Gero Miesenböck: instructing the nervous system

Gero Miesenböck uses light and genetically encoded sensors and actuators to observe and control neural activity. Having caused headless flies to fly at will, he is set to understand how the nervous system encodes behavior.

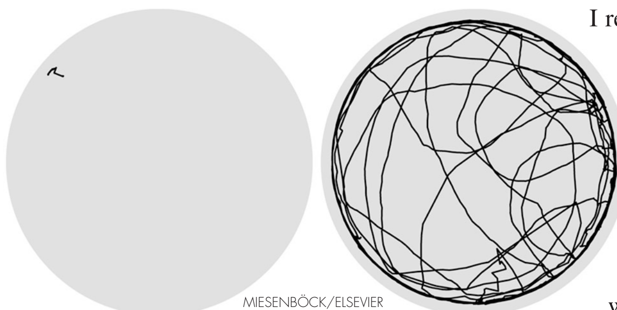
New techniques often drive advances in cell biology. Gero Miesenböck has developed powerful tools that open up whole new regions of neurobiology.

First came tools to measure neuronal activity. The synaptolucins (1), developed with Jim Rothman (Memorial Sloan-Kettering Cancer Center, New York, NY), were based on a luciferase fusion protein targeted to synaptic vesicles. Neuronal activity led to exocytosis, thus exposing the synaptolucin to an extracellular pool of its substrate luciferin. Later came a pH-sensitive GFP (pHluorin) that lit up when exocytosis propelled it from the acidic inside of the secretory vesicle to the neutral extracellular environment (2).

"Rather than passively observing cellular or neuronal activity, we actively controlled it."

Miesenböck started his own lab in 1999 and is currently at Yale University (New Haven, CT). His chARGe system turned light into neural activity: it co-opted a fly visual transduction pathway to detect light and convert it into a depolarizing signal in neurons (3). In a simpler phototrigger system, light removed the chemical protection from ligands, allowing them to bind and activate receptors that could be expressed in any neuron subset of interest (4). He used this latter system to get the headless flies flying. In contrast to direct electrical stimulation of neurons using electrodes, the phototrigger can control neuron subtypes that are dispersed amongst other cells, all the while leaving animals free to roam and behave.

Miesenböck has recorded the first images of information flow between specific classes of neurons in an intact brain (5), and he recently discovered a new kind of circuit within the olfactory system (6). This circuit spreads excitation laterally, perhaps helping to boost otherwise sub-threshold signals so they can be detected (6). We spoke to Miesenböck as he was preparing to move to the University of Oxford, UK, where he will be helping to build up neuroscience in the Department of Physiology.



A light-activated circuit gets a sluggish fly (left) moving (right).

BEGINNINGS

What first drew you to science?

I wanted to become a writer for a very long time. My father was a classicist, and I was tempted to follow him into the humanities. But he influenced me very strongly out of his own frustration with the limited potential for discovery—he said science is so much more exciting. I started reading more and more popular science and original scientific research when I was in high school and I got gripped by it. But I got gripped by it more from an abstract, formal point of view than by tinkering around with a chemistry set in a basement.

And the Rothman lab?

I read the papers and I was just blown away by how beautiful they were. Rothman trained as a theoretical physicist as an undergraduate. In many ways, the papers are more typical of a physicist's approach than of a biologist's in that simplification, abstraction, and synthesis are the most important part whereas many biologists tend to get lost in bewildering experimental detail. I think if Jim Rothman had worked on a different topic I might still have joined him. For me, it was almost a matter of style over substance.

What was the importance of the synaptolucin paper?

It was essentially a classic Rothman-style transport assay but applied to the neuronal synapse and using light as the readout rather than a chemical reaction product. The principle was inspired by earlier work—you separate an enzyme and substrate in space and then measure how transport brings them together.

Gero Miesenböck

To my knowledge this was the first paper where the idea of using genetically encoded probes to observe the function of neural circuits was proposed rather forcefully. The pHluorins became the dominant implementation of the technology because of issues of technical utility, but I think the conceptual foundation actually lies in the earlier synaptolucin study.

And the chARGe system?

I'm very, very proud of that paper because, as with the synaptolucins, it formulated a new experimental strategy—again this combination of genetics and optics but used for a different purpose. Rather than passively observing cellular or neuronal activity, we actively controlled it. That was, I think, another important conceptual step.

TECHNOLOGY

Have you always been attracted to technological solutions and inventing new methods?

