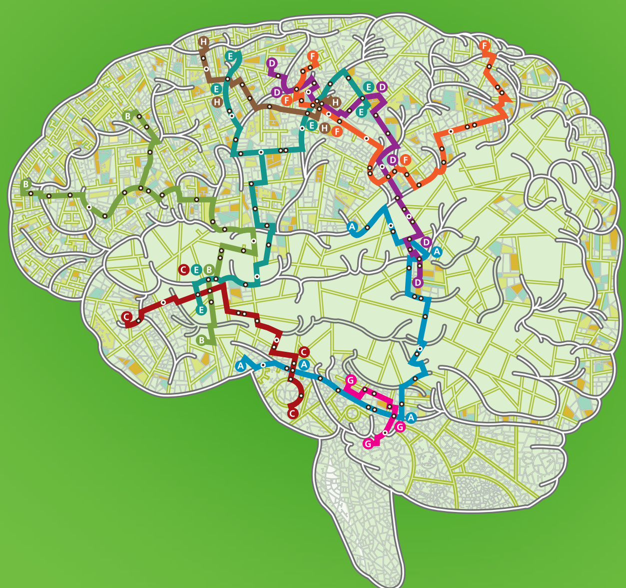
NAVIGATING THE BRAIN'S MYSTERIES



CALTECH RESEARCHERS (AND THE WHITE HOUSE) say it's time to piece together a dynamic map of the brain–one that shows its complex trafficking across trillions of neuronal connections. Addressing this grand challenge could just be the technological moon shot of a generation.

By Kimm Fesenmaier

One morning this past April, nanoscientist Michael Roukes and neurobiologist Thanos Siapas sat amid the scientists and engineers packed into the East Room of the White House. They listened as Francis Collins, director of the National Institutes of Health (NIH), introduced President Barack Obama as "our scientist in chief," and watched as the president took his place behind the podium.

After acknowledging the attendees as "some of the smartest people in the country"—and joking about the questionable appropriateness of his new scientific title—the president got down to the business of the morning: outlining "the next great American project," the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative.

"As humans, we can identify galaxies light-years away, we can study particles smaller than an atom," the president said. "But we still haven't unlocked the mystery of the three pounds of matter that sits between our ears."

Obama went on to describe how his newly proposed initiative would aim to change that. This newest of his Grand Challenges would be to obtain not only a thorough map of the brain and its roughly 100 billion neurons, but a dynamic picture of how that complex organ works in real time. Ultimately, scientists could use this knowledge to pick apart how we think, learn, and remember as well as how to better treat disorders such as schizophrenia, Parkinson's disease, post-traumatic stress disorder, and Alzheimer's disease.

Roukes, Siapas, and many of their colleagues had long awaited an announcement like this one—an acknowledgment of the project they had championed for several years, that of a large-scale effort that would focus top scientists and engineers on revealing the details of the brain.

LET'S BACKTRACK

It all really started taking off for Roukes when, in September 2010, he traveled to Oslo as the director of the Kavli Nanoscience Institute at Caltech to attend the annual Kavli Prize symposium. He struck up a conversation there with the directors of several Kavli neuroscience centers about the maturation of technologies coming out of nanoscience and their potential to improve our understanding of the brain.

Why was Roukes, a physicist and nanoscientist, even thinking about neuroscience? That dates back to a decision made more than 15 years before by former Caltech provost Steve Koonin. In the late 1990s, Gilles Laurent (now a director of the Max Planck Institute for Brain Research) told Koonin that one of the things his field was sorely lacking was the ability to insert tiny electrodes into the brain that would allow scientists to record signals from multiple neurons at the same time. That got Koonin thinking.

"I knew that Michael was expert at fabricating very tiny things," Koonin says. "So I connected Gilles and Michael up and provided a bit of seed money to grease the interaction. My intuition in doing so was nothing more than having two accomplished faculty interested in reaching out across disciplinary boundaries, and knowing that new instrumentation almost always leads to new science. Who knew it would blossom into what it did? Such are the rare pleasures of academic administration."

What blossomed was a close friendship between Roukes and Laurent, and a lasting collaboration at the intersection of neuroscience and nanoscience. After a couple of small pilot projects, Roukes helped Laurent introduce the use of tiny neural probes that could be mass-produced.

