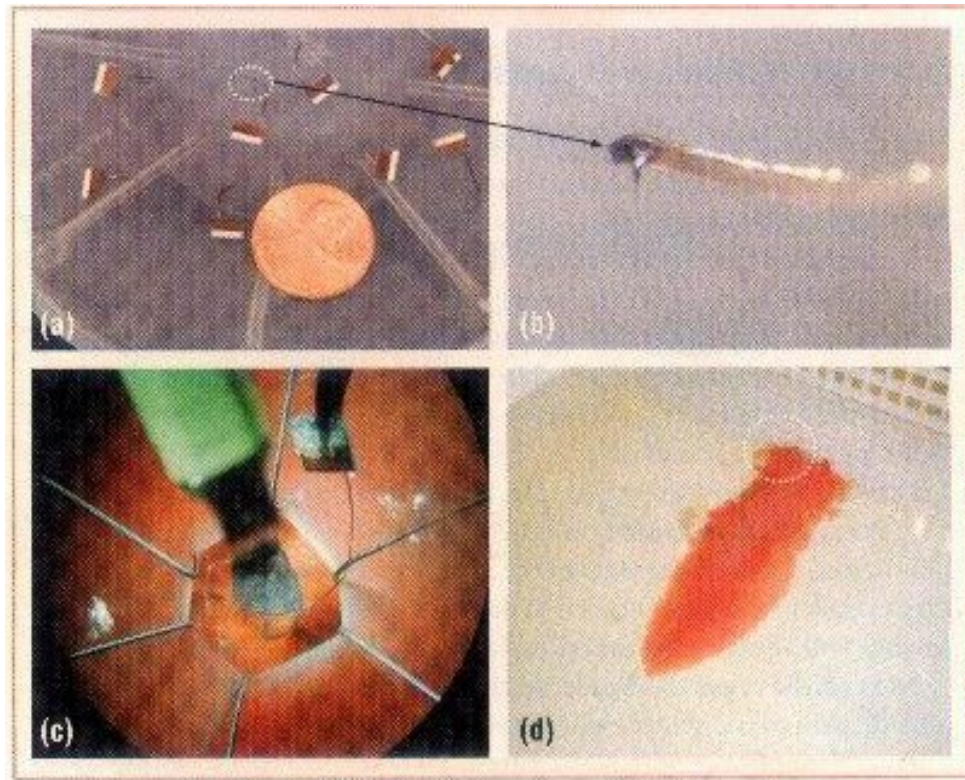
The basic components of a neurochip are commercially available today. They include instrumentation amplifiers, ADCs/DACs, reconfigurable microcomputers, and high-density memory. For example, a Programmable System-on-a-Chip from Cypress MicroSystems integrates a microprocessor, variable-gain amplifiers, an ADC, a memory controller, and a DAC into a single integrated circuit.

First-generation neurochips integrate one or more ICs, passive elements such as capacitors, batteries, and 110 pads on small micro-PCBs. The prototype neurochip shown in Figure 2 used packaged ICs and button cells, and occupied a 1 cm x 3 cm printed-circuit board. The “production” version, due out of processing in early 2003, uses die-on-board technology and thin-film batteries, and is smaller than 1 square centimeter. Future-generation neurochips will integrate all the electronics onto a single silicon chip, and will likely be smaller than 10 mm on a side.

## PROBES

Building the probes that let a neurochip eaves drop on the electrical signaling in a nerve bundle, group of neurons, or single neuron presents a daunting task. Benchtop experiments on constrained animals typically use metallic needles— often made of stainless steel or tungsten—to communicate with nerve bundles, micromachined silicon probes to record from groups of neurons, or glass capillaries filled with a conductive ionic solution to penetrate and record from the inside of individual neurons. In unconstrained animals, flexible metallic needles, attached to the animal with surgical superglue, and micromachined silicon probes still work. However, replicating the performance of glass capillaries in flying, swimming, wiggling animals is a different story entirely.

