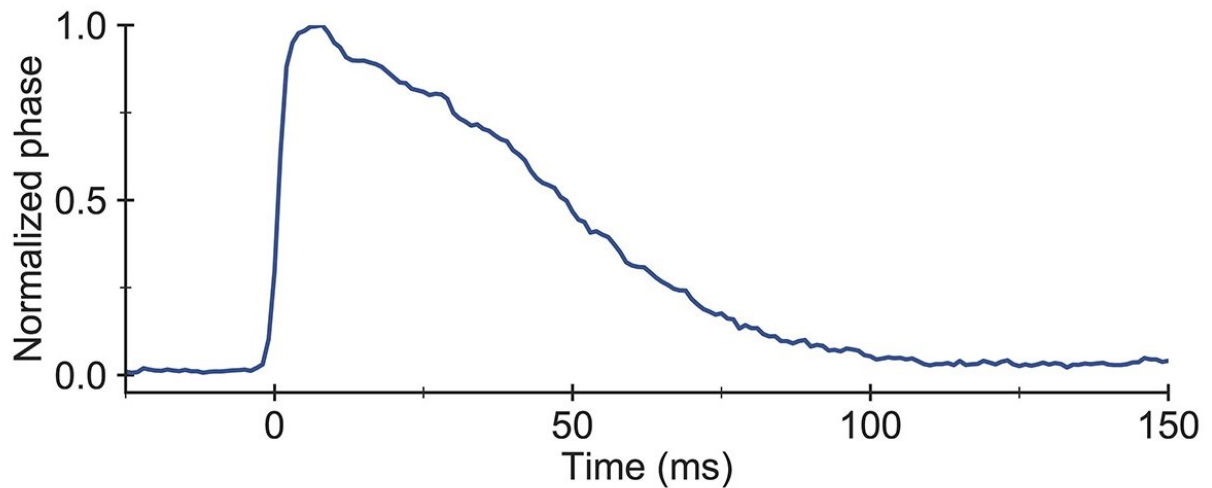


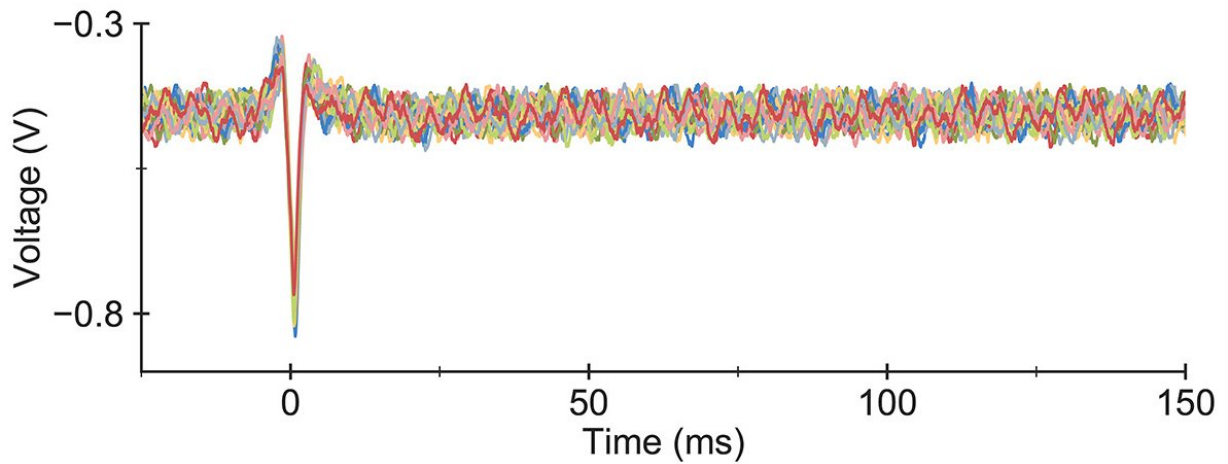
Researchers design technology that sees nerve cells fire

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Optical Imaging



Electrode Array



Signal from optical imaging (top) matches the signal from an electrode array (bottom). Credit: Daniel Palanker, Ph.D., Stanford University.

Scientists have plenty of ways to watch as individual neurons in a brain fire, sending electrical signals from one to the next, but they all share a basic problem. Each method, whether it involves electrical probes, chemical agents or genetic modifications, is in some way more invasive than neuroscientists would like.

That may soon change. As Stanford researchers report Dec. 12 in *Light: Science and Applications*, they have developed a way to watch brain cells send electrical signals using only light, a few lenses and other optical elements, and a fast video camera.

The key to the new approach, said Daniel Palanker, a professor of ophthalmology and senior author on the new paper, is that when neurons fire electrical signals they subtly change shape. That nanometer-scale change can be measured using optical techniques.

So far, Palanker, Tong Ling, a postdoctoral fellow and the lead author on the new paper, and colleagues have measured those miniscule shape changes in networks of neuron-like cells in a lab dish. They are now adapting their methods to study neurons in the brains of living animals. If that works out, it could lead to a more natural way to study at least some parts of the brain.