In 2002, Siapas joined the Caltech faculty as a neurobiologist interested in brain circuits and the functions of memory and learning. These complex functions arise as a result of the coordinated activation of large populations of neurons distributed throughout the brain. In order to elucidate these brain patterns, Siapas wanted to capture large-scale recordings from freely behaving animals. His interests aligned perfectly with those of Roukes and Laurent, and the three began thinking about ways to enhance the scale and quality of electrophysiological recordings as well as develop prototype devices to explore different research directions.

As a result of these interactions, Roukes says he became increasingly fascinated by the brain. "In fact, I've sort of switched the center of my activity toward biological applications of nanotechnology," he says, "with the brain now being a principal effort. And all of this is the result of Steve Koonin saying, 'Get to know this guy, Gilles. See what happens.'"

BAM

A year after Roukes's informal conversation in Oslo with the neuroscience directors, a symposium took place outside of London, hosted by the Kavli Foundation, the Allen Institute for Brain Science, and the Gatsby Charitable Foundation. There, a

number of participants from neuroscience and nanotechnology—including Roukes, Siapas, and Caltech neuroscientist David Anderson—came together to identify new opportunities for technological development at the interface between these disciplines. "There was spirited discussion about the best avenues and approaches to take," Anderson says.

During the course of the symposium, a subgroup of participants—including Roukes; George Church, one of the leaders of the Human Genome Project; Rafael Yuste, a neurobiologist from Columbia University; and others—got together and began to formulate a new project.

Capitalizing on the momentum from that symposium, Roukes wrote a "technical foundations document" along with Church and Paul Alivisatos, a nanomaterials scientist and director of the Lawrence Berkeley National Laboratory. The document laid out a roadmap of sorts, describing the nanotechnologies that would need to be developed to fuel a neuroscience revolution. In June 2012, a group including Roukes, Church, Alivisatos, Yuste, and two others published a paper in the journal *Neuron* describing what they dubbed the Brain Activity Map (BAM) Project. They followed that up earlier this year with a brief overview of the project, this time in the journal *Science*.

One of the central points in all of these documents was that many brain functions may emerge as a result of neuronal activities taking place in physically separate regions of the brain at the same time. Monitoring such disparate activities is no easy task; neuroscientists today are generally restricted to using electrodes that allow them to study brain activity from one neuron at a time up to only a few. But brain circuits involve millions of such nerve cells, each with thousands of connections that might be rearranging all the time. Focusing on individual neurons could lead researchers to miss the forest for the trees.

On the other hand, imaging technologies such as functional MRI and magnetoencephalography (MEG) are able to capture whole-brain activity—but at the expense of single-cell specificity. They allow researchers to see which brain regions are activated while a subject participates in a particular activity, for example, but provide little detail in terms of which neurons are involved, how they're connected, and under which circumstances they fire. In other words, that forest is looking pretty nice, but what happened to the trees?

To get at the elusive middle ground, where researchers would be able to image, understand, and eventually manipulate collections of neurons at the level of brain circuits, the BAM advocates called for the development of new tools that would allow them to record every activity spike from every neuron in a circuit. Current imaging techniques cannot record activity from enough neurons and do not reach sufficient depths within the brain tissue to achieve this goal. Nor are current techniques for gathering electrophysiological measurements able to record activity from enough neurons in dense enough patches. However, the authors argued, there are promising research avenues that could improve the situation in each of these areas. They also suggested that entirely new methods for wirelessly, noninvasively recording neuronal activity could prove useful. For example, they wrote in the *Neuron* paper that they think "it will ultimately become feasible to deploy small wireless microcircuits, untethered in living brains, for direct monitoring of neuronal activity."

To take steps toward that goal, Roukes and Siapas have started a Beckman Institute pilot project at Caltech, in which they are developing arrays of tiny electrodes called nanoprobes that would be able to measure brain activity from far greater numbers of neurons than is currently possible. Typically, to record electrical signals from neurons, researchers insert hand-assembled bundles of four small wires into the brain tissue. Siapas and others have managed to get recordings from as many as 25 of these bundles at once, but it has proved difficult to scale up beyond that.

