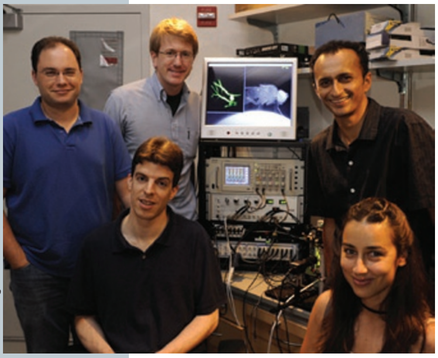
THE AUTHOR FILE

Vivek Jayaraman

Fly brains light the way for neurobehavioral circuits.

Sometimes an aerospace engineer feels compelled to watch fruit flies walk on tiny foam balls. Actually, Vivek Jayaraman is not the only one watching. In his laboratory at Janelia Farms, researchers have manipulated both flies and balls so that the flies' neural activity and behavior can be recorded as the flies respond to visual cues.



Reed George

Vivek Jayaraman (right) with some of his coauthors.

Vivek's initial training in aerospace and computer simulation led him to wonder why artificial intelligence could not more closely model processes in living brains, a question that eventually led him to Gilles Laurent's lab at California Institute of Technology, where he could learn how living brains work.

His first studies probed the neural circuits that let locusts respond to smells, but when the lab worked out ways to collect recordings from *Drosophila* brains, Vivek turned quickly to the fly, for which genetic and other technologies allow a greater variety of experiments. The ability to study brain circuits by manipulating specific neurons appealed to him as an engineer, he says. "I like to be able to tinker with the system, model how a circuit operates and then break it in a very precise way to test the model."

Eventually, Vivek worked out a system to do electrophysiology and imaging simultaneously in live, intact flies. The system could be used to study how flies process sensory input but not how flies acted on this information, says Vivek. "The part that was missing was behavior."

To study this question, Vivek enlisted the help of colleagues at Janelia Farms, which prides itself for recruiting dedicated, inspired tinkerers. The project, admits Vivek, "was to do something that seemed a little bit crazy." He needed a system that would allow a fly to walk even as its exposed brain was held sufficiently stable for precise recording.

This meant creating a fly rig that could constrain the head in a constant position but leave its legs free. Every procedure and component needed to be optimized, recalls Vivek. The first challenge had nothing to do with the fly but in figuring out how to track motion on such a tiny scale. The solution came from Janelia engineer Gus Lott, who literally deconstructed an optical computer mouse, combining the chip inside with the right configuration of lenses and mirrors.

Vivek and his postdocs also spent considerable time watching flies crawl on balls, trying to figure out what led to the most natural gait. (Six millimeters in diameter was a good size.) Johannes Seelig tested several balls searching for one with the right combination of weight distribution and texture such that a fly could walk naturally while sensors picked up the ball's motion. The team ultimately had to build the balls themselves.

The flies used in the experiments were genetically engineered to express proteins that fluoresce in response to calcium. This shows precisely where neurons are activated. Detecting the fluorescence, however, requires not only removing the top of a fly's head but making sure the brain stays very still. To do this, Seelig and postdoc Eugenia Chiappe had to painstakingly dissect away muscles around the head while making sure not to affect flies' behavior. "You have to remove the right muscles but not too much," says Vivek, "It's a combination of hands and judgment and just trying a lot of times."

Seelig was typically understated when initial experiments indicated that mounted flies' responses and recordings were reliable, recalls Vivek. "His idea of a 'eureka' moment is he's verified something seventeen times, and then he says maybe you want to come see something."

Despite the difficulty, Vivek trusts that researchers in other labs will be able to use his published descriptions of fly rigs to either build the equipment themselves or outsource its construction. Scientists in his lab have already moved on to the next set of experiments. Right now, the equipment records a fly's neural responses and behavior when presented with simple visual stimuli, such as a pattern of stripes. Although flies are known to orient themselves in particular ways to particular patterns, Vivek envisions that manipulations could be much more complex. For example, the activity of groups of neurons could be stimulated as well as recorded, or flies could be trained to make choices between different sights and smells.

Ultimately, Vivek hopes to perform experiments in which a fly's neural activity and behavior will not only be recorded but used to direct the stimuli it is presented with. This virtual reality world for the fly is a dream for Vivek, with countless opportunities for very precise tinkering in neural circuits.

Monya Baker

Seelig, J.D. *et al.* Two-photon calcium imaging from head-fixed *Drosophila* during optomotor walking behavior. *Nat. Methods* **7**, 535–540 (2010).