Several centimeters long and quite fragile, the glass capillaries that neurobiologists use to probe the insides of nerve cells typically have tip diameters smaller than 0.3 microns. They impale neurons even more fragile than the probes themselves. Neuro biologists use micromanipulators to painstakingly and precisely drive single probes into single neurons. Fortunately, MEMS technology offers a possible alternative to these glass capillaries. As Figure 3 shows, University of Washington researchers are developing silicon MEMS probes and flexible inter connect structures to mimic the performance of glass capillaries in an implanted preparation. Researchers have already recorded intracellular signals with early prototypes, and development is ongoing.



*Figure 3. Micromachined silicon probes, flexible interconnect structures, and sea slug surgery. (a) Released, flexible silicon devices ready for implantation; (b) a sharp microelectrode on a flexible polyamide support; (c) the implananation procedure places the needle on the exposed brain of a sea slug and the silicon base with the external wires tucks under the slug's skin; and (d) the postsurgery sea slug with implanted device can move freely in the water tank.*

## GLYME

Researchers seek to implant both probes and neurochips inside an animal's brain. Unfortunately, an animal's immune system rapidly and indiscriminately encapsulates all foreign bodies with proteins, without regard for the research value of implanted probes and neurochips. The adsorbed proteins not only attenuate the recorded electrical signals, but can also jeopardize the animal's survival by causing abnormal tissue growth.

Researchers at the University of Washington's Center for Engineered Biomaterials have developed plasma-deposited ether-terminated oligoethylene glycol coatings that inhibit protein fouling, as Figure 4 shows. Preliminary research indicates that these glyme coatings can reduce the protein fouling of probes and neurochips to levels acceptable for week-long experiments.



*Figure 4. A Fluorescence microscope image of a patterned 1,500 $\mu$ m x 1,500 $\mu$ m protein-resistant plasma polymerized tetraglyme (pp4G) pad on a silicon-dioxide substrate, with additional 200 micron x 200 micron gold pads on and around the PP4G pad, after incubation in a solution containing fluorescently labeled proteins.*

*The silicon-dioxide and gold areas adsorb protein and appear light, while the pp4G-coated areas resist protein adsorption and appear dark.*

## **POWER**

Neurochips can derive power from onboard batteries, external radiofrequency sources, a wire tether, or the nerve tissue itself. The ultimate decision on the power source depends on the nature of the experiments and the animal's environment. Batteries are attractive because they avoid the antennas and charge pumps required to capture RF energy, operate in all environments, do not restrict the animal's movement the way a tether does, and provide much more power than tapping nerve cells for energy.

Batteries have a weight disadvantage, but thin-film technologies using LiCoO<sub>2</sub>/LiPON/Li and Ni/KOH/Zn promise flexible rechargeable batteries with peak current densities greater than 12 mA per square centimeter for short-duration experiments, and lifetimes measured in days or longer at low-current densities.

Batteries are ideal for the two sample preparations shown in the "Neuroscience Application Examples" sidebar. The typical hawkmoth flight time is less than 60 seconds. The 12 mA provided by a 200 mg, one-square-centimeter battery easily powers a neurochip for this experiment's duration. The sea slug trolling methodically along the seafloor lies at the opposite end of the spectrum, needing only a few milliamps of current to power a neurochip for a week. The slug can easily accommodate a large battery in its visceral cavity, allowing extended untethered experiments.

## MEMORY

Once implanted, an embedded neurochip must read its experimental procedure from memory, run the experiment, acquire the neural spike trains, then store the results in memory. As with all computer systems, memory size is an issue for neurochips. Fortunately, the electrical spike trains generated by nerve tissue have a stereotyped shape as shown in Figure 2c, suggesting that neurochips should compress the neural waveforms before storing them in memory.

