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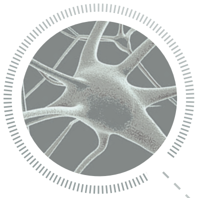
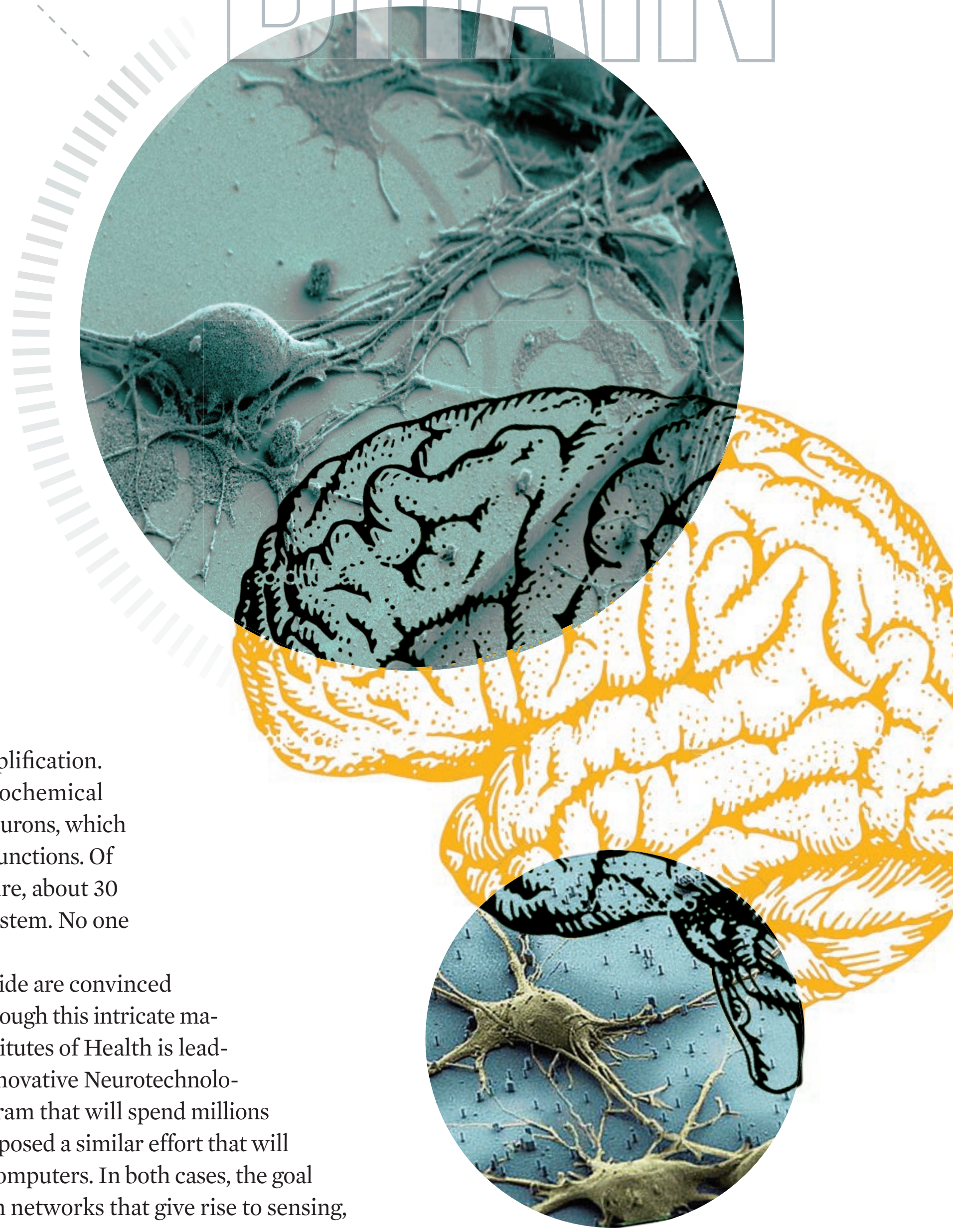
EVER SMALLER-SCALE TOOLS SEEK TO UNRAVEL THAT COMPLEX MYSTERY IN OUR HEADS.

BY ALAN S. BROWN

NEURAL NETWORKS
A micrograph of a typical human brain neuron. The average brain has 85 billion of them, and they form vast networks that stretch from one side of the brain to the other.



