DELVING DEEPLY INTO

Livermore's Biomedical Foundry includes a clean room that is recognized nationally as a unique thin-film neural interface facility. Here, researchers fabricate components for the Livermore Flexible Probes. (Photo by Randy Wong.)

THE BRAIN'S MYSTERIES

Biocompatible microelectrode arrays interface with the brain, promising greater understanding of brain function and new treatments for neurological disorders.

UNDERSTANDING the brain, especially that of humans, is one of the most complex challenges in science today. With an estimated 100 billion neurons joined together by 100 trillion connections in a hugely interconnected network of circuits, the human brain is extraordinarily formidable to investigate. For instance, a brain circuit can encompass not just a group of neighboring neurons but also individual neurons located as far as centimeters away.

Researchers in Lawrence Livermore's Neurotechnology Program, part of the Laboratory’s Center for Bioengineering, are responding to the need for innovative approaches to further understanding of brain function and neural communication dynamics. The group is focused on designing and building extremely small and biocompatible devices called Livermore Flexible Probes—microelectrode arrays that are implanted directly into the brain. Also known generically as neural interfaces, Livermore Flexible Probes monitor and optionally stimulate neural activity. Soft and flexible, the probes do not interfere with normal functions or behavior, allowing for long-term studies of brain circuitry. In animal studies, the probes are already proving to be exceptionally stable and useful.

In fact, research laboratories across the nation are using Livermore Flexible Probes to record neural activity in the brains of both animals and humans. Small-scale animal studies are done at Livermore, while more complex and long-term experiments are being conducted at University of California (UC) campuses and other institutions nationwide with strong neurophysiological programs. There, researchers test and characterize the mechanical and electrical properties of the implants, as well as their suitability for long-term use. At UC San Francisco (UCSF), the Livermore probes have been successfully tested for short periods on patients undergoing surgery to treat severe epilepsy.

Bolstering a National Effort

Shivshankar Sundaram, director of Livermore’s Center for Bioengineering, says, “By providing high-quality,
A 128-electrode Livermore Flexible Probe temporarily implanted in the hippocampus of a patient at the University of California at San Francisco. (Photo courtesy of Dr. Eddie Chang.)

long-term, and continuous recordings of brain activity with high resolution, the Livermore work enhances a larger national effort to revolutionize understanding of the brain and uncover ways to diagnose, treat, and prevent brain disorders. Researchers are hopeful that the vast amounts of data being collected from the arrays will restore lost neural functions such as sight, hearing, mobility, and memory.

Lawrence Livermore’s long history of developing innovative bioengineering systems dates back to the 1970s, when researchers developed the first laser-based cell sorters, and continues through the development of miniaturized polymerase chain reaction systems that revolutionized molecular diagnostics. These pioneering achievements took advantage of a core Livermore strength—precisely recording, measuring, and analyzing data from complex systems, ranging from air turbulence to inertial confinement fusion reactions—and led to Livermore’s involvement in both fabricating implanted biomedical devices and handling the large amounts of data the devices collect. The neural interface work also underscores the Laboratory’s growing leadership in precision medicine initiatives such as the Accelerating Therapeutics for Rare Neurological Disorders—precisely recording, measuring, and analyzing data from complex systems, ranging from air turbulence to inertial confinement fusion reactions—and led to Livermore’s involvement in both fabricating implanted biomedical devices and handling the large amounts of data the devices collect. The neural interface work also underscores the Laboratory’s growing leadership in precision medicine initiatives such as the Accelerating Therapeutics for Rare Neurological Disorders (ATRN) Initiative. Launched in 2013, the ATRN Initiative aims to revolutionize scientific understanding of the human brain by discovering how individual cells and neural circuits interact in both time and space and uncovering ways to treat, prevent, and cure brain disorders and traumatic brain injuries. Participating in the initiative are federal agencies, national laboratories, foundations, universities, institutes, and private industry. A strong relationship with bioengineers, neuroscientists, and surgeons nationwide is critical to Livermore’s research effort. For example, Livermore’s microfabrication know-how complements clinical science expertise at UCSF. A Livermore–UCSF team developed a method to implant the Livermore Flexible Probes into deep brain tissue with the aid of a removable device. Although commercial devices commonly feature only 4 electrodes, Livermore designs offer 32, 64, and even 128 electrodes, enabling the capture of more data at higher rates.

At UCSF, the Livermore team works closely with neurosurgeon Eddie Chang and with Loren Frank, who is focused on neural circuits that underlie learning and decision making. Other collaborators include electronics researchers at Lawrence Berkeley National Laboratory and Professor Charles Della Santina at Johns Hopkins University.

