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A Wiring Diagram of the Brain

The emerging field of connectomics could help researchers decode the brain's approach to information processing.

By Emily Singer

New technologies that allow scientists to trace the fine wiring of the brain more accurately than ever before could soon generate a complete wiring diagram--including every tiny fiber and miniscule connection--of a piece of brain. Dubbed connectomics, these maps could uncover how neural networks perform their precise functions in the brain, and they could shed light on disorders thought to originate from faulty wiring, such as autism and schizophrenia.

"The brain is essentially a computer that wires itself up during development and can rewire itself," says Sebastian Seung (http://hebb.mit.edu/people/seung/) , a computational neuroscientist at MIT. "If we have a wiring diagram of the brain, that could help us understand how it works." For example, scientists previously identified the part of the songbird's brain that is important in the birds' ability to generate songs. Seung would ultimately like to develop a wiring diagram of this structure in order to elucidate the features underlying its unique capability.

Only one organism's wiring diagram currently exists: that of the microscopic worm *C. elegans*. Despite containing a mere 302 neurons, the *C. elegans* mapping effort took more than a decade to complete, in the 1970s. It has been an invaluable research resource and earned its creators a Nobel Prize.

With an estimated 100 billion neurons and 100 trillion synapses in the human brain, creating an all-encompassing map of even a small chunk is a daunting task. Using standard methods, it would take roughly three billion person years to generate the wiring diagram of a single cortical column, a narrow functional unit of neurons in the cortex, estimates Winfried Denk (http://mpg.de/cgi-bin/mpg.de/person.cgi?persId=166764&lang=en&inst=medizinische_forschung) , a neuroscientist at the Max Planck Institute for Medical Research in Heidelberg, Germany.

Denk, Seung, and their collaborators are now developing sensitive new imaging techniques and machine-learning algorithms to automate the construction process. They have already generated a partial wiring diagram of part of the rabbit retina. But they'll need to make their technique a million times faster to finally bring larger maps--like that of a cortical column--into the realm of reality.

Previous efforts to map the wiring of the brain have focused on larger anatomical features, such as the thick wiring tracts that connect different parts of the brain, or on the paths of single neurons, stained a particular color to distinguish them from their tangled multitude of neighbors. But to truly understand how a network of neurons can perform a particular function, scientists need a new kind of map. "A lot of properties of brain function are at the level of the circuit--information is being integrated, processed, extracted," says Elly Nedivi (http://web.mit.edu/bcs/people/nedivi.shtml) , a neuroscientist at MIT who is not involved with the research. "To understand what that means, you need to be able to see who connects to who."

Denk and his colleagues developed a new technique to make more fine-scaled wiring maps using electron microscopy. Starting with a small block of brain tissue, the researchers bounce electrons off the top of the block to generate a cross-sectional picture of the nerve fibers in that slice. They then take a very thin--30-nanometer--slice off the top of the block and repeat the process. Scientists go through the images slice by slice to trace the path of each nerve fiber. "Repeat this [process] thousands of times, and you can make your way through maybe the whole fly brain," says Denk.

Seung and Denk aim to dramatically speed up the tracing process, which takes a single graduate student weeks to complete, with automated machine-learning algorithms. The researchers use data from a manually generated wiring diagram to train an artificial neural network to emulate the human tracing process. They can then use the resulting algorithm to analyze new chunks of brain tissue. To date, they've been able to speed the process about one hundred- to one thousand-fold.

The researchers presented their initial findings to an awed crowd at the Society for Neurosciences (http://www.sfn.org/) meeting in San Diego earlier this month. They showed the three-dimensional reconstruction of part of the rabbit retina called the inner plexiform layer, which is a piece of neural tissue at the back of the eye that senses light and sends visual information to the brain. (See a movie of the reconstruction here (http://www.technologyreview.com/player/07/11/19Singer/1.aspx) .) "But we need to improve 10^6-fold or more," says Denk, who estimates that this would shrink the three billion person years it would take to trace a cortical column down to about two years. "I'm confident in the end that we will be able to do it," he says. "But I don't know how long it will take us--if we're lucky, maybe a year or so."

Earlier this month, scientists at Harvard described a new method of tracing neurons in the living brain by labeling them with up to a hundred different colors. (See "The Technicolor Brain (http://www.technologyreview.com/Biotech/19652/) .") "We're starting to think about wiring diagrams as being fundamental," says Jeff Lichtman, (http://www.mcb.harvard.edu/Faculty/Lichtman.html) one of the researchers who developed the technique.

Researchers say that the two approaches will likely be complementary, allowing scientists to look at neural circuits of different dimensions. Eventually, Seung aims to generate maps of the complete fly connectome, as well as partial wiring diagrams of interesting locations in larger brains, such as the hippocampus, olfactory bulb, and retina.

Just exactly how much light these maps will shed on the brain is still somewhat controversial. "Just knowing the [wiring] data won't take us far if we don't put it in the framework of processing and transferring data in the brain," says David van Essen (http://neuroscience.wustl.edu/research/faculty.php?id=11) , a neuroscientist at Washington University, in St. Louis, and president of the Society for Neurosciences. Seung and others eventually hope to generate maps that incorporate the biochemical and physiological properties of various cells into the wiring diagrams.