NANOTECHNOLOGY FOR THE BRAIN



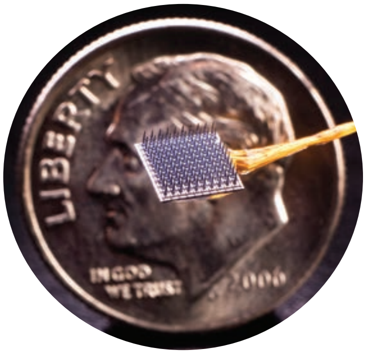
GO ON THE INTERNET TODAY AND IT IS simple to find videos of a paraplegic using a brain implant to manipulate a robotic arm, or a chimp using a similar device to control a robot running on a treadmill. There are scans of different regions of the brain lighting up when we see food, a snake, and an attractive person. All this progress makes it easy to believe researchers are close to unlocking the brain's secrets, and perhaps finding cures to such crippling neurological diseases as Parkinson's, epilepsy, or schizophrenia.

That would be an incredibly gross oversimplification. The brain is an astonishingly complex electrochemical machine. It's composed of tens of billions of neurons, which have thousands of different shapes, sizes, and functions. Of the millions of proteins our bodies manufacture, about 30 percent are found exclusively in the neural system. No one knows what most of them do.

Yet leading scientists and engineers worldwide are convinced that they are on the verge of finding a path through this intricate machinery. In the United States, the National Institutes of Health is leading the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, a public-private program that will spend millions on research. The European Union has also proposed a similar effort that will focus on simulating the entire brain on supercomputers. In both cases, the goal is to understand how individual neurons form networks that give rise to sensing, thinking, and acting.

The BRAIN research will build on two different types of technology. The first is imaging. It includes such techniques as functional magnetic resonance imaging, computer-aided tomography, and electroencephalography. The images formed by these technologies represent the actions of millions of neurons. But their resolution

EMERGENT BEHAVIORS
Animal behaviors, such as sensing and reacting to change, emerge only when individual neurons form large networks.



THOUGHT INTO ACTION A 4 millimeter square sensor (left) implanted in the brain of Cathy Hutchinson uses 96 electrodes to capture neural signals. A computer decodes the data, enabling Hutchinson, who has been paralyzed 15 years, to manipulate a robotic arm and give herself a drink of coffee.

is too low to understand what individual neurons are doing, said Sotiris Masmanidis, a physicist by training and an assistant professor of neurobiology at University of California, Los Angeles.

Electrodes, which researchers can implant into brains to measure neural behavior, are fast and have enough resolution to measure the electronic pulses that race through individual neurons as they communicate with other neurons. Yet electrodes have limitations too. Even the best can monitor about 100 or 200 nearby neurons, but they shed no light on how those neurons form vast networks that stretch across the brain.

Electrodes also have a variety of other issues. To work, they have to penetrate the brain. Most implants are large enough to kill many surrounding neurons. Bodies do not like these intruders, and attack them until they cease to function. Also, even small head movements can tear them free of the neurons they are measuring. The electrodes themselves must be able to both separate individual neural signals from electrical noise, and capture and resend megabytes of information each second—all while using a minimum of power so they don't cook the cells around them.

Measuring more of the brain will be quite an engineering challenge.

THIN STICKS

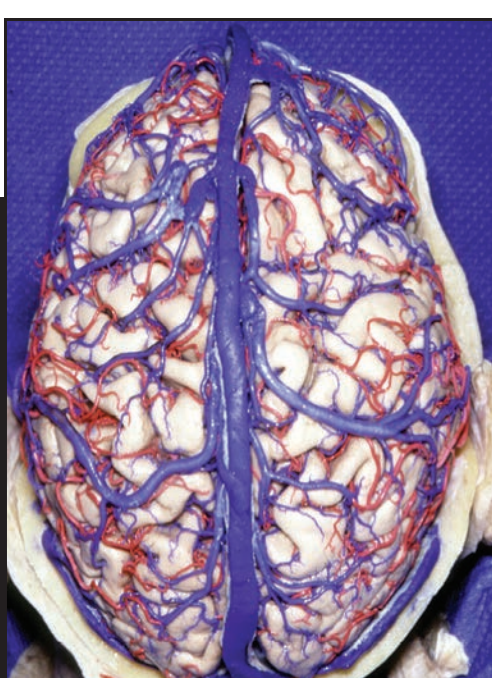
Tim Harris believes nanotechnology provides ways to build electrodes that combine high resolution with the ability to measure thousands and then tens of thousands of neurons. He wants to make probes that are so small he could insert several in different parts of a rodent or chimp brain to measure how neurons communicate along vast networks.

