image them so that he can share his work on the stria terminalis brain region with others.

Brendan Brinkman, senior product manager of the Olympus America Scientific Equipment Group, based in Center Valley, Pennsylvania, has worked with Dong and other neuroanatomists who use slide-scanning and point-scanning confocal technology. To hasten data capture in microscopy further, the company is expanding its multi-point mapping software, Brinkman says. In scanning confocal imaging, a raster scan moves across a sample. To focus only on differences in fluorescence, the scanner can jump from one area to another and capture bursts of data. "You can adjust the scanning path to make it as fast as possible," he says. Olympus has also tailored the software to let scientists capture multiple-channel fluorescent signals. "Certainly, neurobiology is the key group for this kind of technology," he says.

And connectome projects are increasing sales of slide scanners, as researchers seek the quick generation of data from large sample sets. TPG Biotech's Duyk agrees that high-throughput approaches to neuroanatomy could be a commercial boon. "It certainly creates opportunities for the life-science tools companies to push the cutting edge of their technology," he says.

For those lacking these tools, services are emerging. Earlier this year, for example, Renovo Neural, a spin-out from the Cleveland Clinic in Ohio, launched an electron microscopy service. Customers deliver samples, which the company sections with an ultramicrotome from Gatan in Pleasanton, California, then images with an automated serial block-face scanning microscope from Zeiss in Jena, Germany, to return hundreds of ultrastructure images.

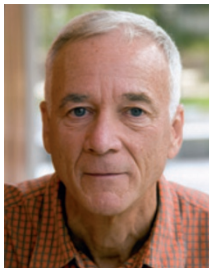
NETWORK SUCCESS

The first complete connectome was obtained for the worm *Caenorhabditis elegans* in 1986. Sydney Brenner and his colleagues at the MRC Laboratory of Molecular Biology in Cambridge, UK, completed their wiring diagram of the hermaphrodite worm nervous system by tracing images of neurons on electron micrographs by hand[7]. The hermaphrodite is one of the animal's two genders; but the male worm has proven to be tougher to pin down, neuronally speaking.

Teams tried to map the male's nervous system as Brenner's group had for the hermaphrodite, but assembling its branching structure by hand was too hard. "The field of connectomics kind of got stuck," Emmons says. Electron microscopist David Hall at the Albert Einstein College of Medicine is the custodian of material from the Brenner lab: notebooks, embedded tissue blocks, thin sections, negatives and the manually annotated *C. elegans* electron micrographs. This year, he, Emmons and colleagues revisited 5,000 of the historic images, analysing them in a new way[8].

They translated their analysis of the micrographs into a map of all the connections and their strengths in the male *C. elegans* posterior nervous system. Of the 170 neurons they studied, 144 were involved in the circuit controlling mating behaviour, allowing the team to make a link between connectivity at the cellular level and behaviour.

Previous researchers had counted synapses but had not included synapse size, Emmons says, which the team now did. Then they applied a mathematical model to use size as a proxy for the functional strength of each neural connection. The result is a map of the neural network's connectivity that includes quantitative cell-biology information. Across the connectome, they found that interaction strengths between neurons varied more than 100-fold.



"With one shot we can cover a whole worm cross-section."
Scott Emmons

Using the existing maps from Brenner's lab made neuron tracing easier. "Somebody has already gone before you and put coloured numbers on them," Emmons says. Elegance (go.nature.com/nvsfnn), the group's software tool, accelerated neuron tracing by translating mouse clicks into map coordinates as the team scrutinized the digitized micrographs.

Emmons thinks that his methods can speed up connectomics efforts in other small organisms. His group will expand its range in several ways; for example, by using their new ATM machine to automatically collect a series of slices for later imaging. Ultimately, says Emmons, using the ATM, "we're hoping for a 20,000 unbroken series, which would cover an entire worm, which has never been done before". Technology like this gives a small lab the tools to tackle large projects such as finishing the male worm's connectome, comparing it to the hermaphrodite or mapping the developing nervous system. The *C. elegans* community is "back in the connectomics business", he says.

Emmons will move on to analyse synaptic connections in the mouse brain, although, for now, his focus is on the worm. The ATM will deliver brain sections aplenty for imaging, but he is confident that his new scanning electron microscope with its bigger field of view is up to the task. "With one shot we can cover a whole worm cross-section," he says.

Applying these techniques to mammalian brains takes more than automation. The human brain has over 80 billion neurons and the mouse brain has around 70 million. And both have more densely woven webs of neurons than in the worm. "So you can't just scale up from a little lab and make a big lab and do it," Emmons says.

Big labs mapping large circuits on the single-neuron level are trying new scale-up approaches. Deciphering mammalian neural circuits is Reid's goal in his new position as senior investigator at the Allen Institute, to which he was appointed as part of the institute's ten-year US$300-million move to map connectomes and to use them to reach a broader understanding of brain function that integrates genes, circuits and behaviour.

This project, called MindScope, is an attempt to go beyond the anatomy and wiring of the brain to how things are computed in the cortex, by having scientists work side by side to study cell types, neural coding, modelling analysis and theory. "It's a dream come true," says Reid.

He will use transgenic mice to identify the different cell types in the cortex and thalamus, and will then focus on deciphering the neural coding in the visual parts of the brain using a combination of techniques: behavioural analysis, physiology, imaging with calcium indicators and electron microscopy. The results will be compiled into what he calls network anatomy, which is a wiring diagram with information piled onto it to map and understand the connectome's dizzying array of functionalities.

As the wealth of data from using different imaging modalities and from integrated large-scale projects comes in and is collected and annotated, labs large and small will still need to put their heads and computing power together for data analysis. "Astronomical amounts of connectomics data are being generated at an exponential rate; extracting meaning from it is the bottleneck that hasn't been broken," says Larry Swanson, neuroscientist at the University of Southern California and president elect of the Society for Neuroscience in Washington DC. ■

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CORRECTION

The article 'Building better biobanks' (*Nature* **486,** 141–146; 2012) wrongly said that Freezerworks sells automated freezers. In fact, it makes data-management software for tracking samples held in such freezers.