It was not a deliberate choice. I wanted to do certain types of experiments, and I couldn't fill that experimental need unless I went out and tried to develop

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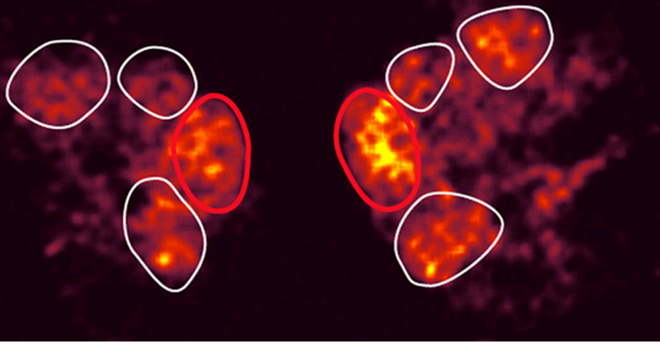

MIESENBÖCK/ELSEVIER

A glomerulus lacking direct connections (red outline) is still active, betraying the existence of a lateral circuit.

Text and Interview by William A. Wells
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something new. For example, there was a clear sense that one needed a new way to look at networks of neurons.

Also, there is a beauty to these developmental efforts that is quite rewarding in its own right. It's really a pleasure to see something through from the conceptual stage, to trying to get it to work and then actually using it. Seeing the first images of a fruit fly smelling an odor as revealed by synaptopHluorin and looking back over the entire arc that began with the engineering of the GFP mutant, I have to say this was a very satisfying moment.

This biological engineering that my lab does—it's almost a little bit like poetry. You have to stay within a tight framework imposed by the biological reality, and there is a tension between innovation and what you actually can do.

What determines a technological winner vs. loser?
Ultimately, what tends to prevail is simplicity. Although there is iterative improvement, it's always the earliest implementations that are conceptually the most important. It's more difficult to come up with a really new idea of how to do things, even if you don't get the ultimate implementation in the first try.

You chose to work on flies because they were cheap, with diverse behaviors and good genetics. Were there any challenges to setting up a fly lab?
I had never in my life worked with fruit flies; I think I had never even seen one in a lab. So I became faculty and student at the same time and had to apprentice myself to some fly people. I still feel like a little bit of a parvenu among real Drosophilists, but we know enough now to get by.

REMOTE CONTROL

What was your first project in your lab?
The initial aim was to study a neural circuit with the synaptopHluorin system. But then very quickly, in the summer of 1999—it was one of those moments where I even remember the time and the date and the room I was in—I had the idea of using light not only to observe but also to control. That then quickly became the second focus of the lab.

Where did the remote control idea come from?
I had the advantage of being a newcomer to neurobiology. I was not too weighed down by received wisdom, maybe not too weighed down by neuroscience knowledge in general. But I had worked in a leading cell biology lab. I had seen that to establish causality and dissect a complex mechanism it's essential to be able to control it. In neuroscience, I felt there was still way too much observation and not enough intervention. So I thought wouldn't it be wonderful if one could use these two ingredients that I had relied on with the synaptopHluorins, namely genetics and optics, and combine them again but for this opposite way of communicating with the experimental system.

Initially, we were completely alone. Now, of course, many people have begun to work with this and similar systems.

With remote control you can say that neuron X does behavior Y. What other more mechanistic questions can you address?
There is a whole range of approaches that becomes possible with the ability to control specific groups of neurons. This allows a connection to brain tissue that is noninvasive and physiological. You can get wiring diagrams of neuronal circuits. You can apply spatiotemporal patterns of input activity and measure what kinds of inputs a target cell or a group of target cells is looking for. This would be not just a mapping of anatomic connectivity but rather a way of deducing the input/output characteristics of a circuit. A still higher level of complexity would be to see what exact features of activity patterns are relevant for perception, action, cognition, memory, and so forth.

Your tools could be used to study many things. How do you choose a problem to investigate?
We initially were attracted to particular circuits for reasons of genetic accessibility. Getting the sensor and the actuator in the right place is not trivial. In the fly olfactory system I knew I could find promoters active in specific, functionally meaningful populations of neurons.

What is your current major objective?
I want to understand multicellular information processing at a depth that currently exists only for single-cell phenomena. Essentially, we want to derive a degree of mechanistic understanding that is common for cell biologists but at a level of organization that includes multiple cell types and many more players.

"This biological engineering—it's almost a little bit like poetry."

Do you see yourself staying in this subject area for quite a while?
Yes. This is where I feel most comfortable—at the interface between cellular and systems problems.

Why the move to Oxford?
I am excited to take on a leadership role—developing neuroscience at Oxford—that extends beyond the confines of my lab. Leaving the increasingly translational focus of US medical schools behind will also be a relief. I think that, before you can translate, you have to have something to say. JCB

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