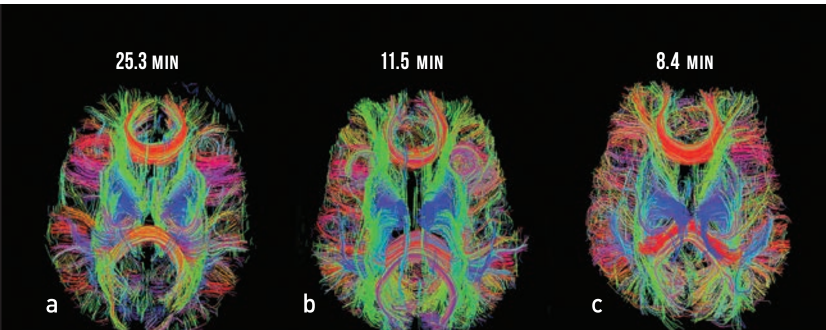
Harris brings a multidisciplinary approach to his craft. Although he trained as an analytical chemist, he heads the applied physics and instruments effort at Howard Hughes Medical Institute's Janelia Farm research center in Virginia.

Harris sees many limitations in today's predominant technology, twisted wire tetrodes. They date back 30 years, and are made by twisting four tiny wires into a group and then bundling them into an array with 24 groups. The result is a sensor whose 96 electrodes extend several millimeters long.

Researchers use them to study the hippocampus, the brain's memory region.

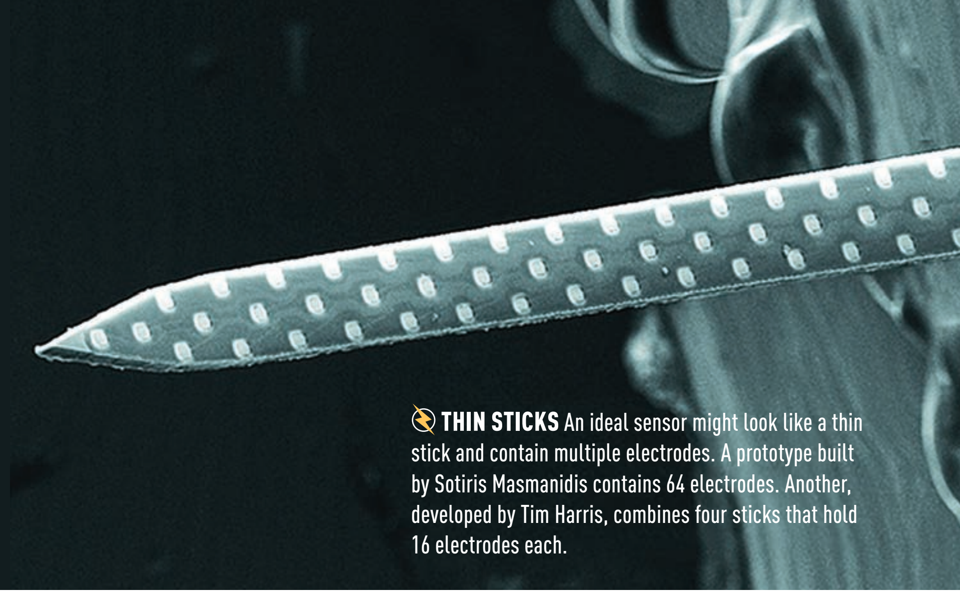
Why the hippocampus? "It's flat and wide, and filled with closely packed cell



