Bugs, Slugs, n' Chips: Downloading Biology

Onboard computers in moths and sea slugs may revolutionize neurobiology and computer science

A prototype chip attached to the underside of a hawkmoth receives information from sensory structures and muscles that control the wings during flight.

Imagine computer chips interfacing directly with living animals—no keyboards, no wires, no intermediaries. Computer chips that not only record what's happening in cells as animals move freely about, but perhaps even control the signals and pathways that direct those movements.

This may sound like a fantasy to some and a nightmare to others. But a team of University of Washington researchers believes that implanting tiny computer chips in the hawkmoth *Manduca sexta* and the sea slug *Tritonia diomedea* may answer questions about how nerve cells make decisions, integrate information, and drive complex behaviors.

"If you want to understand how biological systems are controlled, you need to know the information that they are getting and the information that they send out," says team member Tom Daniel, who is Komen Professor and associate chair of zoology at the UW.

Some of this information can be collected with current technology. However, progress has been hampered by the requirement that animals be physically restrained in order to record the neural and muscular signals that drive behavior.

The electrodes used to record biological signals permit very little movement, and data must be sent via wires to nearby electronic devices to be processed and stored. Because the animals cannot move, they do not receive the same sensory stimuli and are not free to react as they would in their natural environments. The new approach overcomes this problem to a large extent.

Eric Horvitz, senior researcher and group manager of the adaptive systems and interaction group at Microsoft Research, was involved in many of the early discussions that led to the project.

"It's an exciting time," says Horvitz. "We're right at the brink of being able to create little backpacks that sail off with the animal, making them like little Apollo astronauts going about their thing," Horvitz muses. "This would give us an opportunity to record the rich inner activity and correlate that with the outer behavior."

This research ultimately may shed light on our own nervous systems, permitting new treatments for medical conditions such as epilepsy, chronic pain, and visual impairment.

In addition, the information gained from these onboard devices may help inspire the design of future computers.

Chris Diorio, assistant professor of computer science and engineering at the UW, is the architect of the implantable mini-computers. "Biology just does its computations in a fundamentally different way than any kind of artificial machine," he explains. "If we could understand how nervous systems represent information, how they act based on that information, and how they make decisions in light of uncertainty, we could copy the general concept" in synthetic machines, he says.

Daniel also believes that there is a wealth of information to be gleaned from studying complex biological systems. "The core and very heart of biological systems is that they are highly integrated

by Stacey Combes

and highly complex, and to me, that complexity is the joy," says Daniel.

The birth of an idea

The inspiration for implanting computer chips into animals arose at a Microsoft Research/UW summer institute on intelligent systems held at Friday Harbor Laboratories located in the San Juan Islands of Puget Sound. Horvitz, whose training in neuroscience led him to an interest in computation and artificial intelligence, began meeting in 1997 with neurobiologist Dennis Willows, professor of zoology at UW and director of the Friday Harbor Laboratories. Along with Diorio, they submitted a proposal to bring together biologists and computer scientists to discuss their common interests in the summer of 1998.

After the conference, a diverse group of researchers at UW submitted a proposal to make the idea a reality. The group includes UW zoologists Tom Daniel and Mike Tu, who study the integration of neurobiology, muscle function and mechanics in *Manduca* flight, and Willows, whose intimate knowledge of the brain and nervous system of *Tritonia* allows him to identify individual brain cells based on the pattern of signals they emit.

These zoologists are joined by Diorio, who will design the implantable chip and software that will run the experiments. Karl Böhringer, assistant professor of electrical engineering, lends his expertise in MEMS (microelectomechanical systems) technology to the project, and Denice Denton, professor and dean of the college of engineering, will add her knowledge of microfabrication and biocompatibility issues.

"It's a terrific team," says Willows. "The people bring such incredible diversity—there is the potential for catalytic discovery like virtually nothing I've experienced in my academic career."

The work on both *Tritonia* and *Manduca* received support in the amount of approximately $1 million over five years from the Packard Foundation. Most recently, support for the work on *Manduca* was received from the Office of Naval Research for a multi-institution effort in the amount of $5 million over five years.

Bugs and slugs

So why choose moths and sea slugs? Apart from the expertise of the researchers with these particular animals, each creature offers a unique opportunity to probe different aspects of the nervous system and pathways that control behavior.