Roukes and Siapas's research would allow them to mass-manufacture tiny silicon probes that could record neuronal activity from denser populations of neurons by using many recording sites along the lengths of each probe. "Using these techniques, we can make a new generation of needles that are much finer and have many, many more recording sites," Roukes says.

THE DETAILS

If nothing else, the published articles and less formal white papers produced by the proponents of the Brain Activity Map Project sparked a conversation in Washington, D.C., about the potential benefits that could be realized by a large-scale, brain-related national initiative. In February, President Obama even alluded to such a project in his State of the Union address—two months before announcing the BRAIN Initiative. "Every dollar we invested to map the human genome returned $140 to our economy," he said. "Today our scientists are mapping the human brain to unlock the answers to Alzheimer's… Now is not the time to gut these job-creating investments in science and innovation. Now is the time to reach a level of research and development not seen since the height of the Space Race."

The president would later propose getting the BRAIN Initiative started with a budget of about $100 million for fiscal year 2014—with funds coming from the National Institutes of Health, DARPA (the Defense Advanced Research Projects Agency), and the National Science Foundation. Several private organizations, including the Kavli Foundation, have also said they will contribute to the effort. But details about the allocation of funding, the areas of research, and the initiative's goals and milestones are still to be defined.

To that end, the NIH has appointed a high-level working group of neuroscientists to review available information, to recommend goals that are in line with the vision of the initiative, and to come up with a scientific plan for achieving those goals.

Caltech's Anderson is a member of that 15-person group, which NSF director Collins refers to as the BRAIN Initiative's "dream team." The team's charge? First, compile a list of research areas tagged for immediate funding. Then submit a full report in June 2014.

Anderson considers himself privileged to be part of the working group. And even more to the point, he says, "I'm thrilled that the president of the United States has recognized the importance of understanding brain function."

Asked about the group's progress, Anderson notes that he and his BRAIN colleagues are just beginning deliberations. "Our plan," he says, "is to solicit input from a broad range of scientists. I think it will be fascinating and instructive to listen to the different voices in the neuroscience community and see what kind of consensus can be reached."

While many have applauded the initiative and its ambitious scope, there are detractors who worry, among other things, that the project's funding will steal from other neuroscience projects or that the brain is the wrong subject for such a focused project. Anderson, however, sees the BRAIN Initiative as "an exciting opportunity to accelerate progress in our understanding of brain function in health and disease by promoting new technology development and applications."

Roukes agrees. "This is an incredible opportunity to do a moon shot in terms of the technology that will be developed, which will democratize how the next generation of neuroscience is done," he says. "We would be foolish not to capitalize on this moment." E&S

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Yaser Abu-Mostafa is a professor of electrical engineering and computer science. His work is supported by Intellectual Ventures.

Michael Roukes is the Robert M. Abbey Professor of Physics, Applied Physics, and Bioengineering. His neuro/nano work is funded by a National Institutes of Health (NIH) Director's Pioneer Award and grants from the G. Harold & Leila Y. Mathers Foundation and the National Science Foundation (NSF).

Thanos Siapas is a professor of computation and neural systems. He receives funding from the Gordon and Betty Moore Foundation, the Mathers Foundation, the NSF, and the NIH.

Learning From Machines

Neuroscience and nanoscience are not the only fields that are likely to benefit from the new **BRAIN Initiative**. Certainly, trying to understand how hundreds of thousands or millions of neurons connect and behave across a range of timescales will produce what has been called a "data deluge"—and managing and making sense of that flood of information will require new tools for data management and analysis.

A Kavli Futures Symposium was held at Caltech in January, bringing together 16 scientists from a range of fields to discuss this issue. The organizers estimated that recording from a million neurons a thousand times per second would generate 100 terabytes (102,400 gigabytes) of data per day. However, if you compressed the data, you might be able to get down to about 3,000 terabytes of data per *year*—a huge amount of information, but not beyond the range of other big-data projects.

Machine-learning expert Yaser Abu-Mostafa participated in the symposium. "The magnitude of the project and the amount of data will be completely impossible to handle," he says, "unless you have a method that will be able to do the needed mapping, interpretation, and analysis in an automated way." Abu-Mostafa believes that such a method will come from machine learning—an area in which, he adds, Caltech has a lot to contribute.