First, catch a worm

New microfluidic devices sort and screen small animals.

High-throughput genetic and drug screens of *C. elegans* and other small animals are now possible at cellular resolution, thanks to a new set of microfluidic devices developed by Mehmet Yanik and colleagues at the Massachusetts Institute of Technology (Proc. Natl. Acad. Sci. U.S.A. 2007, 104, 13,891–13,895).

“Shuffling worms around, holding them still without killing them, and delivering localized stimuli to them have always been a major headache,” says Shawn Lockery at the University of Oregon. “So it’s not at all surprising that microfluidic strategies are gathering momentum in the field. [This paper] ramps up the excitement with the first practical high-throughput worm handler.”

“It is one of those works that helps bring the long-promised change to the biological laboratory through the use of microfluidics,” agrees Alex Groisman of the University of California San Diego.

The devices—a sorter chip, a screening chip, and an interface chip—can be combined in multiple configurations and have three main advantages, according to Yanik. First, they perform much faster than previous techniques for sorting and screening worms. Second, they can immobilize the animals using microaspiration, thus eliminating the need for anesthesia during subcellular imaging and microsurgery. And third, they eliminate human error by using a sophisticated software system that controls each step.

The sorter chip is designed to image animals at subcellular resolution and select them according to phenotype. The worms flow at high speed through microchannels on the chip, where one animal can be selectively captured by microaspiration while the others are flushed out of the chamber. The isolated one is released but then is recapTURED by an array of aspiration channels that hold its body perfectly straight for high-resolution, subcellular imaging. Current sorters, which were designed to sort cells using large setups, are unable to immobilize animals and thus can take only low-resolution snapshots of the quickly moving worms.

When *C. elegans* is immobilized in the sorter chip, simultaneous white-light and fluorescence images reveal the animal’s body and its neurons and axons, which express green fluorescent protein. (Adapted with permission. Copyright 2007 National Academy of Sciences, U.S.A.)

Once the sorter chip has isolated a batch of phenotypically homogeneous animals, the worms can be sent to the screening chip, which contains hundreds of microchambers, each designed to incubate and monitor a single animal. The screening chip has many potential uses. For example, researchers could perform large-scale reverse-genetics or drug-library assays by exposing the animals in various chambers to an array of RNAi strands or drug candidates and then imaging them to reveal the resulting phenotypes.

The device also could be used in conjunction with laser nanosurgery. In these experiments, the researchers sever single nerves with a femtosecond laser and then monitor nerve regeneration. “By looking at whether regrowth is faster or slower, whether the axon makes a left or right turn to find its target, and whether it makes a synaptic junction, we can tell what role a gene might be playing in neuroregeneration,” Yanik says. The researchers previously have studied neuronal regeneration in *C. elegans* (Nature 2004, 432, 822), but the screening chip allows better immobilization of the animals during the precise procedure and permits higher resolution images to be obtained after surgery.

Time-lapse imaging in physiologically active animals also is possible with this new technology. Currently, fluorescence microplate readers are used to obtain time-lapse images as an animal swims in a well, but because the animal moves around, only average fluorescence is recorded.

The third component of the new system, the interface chip, solves the problem of delivering thousands of compounds to the screening chip’s microchambers. Its array of suction tips can be lowered into microwell plates. After each tip sucks up a minute amount of one compound, the samples are sent sequentially to the chip’s outlet, which can be interfaced with the screening chip. Thus, hundreds of compounds can be tested simultaneously on a small screening chip. “By delivering a different compound to each chamber and performing nanosurgery on animals in individual chambers of the screening chip, we can monitor, for example, how different compounds affect neural regeneration,” Yanik says.

“This is certainly very interesting work and a creative integration of some known microfluidic elements as well as some new microchannel arrays that specifically fit the morphology and physiology of *C. elegans,*” Groisman says. “Most important, of course, is that the microfluidic technology is successfully applied to perform a few basic operations on one of the most popular model multicellular organisms.”

—Linda Sage