The hawkmoth *Manduca sexta* inhabits the night skies of the central and southern United States, flying at speeds up to 40 miles per hour and hovering above flowers to sip their nectar.

Sea slugs are the ocean's equivalent of the slugs in your own backyard, but the name "slug" may be misleading to some. *Tritonia* is actually a ravenous predator that glides along a bed of mucus in search of its prey, and jets into the water when intimidated by a predator.

What distinguishes *Tritonia* from countless other slimy creatures is the massive amount of information that is known about particular cells in its brain and nervous system: their locations, what behaviors they control, and even the details of the characteristic signals they transmit.

Willows and others have spent years accumulating these data from intracellular recordings, where electrode tips are placed inside nerve cells (neurons) to record minute details of the electrical information that a cell is receiving.

Intracellular recordings capture more than just action potentials, that is, the spike in electrical activity that occurs when a neuron receives enough information to pass that information on to other cells. Intracellular recordings can also reveal smaller changes in the electrical potential (or charge separation) across the outer membrane of a neuron as it accumulates electrical information.

"These small, subtle changes in the membrane potential of the cell that do not reach the threshold for action potentials tell you what the cell is thinking," says Willows. "They tell you about intent, they tell you about mood, they tell you about integration, even memory."

But to perform these intracellular recordings, the animals must be completely immobilized so that the electrodes do not rip the cell membrane, and even so, the cells seldom stay alive for more than a few hours. The goal of implanting computer chips into *Tritonia*, says Horvitz, is to gather data over longer periods of time, from creatures "sensing and acting with their environment in a natural manner."

Key to collecting these data is Willows' use of an array of silicon electrodes actually etched onto the back of the computer chip by Böhringer, rather than piercing cells with traditional glass electrodes. This way, the entire chip with the electrodes can be fixed in place and the animal can be released into the ocean to interact with predators, prey, and mates for several days before the chip is removed and the data are downloaded.

In *Manduca*, the goal is not so much to gather data over long periods of time as it is to gain an understanding of how the moth integrates massive amounts of sensory information in a fraction of a second and uses this information to control a whole range of flight behaviors.

Daniel says that the challenge in understanding flight in *Manduca* and other insects lies in understanding this integration. "How on earth can you get something that can move at 30 to 40 miles per hour in one mode, and with the same set of wings and sensors, hover delicately in front of a moving flower while it feeds, and then in mid-flight, curl its abdomen around and glue some eggs to the underside of a leaf?"

To answer these questions, Daniel and Tu will record information from multiple parts of the flight control pathway, including sensory structures in the antennae and wing hinges, as well as from the muscles that power flight and the tiny steering muscles that adjust the exact position and synchrony of the wings.

Because neural feedback occurs so rapidly in *Manduca*, it's more interesting to know when various parts of the control pathway are activated relative to one another than to know the details of how stimuli build up within a single cell. This approach allows Daniel and Tu to focus simply on the time when neurons fire rather than on the magnitude of electrical changes within cells. They can gain this information from extracellular electrodes inserted near neurons, and so do not need to pierce individual cells.

Manduca beats its wings about 25 times per second, and so a flight lasting only a few minutes will provide ample data. This input will be fed into a chip glued to the bottom of the moth, and will ultimately be compared with information about the position of the moth and its wings.

Daniel and Tu hope to use the information they gain from freely-flying moths to answer long-standing questions about how flight is controlled in insects, which are inherently unstable, and about how insects process the seemingly excessive amounts of sensory information that they receive.

"If we were just given all the sensory data that they actually get, we wouldn't know what to do with it," says Daniel.

Diorio adds, "a neuron can have 3,000 excitatory inputs—nothing that computer scientists or engineers build has 3,000 inputs. It's just beyond our comprehension."

Chips and challenges

While the possibilities offered by a direct animal-chip interface in *Manduca* and *Tritonia* stir the imagination, the project is still in its early stages. A complete chip has yet to be fabricated. At this point, says Diorio, researchers are trying to nail down the requirements for processing power and compression. The final chip is likely to be a combination of custom-built and off-the-shelf components.

However, several specific challenges have become apparent in early trials. One is biocompatibility—problems caused by an animal's internal reaction to having a foreign object embedded within it. This problem is particularly troublesome in the case of *Tritonia*, as proteins tend to cling to electrode tips within cells and change their electrical resistance, particularly when the electrodes are embedded for long periods of time.

