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Watch: 'Taste of the future': New microscopy technique captures stunning images of a fly's brain

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By combining expansion microscopy and lattice light-sheet microscopy, scientists can identify subsets of neurons in the fly brain and color code them by region. *Gao et al./ Science 2019*

A few years ago, neuroscientist Ed Boyden[4] and his colleagues at the Massachusetts Institute of Technology were brainstorming how to get a better look at the intricacies of brain cells and came up with a novel idea: just blow samples up like a balloon. Making a specimen bigger, they reasoned, would make everything easier to see.

Around the same time, Nobel Prize-winning scientist Eric Betzig and his colleagues at Howard Hughes Medical Institute's Janelia Research Campus in Virginia announced their own powerful new microscopy tool[5], which harnesses a sheet of light to illuminate tissue without doing as much damage as many microscopes do to samples. Now, those two teams of researchers have married their techniques to capture the nooks and crannies of a fruit fly[6] brain and the mouse cortex in stunning detail. Their research, which was published Thursday in Science, could allow scientists to create more precise maps of the brain and find clues to the causes of brain diseases, Boyden said.

The technique that Boyden and his colleagues pioneered, called expansion microscopy, starts with a preserved specimen, such as a thin slice of tissue.

It's infused with a swellable, absorbent polymer that's akin to the technology used in baby diapers. When the specimen gets doused with water, it swells. In this case, the scientists expanded fly brain tissue fourfold.

The process turns the sample nearly transparent — which, as it turns out, makes it particularly well-suited for Betzig's lattice light-sheet microscope, which shines light from one side and takes a picture from the other side.

"It allows you to image with nanoscale precision, blazingly fast," said Boyden, who is also a Howard Hughes Medical Institute investigator.

Researchers from Boyden's lab approached Betzig about the idea of sticking their super-sized samples of fruit fly brains under the microscope. Betzig said they could give it a go — but he wasn't convinced it would work.

"Having been in the super-resolution business for 30 years now, I'm pretty cynical," he said.

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Because the samples were so large, the microscope could capture only small sections at a time. The scientists would image a tiny section, shift the sample, image another tiny section, and so on. And the samples were finicky: They swelled and shrank and didn't stay completely constant. By the time one row of images was completed, the whole thing might have shifted. All told, the imaging process took just over 62 hours — lightning speed compared to the time it would take other microscopes.

“They were able to use the fancy samples to improve the resolution, use the fancy microscope to acquire data quickly, and use the [computational] pipeline to stitch all the data together correctly,”said Joshua Vaughan, a fluorescence microscopy expert at the University of Washington who wasn’t involved in the research.

That last step was a particularly painstaking process. The researchers had to stitch together some 50,000 “cubes” of data — each representing a 3D bit of the brain — and then make sense of it. They developed a computing system to piece together a complete picture that accounted for all those minuscule movements during the imaging process. That made it possible to count the synapses across the entire fly brain — roughly 40 million— and detail how the density of those synapses varies in different areas. They traced proteins, tiny cellular protrusions known as dendritic spines, and dopaminergic neurons. The scientists also carried out similar studies to zoom in on the complexities of the mouse cortex.

“This is a taste of the future,” Vaughan said. “We’re getting these huge rich data sets and we’re starting to get better tools to squeeze information from them,” he added.

The scientists behind the new study still want to sharpen those tools. In the new paper, they used fluorescent proteins and antibodies to light up the specimen so synapses and other details could be seen under the microscope. But there are certain parts of the brain that can’t be tagged well with those technologies, such as lipids. There are also certain tissues that don’t take well to expansion, like connective tissue that’s rich in collagen.

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Betzig added that it could be tricky to expand tissue big enough — and get it to stay fluorescent enough under the microscope — to be able to trace some of the brain's most minute details.

But Boyden is hopeful that it will one day be possible to make maps of the brain that allow scientists to pinpoint the molecular changes that might drive diseases such as Parkinson's and Alzheimer's.

"If we can figure out exactly where diseases begin," Boyden said, "that could be pretty powerful."

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