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SCIENCE

Expansion Microscopy Stretches Limits of Conventional Microscopes

By JOHN MARKOFF JAN. 19, 2015

A new laboratory technique enables researchers to see minuscule biological features, such as individual neurons and synapses, at a nearly molecular scale through conventional optical microscopes.

In a paper published last week in the journal Science, researchers at M.I.T. said they were able to increase the physical size of cultured cells and tissue by as much as five times while still preserving their structure. The scientists call the new technique expansion microscopy.

The idea of making objects larger to make them more visible is a radical solution to a vexing challenge. By extending the resolving power of conventional microscopes, scientists are able to glimpse such biological mysteries as the protein structures that form ion channels and the outline of the membrane that holds the genome within a cell.

The researchers have examined minute neural circuits, gaining new insights into local connections in the brain and a better understanding of larger networks.

The maximum resolving power of conventional optical microscopes is about 200 nanometers, about half the wavelength of visible light. (By contrast, a human hair is about 500 times wider.) In recent decades, scientists have struggled to push past these limits.

Last year, three scientists received a Nobel Prize for a technique in which fluorescent molecules are used to extend the resolving power of optical microscopes. But the technique requires specialized equipment and is costly.

With expansion microscopy, Edward S. Boyden, a co-director of the M.I.T.

Center for Neurobiological Engineering, and his colleagues were able to observe objects originally measuring just 70 nanometers in cultured cells and brain tissue through an optical microscope.

They were also able to produce super-resolution animations in which the viewer “flies” through a detailed three-dimensional image of a mouse hippocampus.

“We hope we have a technology that will allow you to scan the nervous system of entire animals,” Dr. Boyden said.

The idea began as a joke during a brainstorming session several years ago, according to Dr. Boyden. But he and the graduate students Fei Chen and Paul W. Tillberg realized it might be feasible after exploring the work of the M.I.T. physicist Toyoichi Tanaka, who in the 1970s discovered a class of “intelligent” gels that respond to stimuli such as water.

One of those materials is a polymer widely used today in diapers, which absorbs 200 to 300 times its mass in water. The researchers realized it was perfect for forcing biological tissue to swell.

Eventually, the researchers perfected an unusual procedure. First, they apply fluorescent dye to the tissue sample. The molecules attach to particular structures, such as nerves and synapses, that the scientists will want to see.

Then they infuse the tissue with the chemical building blocks of the polymer, making sure they evenly permeate the sample. The blocks come together to form the polymer inside the tissue, which is then chemically “chopped up” so it can be enlarged.

Then, just add water. The tissue expands in all directions uniformly and becomes transparent, and suddenly the tiny structures limned in fluorescence burst into view. Relative to one another, their positions do not change.

Expansion microscopy may permit scientists to create three-dimensional models of large areas in the brains of animals, making it possible to map biological processes from one region to the next. And the technique may reveal the structures of individual proteins, structural detail inside cells and other biological features in near-molecular detail.

One of the research groups that have begun using the new technique is the OpenWorm project, an effort to create a complete digital simulation of the C. elegans nematode.

“We are hopeful it will allow better resolution of structural aspects of C. elegans like ion-channel type and density on a cell-by-cell basis," said Stephen Larson, a neuroscientist who is a co-founder of the OpenWorm project, in an email message.

The new approach also could bring super-resolution microscopy into wide use, because it requires less expensive equipment and is based on simpler laboratory procedures.

The technique has been perfected to enlarge tissue samples by about four and a half to five times, but that is not an ultimate limit, Dr. Boyden said. By tuning the chemicals and the procedure, he believes it might be possible to expand tissues by 10 times or even more.

Although the imaging technique will not directly capture dynamic processes in the brain, it should be possible to gain insight into brain function by taking samples before and after events, he said.

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