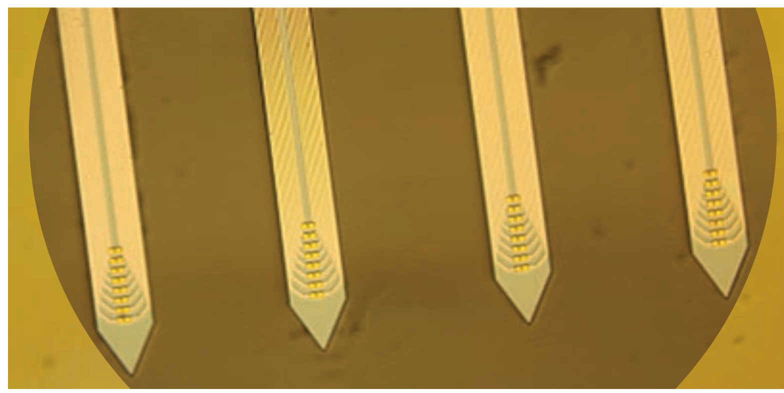


CONNECTED The human brain may look like any other organ (left), but better imaging techniques have improved our understanding of the brain's vast interconnections.

"We're not interested in measuring the activity of individual neurons but of large-scale networks that extend over a large area of the brain."



THIN STICKS An ideal sensor might look like a thin stick and contain multiple electrodes. A prototype built by Sotiris Masmanidis contains 64 electrodes. Another, developed by Tim Harris, combines four sticks that hold 16 electrodes each.



bodies. In a mouse or a rat, you can't miss it," Harris said. "Think about using the same array, 3 millimeters by 3 millimeters square, to study the cortex, which is only 1 millimeter thick in a rodent. It will cause lots of damage. Neurons in the cortex communicate vertically, and there's no way to target those different layers. What's ideal is an array that starts at the top, goes to the bottom, and causes little damage. What you want is a really thin stick."

Picking the right size stick was a quest for a happy medium. Thickness may maximize the number of electrodes and wires, but sticks too thick can kill nearby neurons. Extreme thinness limits the number of sensors and reduces mechanical strength, so that sticks might buckle or break when inserted into the brain. Harris tested several sizes for his prototype before settling on 70 micrometers wide. That is enough real estate for 16 electrodes spaced 10 μm apart.

This design spawned another problem: background noise, caused by electrical resistance, drowned out the neurons' electrical pulses. Resistance increases as wires grow thinner. Since the sticks had very thin wires, they produced lots of noise.

He solved the problem by coating the electrodes with a conducting organic polymer. "The polymer is like spaghetti. It increases the surface area, which raises the capacitance, lowers the resistance, and reduces the noise," he said. The signal-to-noise ratio was so much higher that the stick's closely packed electrodes could pick up signals from nearby neurons without direct physical contact.

Harris teamed with Jeff Dalley, a neuroscientist at the University of Cambridge, to test the invention. He assembled four sticks into a tiny pitchfork with 64 sensors. Dalley implanted it in rats that had been taught to look for a flashing light, then wait several seconds before pushing a lever for a reward.

The stick helped researchers identify three unique clusters of neurons that behaved differently during each phase of the experiment.

Harris is now working with several research and engineering groups to build sticks with 384 electrodes. "If we're going to put a stick into the brain, we want to get every piece of data a stick is capable of giving," he said. "We hope we can satisfy all the needs of the neuroscience guys for a decade, and if we do that, we'll learn what to do next. A likely follow-up project is to make larger sticks with even more sites. We could put a dozen of them in a monkey brain. The BRAIN target of listening to 10,000 neurons in a primate is totally reasonable."

Masmanidis is also building sticks, but his have 64 electrodes. Measuring 90 micrometers wide, 22 μm thick, and several millimeters in length, they're long enough to reach any part of a rodent brain. Wires 300 nanometers wide and 100 nm thick run along their length.

Noise is a top concern. "The signals running along these wires are weak," he explained. "By the time they get to the processor, there is all sorts of electrical contamination. The electromagnetic interference from a light bulb can do it, or any movement relative to the Earth's magnetic field that induces a current. The longer the conductor, the greater the interference."

Embedding powerful new signal processing chips within a few centimeters of the probes may provide a solution. The chips amplify and buffer the electrode signals, then condense, or multiplex, them into a single signal that travels to a computer capable of resolving gigabytes of information per second. This combination of amplification and multiplexing reduces the number of wires and lets engineers fit many more electrodes onto a single probe.

Like Harris, Masmanidis wants to boost the number of electrodes on his probes. He also wants to develop systems that transmit data wirelessly.