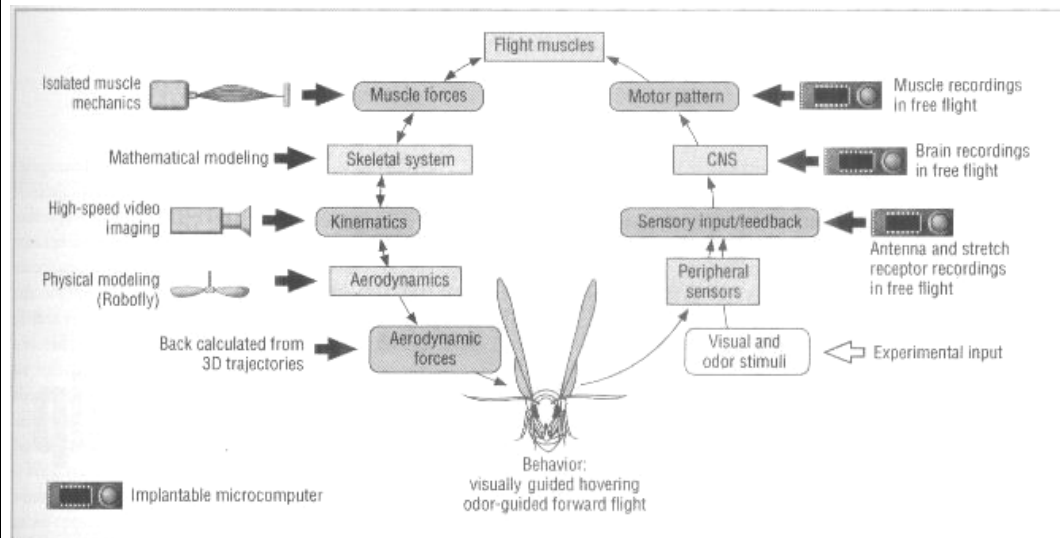
Compressing the signals has two advantages. First, it effectively increases the onboard storage capacity. Second, it decreases the frequency of memory writes, reducing power consumption. Even simple compression algorithms such as run-length encoding can achieve better than 10 to 1 compression ratios on neural signals.

Custom algorithms that apply vector quantization, run-length encoding, and Huffman encoding to different parts of the neural waveform can achieve up to 1,000 to 1 compression ratios. Given the limited computing power of an implantable microcomputer, simpler is better when it comes to compression, but even simple RLE offers huge power and memory-size benefits.

## A STIMULATING WORLD

Passive neurochips that do nothing more than record will provide neurobiologists with a wealth of data. But even now, with the first neurochips barely in production, neurobiologists are already calling for designs that stimulate nerve tissue as well as record from it. Active neurochips will allow stimulus-response experiments that test models of how nervous systems control behavior, such as how sensory inputs inform motor-circuit loops and the logic or model behind the response.

Indeed, the neurochip project's long-term goal is to develop a hardware and software environment in which a neurobiologist conceives a stimulus-response experiment, encodes that experiment in soft ware, downloads the experiment to an implanted neurochip, and recovers the data when the experiment concludes. Figure 5 shows a model of integrative biology in which neurochips play a key part.



## CONCLUSION

With advances in integrated circuit processing will come ever more capable and power-efficient embedded computers. The simple neurochips of today will become the complex embedded systems of tomorrow, when embedding in this ultimate sense will mean computer electronics embedded in nerve tissue.

Enabling neuroscientists to better understand the neural basis of behaviour is reason enough to develop such devices. The long-term promise is much greater, however, perhaps leading one day to neural prosthetics, hardware-based human-computer interfaces, and artificial systems that incorporate principles of biological intelligence.

## APPENDIX I

### Wiring a sea slug

Beneath a research vessel anchored in the Puget Sound, two scientists clad in scuba gear hover over the bright orange sea slug shown in Figure A. From the outside, this slug looks like any other. But this particular slug has a battery-powered microcomputer implanted in its brain and minuscule silicon needles communicating with its neurons. The microcomputer faithfully performs a biology experiment as the animal goes about its normal behavior.