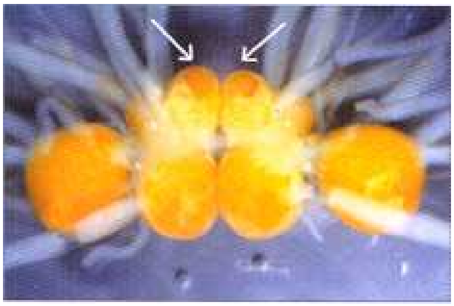
The team hopes to minimize this problem by coating the electrodes with a substance that seems comfortable to the cell, a challenge that Denton and researchers at the UW engineered biomaterials program are tackling.

In addition, intracellular recordings in *Tritonia* will produce huge amounts of data—continuous records of the electrical potential of cells over several days or weeks.

If these data could be transmitted remotely to, say, a ship hovering 100 meters away, accumulating this quantity of data wouldn't be a problem. But unfortunately, sea slugs live under seawater, and electromagnetic signals cannot be transmitted through the salty brine.

Diorio believes that ultimately they will be able to compress and store at least several days worth of data on an embedded 64-megabtye chip. Once that task is accomplished, says Willows, he and graduate student Russell Wyeth will face the challenge of analyzing and making sense of the "huge, massive amounts of electrical information" from the experiments.

In *Manduca*, data from a 30- to 90-second flight presents less of a challenge in terms of data storage, but providing lightweight power to a computer chip on a moth flying through the air is much more difficult than supplying power to a sea slug crawling through water on the ocean floor.

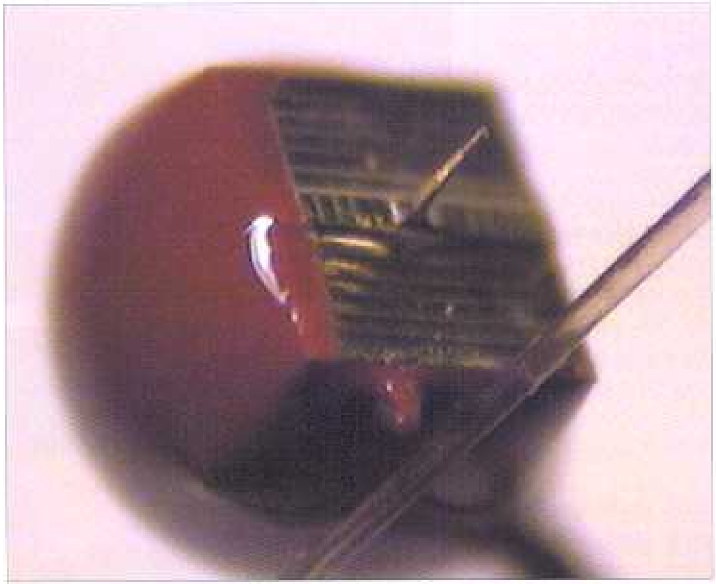


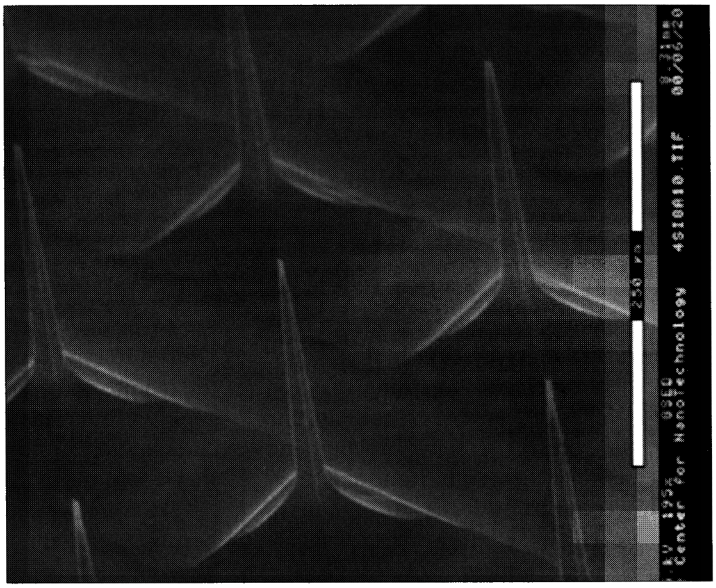
(Top) The sea slug *Tritonia diomedea* (right) stalks one of its favorite meals: a sea pen. The slugs move by secreting a stream of mucus and beating millions of hair-like cilia to row through the slime. (Bottom) The brain of *Tritonia* contains easily identifiable neurons (indicated by arrows), some of which are nearly a millimeter in diameter. This allows researchers to record the "internal electrical attitude" of individual cells, says UW zoology professor Dennis Willows. Photos: James Beck

