Photonics techniques key to unraveling the mysteries of the brain

BiOS neurotechnologies plenary talks reveal cheaper, simpler techniques to boost access to life-enhancing treatments.

The human brain is a notoriously enigmatic subject. The occurrence and cost of brain disorders has increased in recent years because of higher population and ageing – yet researchers still lack a detailed understanding of the organ's structure and function. Disease detection is difficult; clinical trials for treating brain disorders fail at high rates. To improve these prospects, experts are developing new methods to image and study the brain, which they presented at Sunday's neurotechnologies plenary session.

One technical challenge is imaging large brain sample-slabs that are centimeters thick, for example, says Raju Tomer of Columbia University. He presented his group's microscopy method that can image deeper and faster than conventional light sheet microscopy (LSM). Like LSM, their method uses light sheets to illuminate a sample. However, they rotate the plane of the light sheet so that it hits the sample at an angle. Then, after scanning the illuminated part of the sample, they move the light sheet and repeat the process. This enables them to image an entire brain sample quickly. The goal is to create a "Google maps" of the brain, Tomer explains. Vermont-based company MBF Biosciences is developing a commercial version of the technique.

Denise Cai, a neuroscientist at the Mt. Sinai Health System, presented on the Miniscope, a do-it-yourself miniature microscope whose designs and instructions are all open-source. Cai's team has used the Miniscope to study live mice. Weighing 3 grams, the instrument comes in several different versions, including a wireless battery-operated design that attaches to a mouse's head.

The Miniscope is based on a design by Stanford researchers, first published in 2011. Stanford's original scope is commercially available, but for a hefty price, says Cai. So over the past four years, she and her collaborators developed this more affordable version. The materials to build the miniscope amount to about 1000 dollars, she says.

To teach people – largely neuroscientists – how to build the Miniscope, Cai's team has led workshops in countries around the world including New Zealand, Germany, and France. "After two days, everyone will have built their own miniature microscope system," she says. To Cai, open-source technology provides more people with the opportunity to pursue important scientific questions. "I really think it's the future of neuroscience," she says.

Emily Gibson of the University of Colorado at Denver discussed her team's lightweight microscope, used to image neurons in moving mice with two-photon microscopy, a technique that can also penetrate the brain relatively deeply. They aim to use the microscope to study how groups of neurons reflect animal behavior, says Diego Restrepo, Gibson's colleague at CU Denver. The group is also working with Denver-based company 3i to commercialize the instrument.

Researchers have been able to perform two-photon microscopy in mice only recently, and it usually requires bulky machines, says Gibson. Their two-gram microscope affixes to a mouse's head and consists of a liquid droplet lens shaped electrically. It can achieve a 2µm resolution laterally and a 10µm resolution axially. One challenge of two-photon microscopy is the quality of the light source. Her group compresses the light into an intense pulse shorter than 100 femtoseconds.

Lin Tian of the University of California, Davis, presented on a new fluorescence-based sensor for imaging dopamine activity inside live mice. Studying the dynamics of dopamine, a molecule involved in motor control and pleasure, can shed light on many types of diseases including depression and addiction. To image dopamine, they modify the dopamine receptor, a protein on a neuron that binds to dopamine, by attaching it to a green fluorescent protein.

This method improves on other dopamine imaging methods by achieving good temporal and spatial resolution simultaneously – a resolution of about 2 µm at ten frames per second. In addition, the method could be easily adapted to sense other types of neurotransmitters, such as serotonin, says Tian.

Blood flow

Vivek Srinivasan, also from the University of California, Davis, presented a noninvasive technique for monitoring blood flow inside the human brain. This work improves upon a state-of-the-art technique known as diffuse correlation spectroscopy (DCS), in which near-infrared laser light is beamed into a person's head at a particular point (NIRS). Fluctuations in the intensity of the detected light indicate the rate of blood flow in a region of the brain several cubic centimeters in volume.

However, because this signal is so faint, DCS requires expensive detectors for counting single photons. Srinivasan's group devised a potentially cheaper and more scalable alternative – by using interference. They split the laser light into two different beams: a reference beam, which is not directed at the person's head, and the sample beam, which is.

The photons emerging from the head are recombined with the reference beam. The resulting interference fringes produce a larger signal compared to that of DCS. This means they can capture the signal using cheap CMOS cameras. Now that they've demonstrated the technique on human subjects, Srinivasan wants to develop a clinical prototype based on this technique.

Measuring brain signals can also be used as a teaching aide, said Xavier Intes of Rensselaer Polytechnic Institute. Intes's team has used functional near-infrared spectroscopy (fNIRS) to observe brain activity in surgeons and medical residents as they performed practice tasks relevant to laparoscopic surgery.

The process involves beaming near-infrared light into a person's head and measuring an emerging signal from another point on the head. This signal indicates the relative amounts of oxygenated blood, and thus the level of activity in that part of the brain. Intes's team found that the less experienced residents displayed more activity in the front part of the brain involved in planning, while more experienced surgeons had more activity in parts of their brain that involve fine motor control.

These interdisciplinary projects that combine neuroscience and photonics have increased in recent years, session co-chair David Boas of Boston University pointed out. The goal, he said, is to get more neuroscientists and photonics researchers to talk to each other.

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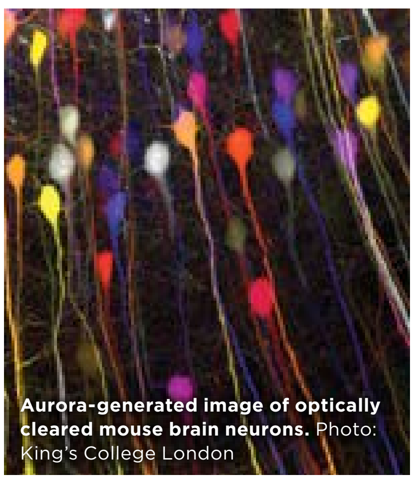

Aurora-generated image of optically cleared mouse brain neurons. Photo: King's College London

Brain power

Maximizing the performance of bio-imaging systems is achieved with the combination of improving resolution and field of view while minimizing photo-toxicity. Photonics company M Squared, based in Glasgow, UK, has improved this performance with its Aurora Imaging System, which creates a sheet of light in a technique known as Airy Beam Light Sheet Microscopy. This leads to amplitude and phase spread of a light beam, ultimately revealing more information about the subject cells.

M Squared CEO Graeme Malcolm told *Show Daily,* "This technique creates a large field of view with comparable resolution, a 600µm field of view 20 times larger than a conventional Gaussian light sheet.

"The Aurora imaging system enables deeper penetration with a lower photon dose for longer imaging times. The wider field of view allows more of a specimen to be imaged while maintaining a high 3D resolution, which is unique to this market." (Booth 657).

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