Meanwhile, the scientists videotape the slug's feeding, fleeing, and social behaviors while measuring water currents and geomagnetic fields. Later, these scientists will study the environmental measurements and electronic recordings in an attempt to decode how the slug's brain patterns correlate with behavior. The anticipated outcome: groundbreaking findings in behavioral neurobiology.

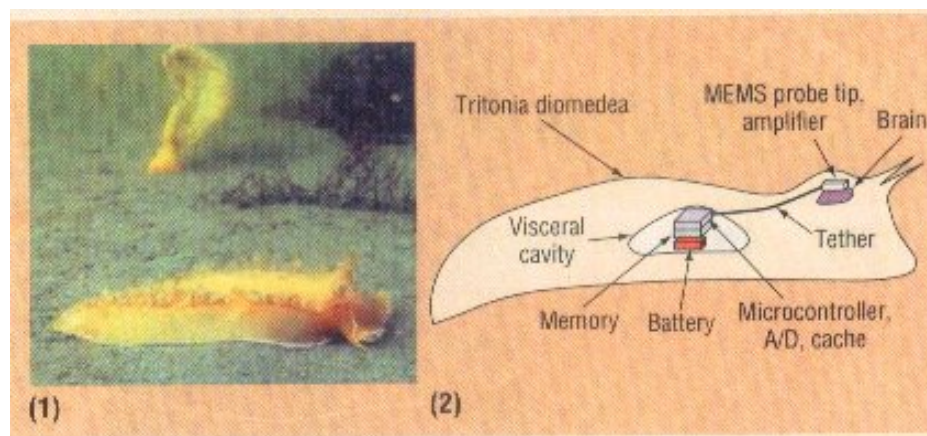


Figure A. Monitoring a giant sea slug. (1) *Tritonia diomedea*-shown with its prey, an orange seapen, in the background-is typically 20cm length, has a readily accessible brain with large and well-characterized neurons, and is extraordinarily tolerant of

*surgical insult. (2) Artist's conception of a neural recording setup implanted inside Tritonia.*