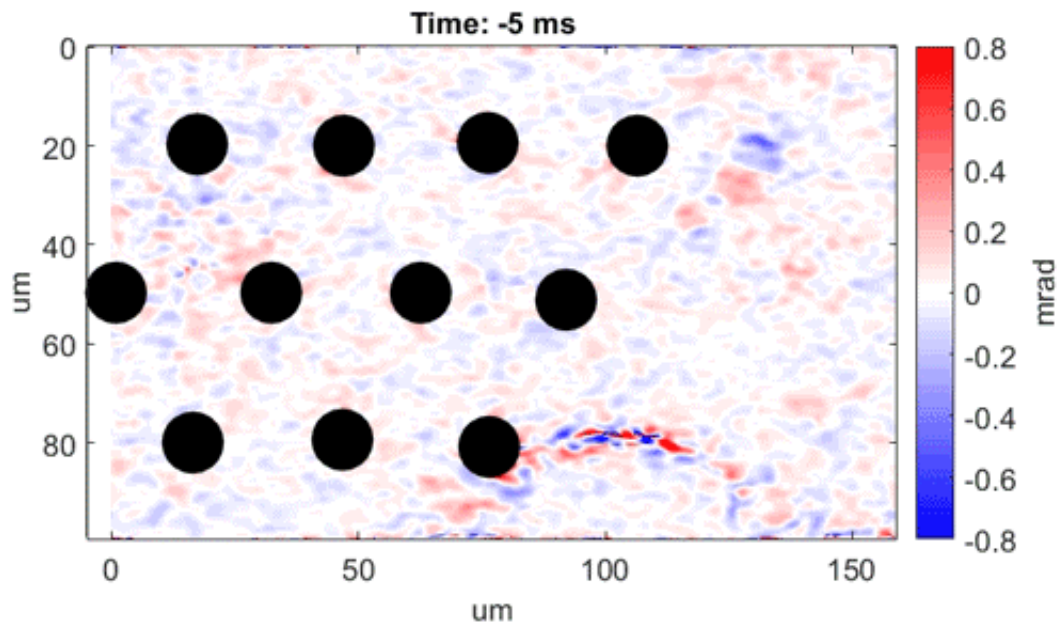
"It's all natural, no chemical markers, no electrodes, nothing. It's just cells as they are," said Palanker, who is a member of Stanford Bio-X and the Wu Tsai Neurosciences Institute.

The shape of things

A lot goes on when neurons fire. There is of course the electrical signal itself, which can be picked up by electrodes. There are also chemical changes, which can be detected using fluorescent molecules that light up when a neuron fires.

And then there's shape. Researchers first realized that neurons change shape by studying crayfish neurons more than 40 years ago. In 1977 a team of Stanford and UCSF researchers bounced a laser off a crayfish neuron as it fired and showed its width changed by roughly the thickness of a strand of human DNA.

Yet translating those results into a way of optically observing neurons firing in human or other mammalian brains faced a number of challenges. For one thing, crayfish neurons are 10 to 100 times thicker than mammal neurons. For another, the technique that original group used—a simple form of what's called interferometry—can only measure changes in a single point at a time, meaning it could be used to study only a small area of one cell at a time, rather than imaging the whole cell or even a network of neurons communicating with each other in the brain.



Video shows a field of cells firing in a wave from left to right. Black dots are electrodes recording simultaneous electrical signals. Credit: Daniel Palanker, Ph.D., Stanford University.

Shining new light on neuron firing

To solve some of those problems, Ling, Palanker and colleagues first turned to a variation on standard interferometry called quantitative phase microscopy which allows researchers to map out entire microscopic landscapes—for example, the landscape of a network of cells arrayed on a glass plate. The technique is simple enough that it can be done by shining laser light through those cells, passing it through a few lenses, filters and other optical elements and filters, and recording the output with a camera. That image can then be processed to create a topographic map of the cells.

Ling, Palanker and the team reasoned they could use the technique to

measure how much neurons change shape when they fire. To test the idea, they grew a network of neuron-like cells on a glass plate and used a video camera to record what happened when the cells—actually kidney-derived cells modified to behave more like neurons—fired. By syncing the video with electrical recordings and averaging over several thousand examples, the team created a template that describes how cells move when they fire: over about four milliseconds, cell thickness increases by about three nanometers, a change of roughly one-hundredth of 1 percent. Once it reaches maximum thickness, the cell takes about another tenth of a second to shrink back down.

Watching brain cells at work

In the initial phase of the experiment, the team needed electrodes to figure out when the cells fired. In the second phase, the team members showed they could use their template to search for and identify cell firing without relying on electrodes.

Still, there are a number of steps to take before the team can make the method work in real brains. First, the team will need to make the technique work in actual neurons, as opposed to the neuron-like cells they've looked at so far. "Neurons are more finicky," Palanker said, but the team has already started experimenting with them.

A second challenge is that neurons in real brains aren't arranged in a single layer on a glass plate, as were the cells Palanker's lab studied. In particular, the team can't shine lasers through the brain and expect to see much of anything come out the other side, let alone useful data. Fortunately, Palanker said, the techniques they used with transmitted light work similarly in reflected light, and most neurons reflect enough light that the approach should in theory work.

There is one limitation that the team probably won't be able to get

around—since light doesn't penetrate deep into the brain, the new method will only be able to probe the outer layers. Still, for projects that only need to study these layers, the technique could give researchers a cleaner, simpler way to study the brain.

"Usually, invasive methods affect what cells do, hence making the measurements less reliable," Palanker said. "Here you do nothing to the cells. You basically just watch them move."

More information: Tong Ling et al, Full-field interferometric imaging of propagating action potentials, *Light: Science & Applications* (2018).

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