

# GPS for the Nematode

*Janelia scientists have made it easier to navigate C. elegans territory.*

YOU'D THINK THE GENETICS OF A CREATURE AS SMALL AS THE EYELASH-sized roundworm *Caenorhabditis elegans* would be simple. But scientists are finding surprising complexity: they now know that more than one genetic pathway can drive the worm's cells to a single developmental fate. The large-scale studies needed to yield this kind of result are possible for two reasons: in *C. elegans*, the name and fate of

each cell on the pathway from egg to adult are well known, and now there's a powerful tool for analyzing this treasure trove of data.

Large collections of drawings and microscope images have been compiled into print and online worm atlases that offer researchers abundant anatomical information. But navigating their pages and relating them to the cells in an image of an actual, individual lab worm can take days for a skilled worm researcher and, in some cases, yield ambiguous results.

Thanks to Janelia Farm scientists Eugene Myers, Hanchuan Peng, and Fuhui Long, the tedious task can now be turned over to a computer. Using a new "digital atlas," researchers can prepare a worm for microscopy, snap a digital image, and in a few hours retrieve a navigational map of its cells—kind of a WPS, or worm positioning system.

The idea for the digital atlas grew from a conversation between Myers and Stanford University developmental biologist Stuart Kim. Kim's lab group studies changes in

gene expression as animals develop and age. They wanted to measure gene activity cell by cell to learn how each cell's genes control its fate.

They needed an efficient way to identify a worm's cells and then match up gene expression profiles to each cell's developmental path. More specifically, they needed a computer program that could discern individual cells in a digital image and then correlate them to the identities documented in the worm atlas.

Image interpretation doesn't come as easily to a computer as it does to a human, Myers says. Variations in an object's shape, inconsistencies in the staining of a sample, and blurry edges contribute to a computer's

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## BREAK IT DOWN

**TO CAPTURE DATA FOR THE DIGITAL WORM ATLAS**, the computer first has to mathematically straighten out kinks and contortions from the worm's body so that it is shaped like every other worm, says Hanchuan Peng. Then it must sort out where one cell ends and another begins. ¶ Before imaging, researchers stain the worm's DNA blue, so the computer can recognize each cluster of blue as an individual cell nucleus. The digital image is then stretched and rotated so that its size and orientation match that of the computer's "reference" worm. ¶ Finally, the computer must identify and name each cell. A genetically encoded fluorescent label in the muscle cells that line the

worm's body visibly outlines the worm and provides the first clues; the computer calculates the identity of the remaining cells based on their size, proximity to their neighbors, and position relative to the fluorescently labeled body-wall cells. ¶ The end result is a three-dimensional digital atlas—described in the September 2009 issue of *Nature Methods*. The atlas is freely available online, and it can identify 357 cells in the larval L1 worm with about 86 percent accuracy. The remaining cells are so tightly packed in the worm that even the human eye can't sort them out. "We've reached a performance level that's usable for a high-throughput study," says Eugene Myers. —J.M.



confusion when it tries to understand what it is “seeing.” Humans draw on prior knowledge for clues as to what an image is likely to represent, he says—“but how do you teach a computer to do that?”

Myers’ team started by teaching the computer to recognize the 558 cells in the worm’s L1 stage of development—the 1/4-millimeter-long larval form that emerges from the egg. To make the visual processing logical and accessible for the computer, they divided it into a series of steps (see sidebar, “Break It Down”).

In the first high-throughput study using the digital atlas, reported in *Cell* on October 31, 2009, the *Janelia Farm* scientists

collaborated with Kim’s team to correlate the expression of 93 genes to cell fate. They created worms in which the activity of a specific gene was linked to fluorescence and then used a computer to measure the fluorescence cell by cell. This automated cell identification rapidly generated a data table giving the gene’s activity in each individual cell. The researchers found that expression patterns varied, even among cells with identical developmental fates.

For the *Janelia* team, the new worm atlas is a triumph for the field of computer vision. Peng hopes to see the atlas used as a tool for functional studies, as well—for example, to guide a laser as it destroys or activates

specific cells in studies comparing a cell’s role under many different conditions or genetic backgrounds.

The researchers plan to expand the digital atlas to represent the later stages in the worm’s life cycle. While no other animal’s cellular anatomy is as well defined throughout its life as that of *C. elegans*, Myers notes that most organisms pass through carefully laid out body plans during development. He expects to eventually see digital atlases of embryonic forms of well-studied organisms, such as the fruit fly. “These are very hard problems and it’s still early days,” he says, “but this is a milestone.” ■

—JENNIFER MICHALOWSKI