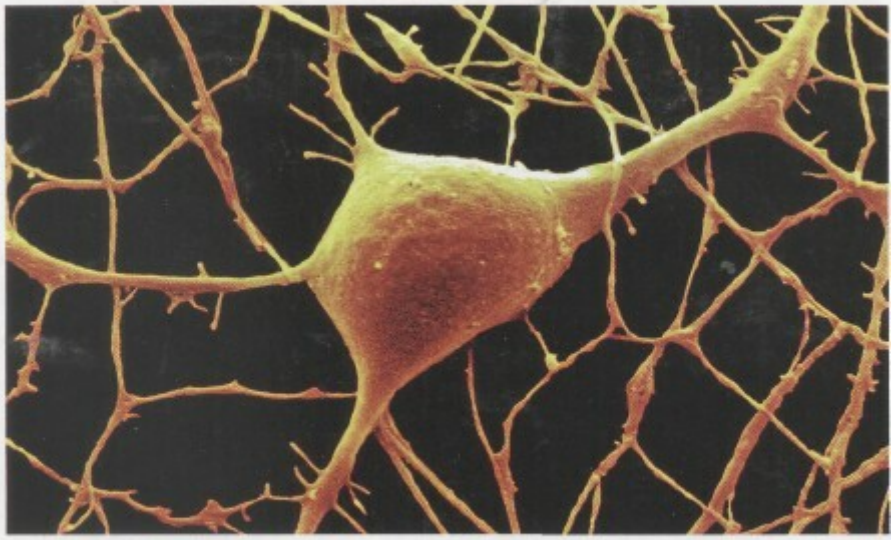

Neurology

Wired

Connectomics aims to map the atlas of the brain

WHEN last year's Nobel prize for chemistry was awarded to the discoverers of green fluorescent protein, the pages of newspapers (this one included) lit up with photographs of "brainbows". Jeff Lichtman, the neurobiologist who created those pictures, had used the discovery to invent a way to tag nerve cells with genes whose products fluoresce green, red and blue. By mixing these three hues in different proportions he was able to "paint" the cells in question in more than a hundred different colours.

Besides looking pretty, the resulting pictures allow the numerous protrusions of individual nerve cells that connect those cells together to be followed through the labyrinth that constitutes the average brain. Dr Lichtman hopes to use his brainbow mice to answer questions about neurological development, such as why the nerve cells of babies have far more connections than do those of adults. That could shed light on what happens when the wiring gets connected wrongly and, as it were, blows a neurological fuse. Such faulty wiring—connectopathies, in the jargon-may be the underlying explanation of such disorders as autism and schizophrenia.

Dr Lichtman's work is the most famous example of the emerging science of connectomics. But it is not the only one. For, just as every organism has a genome (the complete set of its genes, as encoded in its DNA), every organism with a nervous system has a connectome (the complete set of its nerve cells and the connections between them). In practice, of course, a connectome will change over the course of time as new connections form and old ones die. But that does not stop people like Dr Lichtman dreaming of a Human Connectome Project inspired by the success of the Human Genome Project.

Weaving the fabric of reality

Connectomics actually started before the word existed. In 1972 Sydney Brenner, a biologist then at Cambridge University, decided to work out the connections of every cell in the nervous system of a small nematode worm called C. elegans. He picked this animal because its body has a mere 959 cells, of which 302 are nerve cells. It is also a hermaphrodite, fertilising itself to produce clones. That means individual worms are more or less identical.

Dr Brenner and his team embedded their worms in blocks of plastic, sliced the blocks thinly and then stained each slice so its features would show up in an electron microscope. The resulting pictures let the path taken by each nerve cell to be traced through the worm's body. They also revealed the connections between cells. Over the course of 14 painstaking years the team managed to map the complete nervous system of C. elegans, work for which Dr Brenner, too, won a Nobel prize.

The scale of that work, though, hardly compares with today's quests to map the brains of mice and fruit flies. The cerebral cortex-the part of a mammal's brain that thinks-is composed of 2mm-long units called cortical columns. Winfried Denk of the Max Planck Institute for Medical Research in Heidelberg, Germany, estimates that it would take a graduate student (the workhorse of all academic laboratories) about 130,000 years to reconstruct the circuitry of such a column. But efforts to automate the process are gaining ground.

Dr Brenner's method used what is known as a transmission electron microscope. In this the electrons that form the image pass through the sample, so the individual slices have to be prepared and examined. Dr Denk is speeding matters up by using a scanning electron microscope instead. This takes pictures of the surface of an object. Dr Denk (or, rather, his graduate students) are thus able to load the machine with a chunk of plasticised brain and a slicer. Once the microscope has taken a picture of the exposed surface of the chunk, the slicer peels away a layer 25 billionths of a metre thick, revealing a new surface for the next shot. The slice itself can be discarded, so the process is much faster than using a transmission microscope.

Researchers have also devised sneaky ways to tag parts of the brain that are of special interest, so that they can be followed more easily from slice to slice. Dr Denk, for example, tracks the myriad branches of a single nerve cell using an enzyme from horseradish. This gets stuck on the cell's surface and then reacts with a stain that is added to the sample.

It is also possible to trace neural pathways from cell to cell. Ed Callaway at the Salk Institute in La Jolla, California, does so using rabies viruses. Rabies hops between nerve cells as it races to the brain, which is why even an infected bite on the ankle will eventually drive someone mad. That ability to leap the gap between cells means the connections branching from a single cell can be mapped.

Even when the images are in, however, making a map from them is another matter. Dr Brenner's team traced each cell by eye-matching shapes through hundreds of cross-sections. Sebastian Seung, a computational neuroscientist at the Massachusetts Institute of Technology, is working on a program that will automate this process, too. It will allow a computer to learn how to match cells from one slice to another by trial and error, as a human would, but with the infinite patience that humans lack.

The result of all this effort, it is hoped, will be precise circuit-diagrams of brains. The first brains to be mapped will probably have belonged to mice. Besides being cheap and disposable, a mouse brain weighs half a gram and packs a mere 16m neurons. Human brains (14kg and 100 billion neurons) will come later, when all the wrinkles have been ironed out in rodents, and proper methods devised to analyse the results. But come they will. And when they do, the most complicated object in the known universe will begin to give up the secrets of how it really works. •

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