He also wants to create probes with light sources on them. Building on work by Ed Boyden of Massachusetts Institute of Technology, Masmanidis believes researchers will increasingly use viruses to inject proteins found in algae into neurons. When light activates these proteins, they can polarize or depolarize neurons, effectively turning them on and off. This would enable future researchers to understand exactly which neurons contribute to what behavior.

While most devices have features measured in micrometers, Harvard Uni-

versity chemistry professor Hongkun Park is working toward implantable chips with tens of thousands of nanoscale electrodes. He is designing them to penetrate individual neurons, to record what happens as they ramp up to an electrical spike.

Park likens his approach to the semiconductor sensors used to capture millions of pixels of information in cameras and smartphones. “In our case, we’re building a coarser chip, but it will work much faster because we need to make measurements 10,000 times per second,” he said.

Park starts with custom processors designed and fabricated by Taiwan Semiconductor Manufacturing. His own laboratory is making the tapered nanowires, or needles, as he refers to them, which are under 100 nm in diameter and 50 to 100 μm long. He dopes the surface with ions to improve conductivity, etches away most of the surface to leave behind an array of elongated needles, and then treats the surface with oxygen to form silicon dioxide, or glass, to reduce biological reactivity. The needle arrays are then bonded to the processor using conventional semiconductor techniques to form probes a centimeter square. Park prototyped the process using 16 needles, but plans to increase that number to 10,000, with 250,000 needles being his ultimate goal.

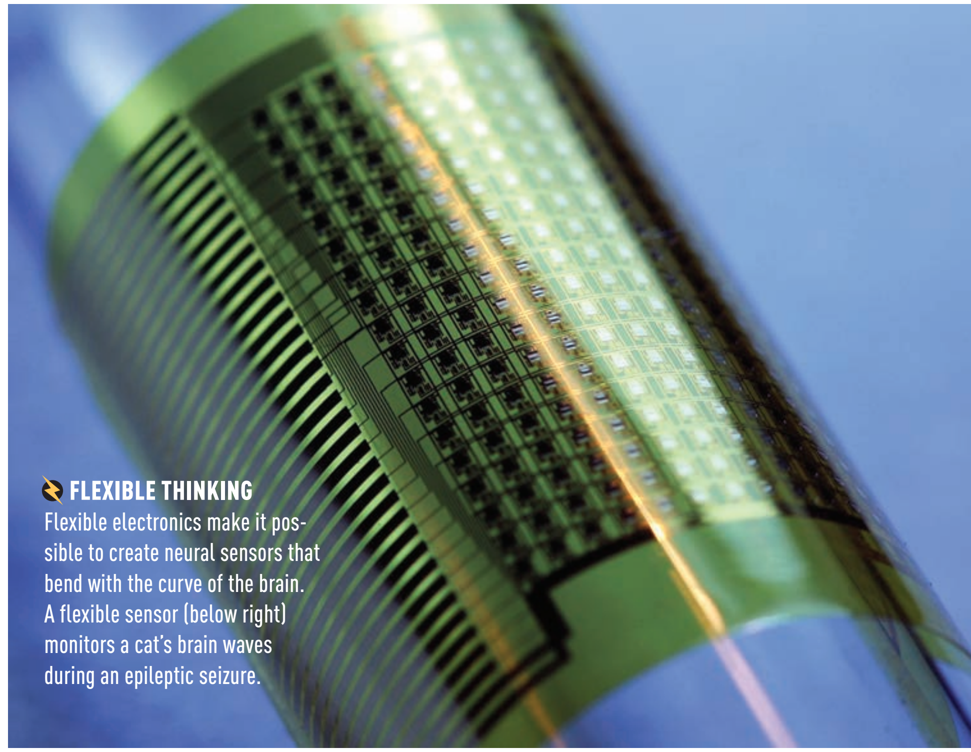
This presents a problem. “If they were coupled to neurons all the time, they would make an excellent fryer,” Park said. “They would get hot the way a computer does and cook the cells.” Initially, he plans to minimize the problem by powering only the few needles actually penetrating neurons. As the probes improve and a greater percentage of needles contact neurons, he plans to manage power better.

Meanwhile, the first chips will be good enough to study retina neurons. “Starting from some random cortical region is not the way to go,” Park said. “We want to go with a system where we know what we are measuring, but there are still enough unknowns to make it scientifically interesting. We’re going to couple the chip to different layers and learn about how they are wired and how they work together.”

