Massively Parallel Brain Imaging

Mark Schnitzer is building tools to visualize neural activity in the fruit fly brain—100 flies at a time

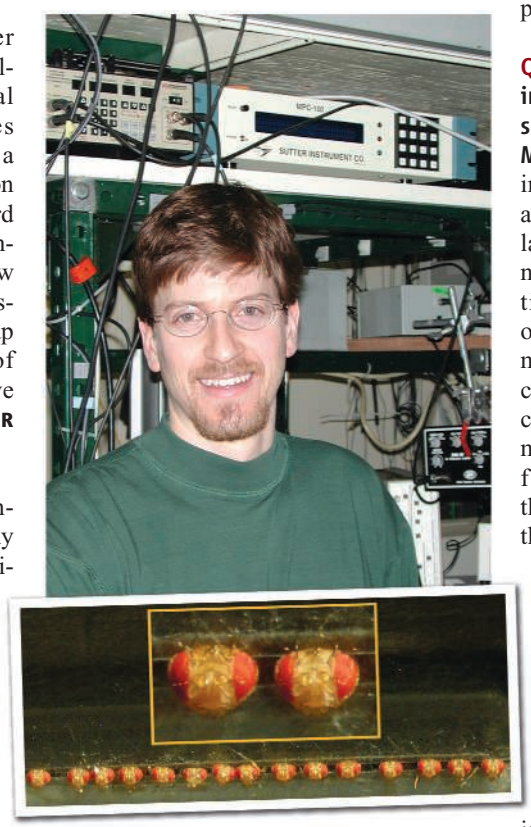
INVENTING TECHNOLOGY THAT PUSHES THE frontiers of brain research is the passion of applied physicist and neuroscientist Mark Schnitzer. His lab at Stanford University in Palo Alto, California, has cranked out several cutting-edge devices in recent years, including a 1.1-gram fluorescence microscope that can be mounted on a freely moving mouse to monitor the activity of neurons and glial cells and a 2.9-gram fiber-optic two-photon microscope for imaging cells deep inside the brain of an active rodent.

Now he's working on an even bolder project, developing optical imaging technology for simultaneously recording neural activity in the brains of 100 fruit flies (*Drosophila melanogaster*), thanks to a $1.3 million grant from the Keck Foundation and a $2.5 million Director's Pioneer Award from the National Institutes of Health. Compared with current methods, which allow imaging only one fly at a time, such "massively parallel brain imaging" could open up research questions that have been out of reach, Schnitzer says. His comments have been edited for brevity. **–GREG MILLER**

Q: What was the impetus for this project?
M.S.: The basic idea was that neuroscientists have been starved for data, particularly brain-imaging data in awake, behaving animals. With invertebrates, and in particular with genetic model species like *Drosophila*, there's an opportunity to achieve a greater level of throughput and automation and at the same time to look at activity in populations of individual neurons as an animal executes a behavior.

Q: How do you hope to accomplish that?
M.S.: It's very early days, but our goal is to be able to examine 100 fruit flies in parallel. [The brains of individual] fruit flies have been examined previously by two-photon imaging with genetically encoded sensors for intracellular calcium, which is often used as an indicator of excitation in neurons. One of the limiting steps in this is the need to manually dissect the cuticle of the fly to access the brain optically. The first part of achieving higher throughput is to automate this step, so we're developing computer-directed laser microdissection. The basic idea would be to have a tray of flies, each fixed in place, and have the laser do the cutting automatically.

With two-photon fluorescence microscopy, one can record in real time the calcium dynamics of neurons that have been genetically labeled with a calcium indicator. With a grid of laser beams, you could do that with an array of flies and collect multiple streams of data, each coming from the brain of an individual animal.



A brainy idea. Mark Schnitzer wants to develop high-throughput methods for optical imaging in fruit flies (shown here in an early prototype).

Q: Given that the flies have to be fixed in place, won't that limit the range of possible experiments?
M.S.: Flies can exhibit motor behavior while fixed in place by walking on a stationary ball that rotates under their feet. That paradigm has been used for decades and was a point of inspiration for us. They can also respond to both odors and visual stimuli.

Q: Is the goal here just to collect data more quickly?
M.S.: Speed is certainly important. But I think if it really is possible to look at 100 flies in parallel, it will open up questions that can't be addressed today because the experiments are simply too prohibitive. One class of experiment would be to examine many flies of the same genetic strain and try to understand any differences in brain function, to look for elements of individuality among animals with the same genome. A complementary type of experiment would be to look at many flies that each have a somewhat different genetic makeup and try to understand how these flies behave and process information differently.

Q: Do you envision this as something an individual lab would have, or would it be a shared resource?
M.S.: It depends on a number of things, including how successful the technology is and how much it costs. If it turns out to be a large, pricey device, or if it's used in combination with other methods, that might justify a centralized location. For example, other groups are working on techniques for mapping all of the connections in neural circuits and on ways to automate tissue processing and histology. Some of these tools might get packaged together. One might first examine a large number of flies when they're alive and then subsequently look at them as histological specimens.

Q: Going forward, how do you think such methods might change the way neuroscience is done?
M.S.: High-throughput experimentation allows you to be much more systematic. I think we'll see a trend towards trying out all, or at least a large number, of the logical possibilities, as opposed to testing one hypothesis at a time. And I think as large data sets develop, the field will necessarily become more collaborative. It will require specialist skills in data mining and statistical and computational tools. We're already seeing a lot of that.

Q: What motivates you to build microscopes?
M.S.: The challenge of being able to watch the underlying cellular components that give rise to behavior, the challenge of seeing macroscopic phenomenon come to life out of microscopic components.

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