While the chip will probably weigh less than 100 milligrams, the battery needed to power it will weigh nearly three times that amount. To be sure that this extra load does not alter the flight performance of *Manduca*, Daniel and Tu, with the help of undergraduate Carlos Moreno, will compare the performance of loaded and unloaded moths feeding from a robotic flowering bush.

With this device, the researchers can quantify how well the moths are able to match their movements to the three-dimensional movements of artificial flowers, and record how much nectar they are able to extract. These measures allow Daniel and Tu to assess performance in a way that is relevant to the natural behavior of the moth.

While it would be possible to leave the battery off entirely and power the chip remotely with radio waves, designing a stand-alone system will make it much easier for the team to tackle the final phase of the project: using the chips not only to record information, but also to stimulate specific neurons and pathways.





(Left) A prototype microchip with a silicon electrode to record the inner workings of *Tritonia* brain cells. A human hair is shown for scale. (Right) Future chips will contain a whole array of tiny silicon electrodes.

The point of this portion of the project, says Diorio, is that "if you think you understand how the loop works, see if you can talk to it—inject a signal into the flight control loop of Manduca" and see if you get the result you expect.

"What if you give the moth an electrical optical illusion" by stimulating sensory cells that tell the moth that the visual world is slipping to the left or right, asks Daniel. "Will you drive the moth to alter its flight trajectory? How much does all of the other sensory information override it or confuse it? And to what extent is that context-dependent?"

In the short term, researchers will most likely use these stimulus-response experiments to test only small pieces of the pathway, but eventually the chips could be used to test more complete models of sensory integration and flight control.

Evolving the animal-chip interface

The potential applications of information gained from the project are diverse. There are serious efforts underway to develop autonomous micro-air vehicles (flying robots), but flying insects have "controls and ways of running these moving systems that we don't actually mimic or understand very well," says Daniel.

In addition, insects display an immense diversity of flight modes that could inform robotics engineers of key features in flight control systems. "We really still have only a rudimentary understanding of that diversity and what drove it in an evolutionary context," says Daniel.

Horvitz hopes that the research will not only provide clues as to how the nervous systems of *Manduca* and *Tritonia* work, but will even shed light on our own nervous systems.

"From my point of view, there is very little difference between the nervous system of *Tritonia* and our nervous system," says Horvitz. "We're essentially built of the same components, and from the point of view of an alien looking down, we're basically very similar in terms of circuitry and design."

Therefore, developing a microcomputer capable of sensing what goes on in cells and stimulating them could potentially have beneficial medical applications down the road. "We already know that various kinds of stimulation can be useful for suppressing epileptic seizures and chronic pain," says Horvitz. "There have even been prototypes in which long-term stimulation of the visual cortex can be used to create coarse versions of vision in blind people."

In addition, probing the nervous systems of *Tritonia* and *Manduca* may provide clues to computer scientists about how the nervous systems of animals perform as well as they do.

Nervous systems are incredibly efficient, consuming far less energy per unit computation than digital machines. And animals excel at pattern recognition and learning, a feat that computer scientists have not been able to recreate.

Diorio points out that nervous systems and computers operate in the same fundamental way, encoding information as electrical charge distributions, maintaining a charge separation, and generating exponential current flows.

"At that fundamental level, it doesn't really matter whether you're in silicon and metal or you're in hydrocarbons in aqueous solutions," says Diorio. "The fundamental underlying physics are roughly the same.

"It's how each system uses that physics" that gives computers and biological systems each their special attributes, says Diorio. And while the mechanisms that allow computers to perform calculations at lightning speed are well understood, Diorio feels there's something more clever going on in nervous systems that could be applied to computers.

However, all of the researchers agree that we would never want computers that perform exactly like the nervous systems of animals. "I think imitation is dangerous," says Daniel. "But I think inspiration is wise."

And while they may not fulfill the mind-control fantasies of an avid science fiction reader, these mini-computers riding piggyback on moths and sea slugs are likely to provide inspiration for decades to come. ■

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