If Park advances true nanoscale probes that contact tens of thousands of neurons, then Jonathan Viventi, an assistant professor of neural science and electrical and computer engineering at New York University, is moving in the opposite direction.

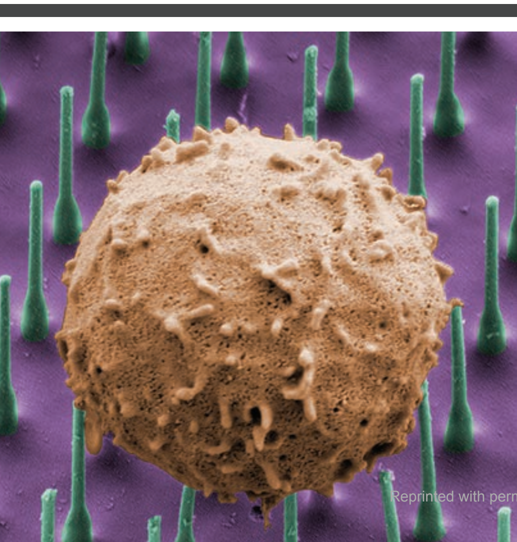
“We’re not interested in measuring the activity of individual neurons but of large-scale networks that extend over a large area of the brain,” Viventi said. Rather than make those measurements from outside the brain, he plans to achieve higher, faster resolution by placing sensors inside the cranium, on the surface of the brain itself.

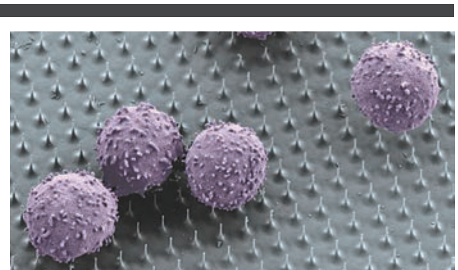
To do that, he is teaming up with John Rogers, a materials engineer at the University of Illinois and a MacArthur Fellow who received ASME’s Robert Henry Thurston Lecture Award in 2013. Rogers developed a family of flexible silicon electronics that makes conformal sensors possible. So far, Viventi has built flexible probes with 360 silicon electrodes 300 micrometers



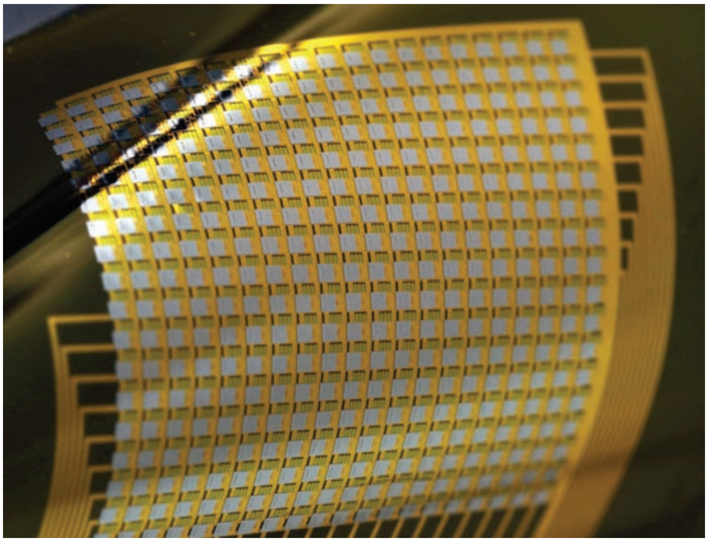
FLEXIBLE THINKING
Flexible electronics make it possible to create neural sensors that bend with the curve of the brain. A flexible sensor (below right) monitors a cat’s brain waves during an epileptic seizure.

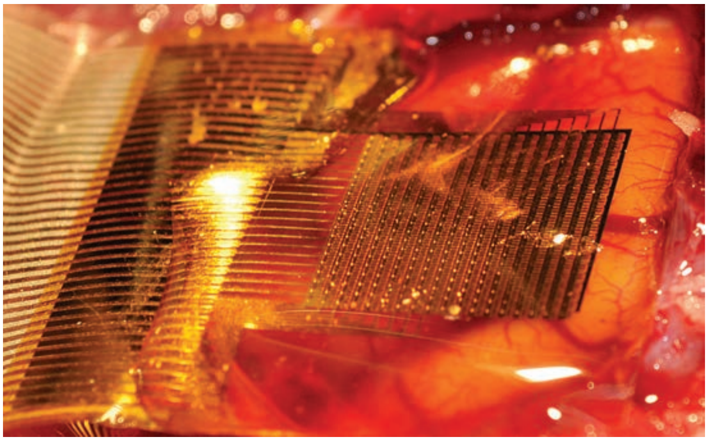
> “Measuring electrical pulses without also measuring chemistry is like listening to an orchestra and hearing only the rhythm but not the notes.”