Recording at High Density

A 128-electrode Livermore Flexible Probe temporarily implanted in the hippocampus of a patient at the University of California at San Francisco. (Photo courtesy of Dr. Eddie Chang.)

explains Razi Haque, head of Livermore’s Neurotechnology Program and leader of several projects involving neural implantable probes. Haque says, “The devices’ flexibility allows placement underneath imaging windows without danger of breakage, making possible combined electrophysiology and imaging studies.” The Livermore devices also support optogenetic stimulation, a technique that uses light and light-sensitive proteins to manipulate neural activity.

Manufacturing in Clean Rooms

Livermore Flexible Probes are produced with Laboratory microfabrication techniques—many of them patented—at the Biomedical Foundry, in the Laboratory’s Center for Micro- and Nanotechnologies. The foundry includes a clean room with dedicated processing and characterization equipment and is recognized nationally as a unique thin-film neural interface facility. “We have a singular skill set in microfabrication coupled with tight control over manufacturing,” declares Haque. In fact, quality control is key for the Livermore Flexible Probes that has been approved for use in humans. The clean room-produced probes consist of metal layers separated and insulated by flexible, biocompatible polyimide films. Fabrication employs the same photolithographic process that the electronics industry uses to manufacture integrated circuits, building a device layer by layer. (Photo by Randy Wong.)

A researcher in the clean room holds wafers on which Livermore Flexible Probes electronics have been manufactured. The wafers consist of metal layers separated and insulated by flexible, biocompatible polyimide films. Fabrication employs the same photolithographic process that the electronics industry uses to manufacture integrated circuits, building a device layer by layer. (Photo by Randy Wong.)
four to six weeks. The final device used in many studies consists of a polymer probe nearly as narrow as a human hair in many studies consists of a polymer for providing a direct, passive connection to external devices. In cases of animal probes coated with the original platinum surface (center) and other biosensor-enabled coatings. Each scale bar represents 20 micrometers.

The artificial retina received an R&D 100 Award in 2009 and a Popular Mechanics Breakthrough Award in 2010. “We are leveraging much of that retinal prosthetic endeavor,” says Haque. “The artificial retina is a great foundation from which to work.”

One of the most important features of Livermore Flexible Probes are their large number of electrodes. Whereas commercial devices commonly feature 4 electrodes, Livermore designs offer 32, 64, or even 128 electrodes. With this arrangement, a single electrode is likely to detect the activity of more than one neuron, and the activity of a single neuron could be detected by multiple electrodes. Software algorithms are often used to differentiate signals from individual neurons when the number of electrodes would make the job overwhelming for humans. “The human brain has 100 billion neurons, and a 128-electrode Livermore device can pick up activity from several hundred of the cells,” explains Haque. Efforts are underway to increase the electrode count. Electrical engineer Angela Tooker, who is spearheading the creation of ultrahigh-density arrays, says, “Scientists would like more electrodes—1,000 per device—to record activity at very high densities throughout entire brain structures, such as the cortex, and across multiple brain areas.” The group’s long-term goal is to develop systems that can record activity from 10,000 neurons or more to study memory, learning, addiction, and anxiety. The hippocampus, the region of the brain associated with memory, is composed 100,000 neurons, so several high-electrode-count arrays could record approximately 1 in 10 of those cells.

Livermore engineers developed a flexible microelectrode array that conforms to the curved shape of the retina. Approved by the U.S. Food and Drug Administration (FDA) as the first high-density, microfabricated, and fully implantable neural prosthetic ever produced, the device partially restores sight to blind individuals.

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Livermore researchers are investigating the potential of implantable microelectrodes to alleviate severe depression by disrupting accompanying neural signals, an emergent treatment called deep brain stimulation. This artist’s concept depicts a variety of components that such therapy might feature, including Livermore Flexible Probes, a telemetry hub, and associated electronics. (Illustration by Kwei-Yu Chu.)

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Stimulating Selected Neurons

One therapeutic use of present Livermore Flexible Probe designs is deep brain stimulation (DBS). Currently used to treat some neurological disorders such as Parkinson’s disease, essential tremor, and epilepsy, DBS is also being clinically investigated as a possible treatment for depression and other psychiatric disorders, PTSD, traumatic brain injury, and chronic pain, among other conditions. In DBS, surgically implanted electrical leads deliver...
The Livermore team is pushing the frontiers of neurotechnology by furthering understanding of the brain and speeding development of new neurological therapies.

Researchers such as Alison Yorita can use Livermore Flexible Probes to collect an extraordinary amount of neural signaling, as seen on the monitor. (Photo by Randy Wong.)