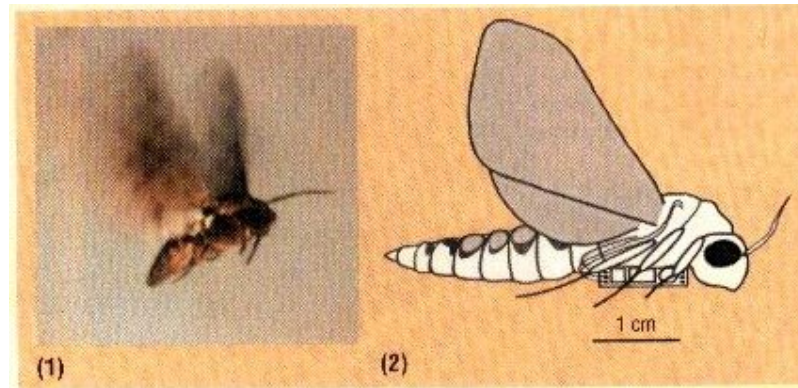
## APPENDIX II

### **Monitoring a moth's flight controls**

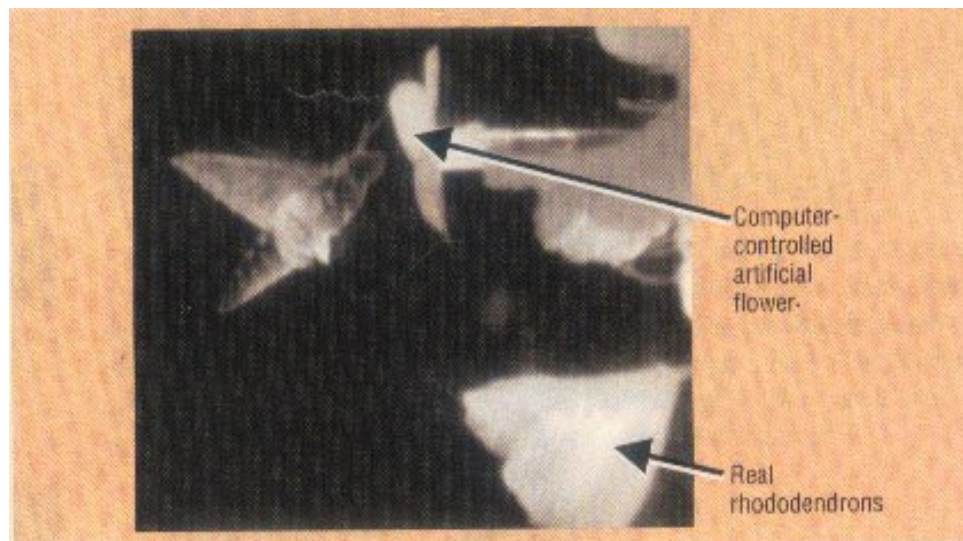
In a small, dark zoology lab, a giant moth performs an aerial ballet as it feeds from a robotically controlled artificial flower, unaware that the flower's movements are programmed to test the moth's flight dynamics. The ultra-high-speed infrared video recorder tapes the moth's every movement. But the special part of this experiment is neither the flower nor the videotaping. It is the tiny battery-powered microcomputer attached to the moth's thorax that records electrical signals from the flight muscles and sense organs and stores this data in onboard memory.

Suddenly, the moth appears to struggle to keep up with the flower. But the flower's movements haven't changed. Rather, the onboard microcomputer has begun stimulating the nerves that enervate the moth's wing muscles, adjusting the wing-stroke phase in subtle ways that will let scientists measure the impulse response of the moth's flight-control loops.

These experiments and others like them will soon be played out in biology laboratories across the country, if the multidisciplinary team of computer engineers and zoologists that is developing these implantable computers has its way.



*Figure B. Tracking a moth's movements. (1) Manduca sexta is typically 4cm in length with a wingspan of about 12cm; at 2.5gm, it is one of the largest flying insects. It can carry loads up to a gram and fly at speeds up to 30 miles per hour, flapping its wings 25 times a second. (2) Artist's conception of a neurochip attached to Manduca's thorax.*



*Figure C. High-speed infrared video captures Manduca hovering and sipping nectar from a moving flower. Visually guided flight control lets the animal compensate for rapid changes in wind direction and the flower's swaying movements.*

## APPENDIX III

### Neurochip Technology Forecast

Even as the first miniature neurochips record neuronal action potentials, researchers at the University of Washington are testing stimulus paradigms to evoke controlled muscular extension and contraction. Rather than driving the muscles directly using high-resolution voltage stimulus waveforms generated by digital synthesis and a digital-to-analog converter, they tried stimulating nerve bundles instead, using simple digital waveforms directly. They derived pulse-width modulated signals directly from logic gates, and drove these waveforms into the nerve bundles that enervate the muscles.

Early results show great promise, not only because the technique actually worked, but because a microcontroller can easily generate digital pulses, and the drive currents needed for nerve stimulation are up to 100 times smaller than those needed to drive muscle tissue directly. This power savings will allow functional stimulation by miniature neurochips.

Next on the research agenda: statistical machine learning. Researchers already plan to use smart algorithms, smart software, and smart chips to interact dynamically with nerve tissue. They suspect that machine learning can help them study the cause-and-effect relationships involved in the behavior of sensory motor circuits. Beyond that, they won't speculate, but the applications of this neurochip research to robotics, medical prosthetics, and a host of other applications seem obvious.

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## **ABSTRACT**

Recent advances in microelectromechanical systems, CMOS electronics and embedded computer systems will finally let us link computer circuitry to neural cells in live animals. The key components of such a brain – computer system includes neural probes, analog electronics and miniature microcomputer. These bioembedded systems are called neurochips. By enabling better study of animal behavior’s neural basis, implantable computers may revolutionize field biology and eventually lead to neural prosthetics, hardware based human-computer interfaces and artificial systems that incorporate biological intelligence principles.

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