CELLULAR INJECTION
Hongkun Park is developing nanowire arrays that can inject neurons with chemicals or measure electrical activity as it develops in the cell. Here, Park’s array interrogates immune system T cells.





square spaced 500 μm apart. The devices also incorporate electronics to amplify and multiplex their signals, allowing all the sensors in a column to communicate along a single wire. His next-generation probes will fit 1,024 electrodes on the same space.

Researchers attach the sensor by cutting through the skull, making a tear in the membrane that covers the brain, and slipping in the device. Because it does not penetrate the brain but sits on top of its surface, Viventi does not expect that the brain will attack it as a foreign body. "The big benefit is that it will form a stable interface with the brain that lasts the lifetime of the patient, with a high-performance signal that stays constant over time," Viventi said.

Instead of imaging millions of neurons as conventional systems do, each sensor averages signals from about 10,000 neurons. "It's still averaged, but the information is much more localized," Viventi said.

The sensor has been used to study epilepsy in cats. "Before, the seizure was seen as an irregular wave form with a repeating pattern," he said. "When we look at a finer spatial scale, we see waves of electrical activity that form complex patterns across the brain. We see an alphabet of repeating patterns that we couldn't see before."

"Someday," he added, "we'd like to not only predict epilepsy, but stimulate neurons and stop those waves from propagating."

NEW DIRECTIONS

Measuring neurons' voltage spikes is a good and easy way to measure neural activity. Yet neurons do not communicate by zapping each other with electric sparks. Rather, the electrical pulses cause neurons to release small molecules called neurotransmitters, which jump from the end, or synapse, of one neuron to another. The 100 known neurotransmitters are the alphabet that encodes neural communications.

"Measuring electrical pulses without also measuring chemistry is like listening to an orchestra and hearing only the rhythm but not the notes," said Paul Weiss, a professor of biochemistry and materials science and engineering at University of California, Los Angeles. It is impossible to understand how a functioning circuit in the brain differs from a malfunctioning one without looking at the interplay between those neurotransmitters. "If we can understand those differences, we can treat them," he said.

It will take nanotechnology to make those measurements, because the synapses, the structures that release neurotransmitters, measure only about 20 nm. This is as small as the smallest features of the latest generation of semiconductor electronics. Moreover, neurotransmitter chemicals themselves are small and difficult to detect.

Weiss and Anne Andrews, a professor of psychiatry at UCLA, have developed sensors that detect the important neurotransmitter, serotonin, by engineering surfaces which bond with it exclusively and not with related molecules. The next step is to create transducers that signal when sensors capture a serotonin molecule. They hope to work with Masmanidis to create nanoscale probes that simultaneously measure serotonin release and electrical spikes at microsecond speeds.

When it comes to measuring the brain, many researchers are starting to make some headway, Weiss said. "The advantage of the BRAIN initiative is that will have the economies of scale to make measurement platforms that many people can use" he said. "By collaborating and using common platforms, we believe we can move the field along quite quickly."

Nanotechnology will play a vital role in that advance. "We made an enormous investment in nanotechnology over the past decade," Weiss added. "Here's one place where there's going to be a substantial payoff."

Masmanidis agrees, and believes mechanical engineers have a special role to play: "Mechanical engineers can have a huge impact on future technology development," Masmanidis said. "Right now, the state of the art is a few hundred micrometer-scale electrodes.

"Wouldn't it be cool to make a more powerful probe that was so small, it would cause little damage when it was implanted? One that could transmit information wirelessly. Then there would be a good chance of implanting it in paraplegic patients, and using it to control devices that help them get around and take care of themselves."

Yes, the brain is complicated. Understanding it presents enormous challenges. Yet many researchers believe that they now have the tools to make real progress. Who knows where it could lead? **ME**

ALAN S. BROWN is associate editor of *Mechanical Engineering*.