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Injectable Electronics Unfold in the Brain, Record Neurons

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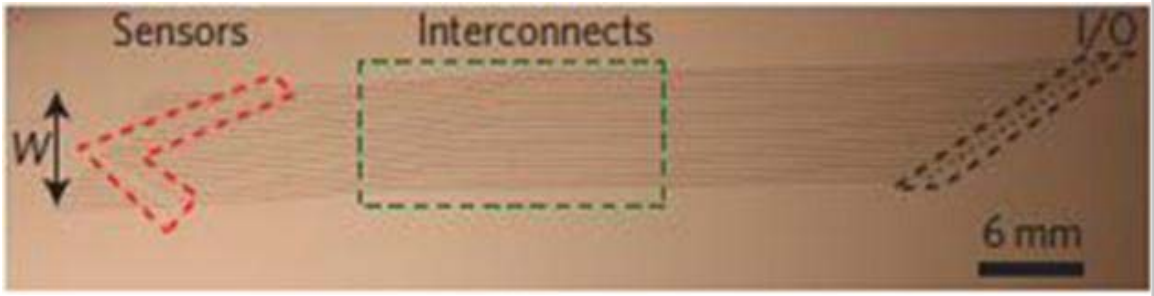
Time for your injection of … electronics? We now have the technology, according to a study published June 9 in Nature Nanotechnology. Researchers have created flexible mesh electronics that roll up to fit inside a syringe, then unfold when injected into a rodent's brain. Once inside, the electronics made nice with neurons and did not trigger an inflammatory response. For now, researchers managed to fit a 16-channel electrode into the injectable mesh and recorded neural activity in the hippocampus; however, study leader Charles Lieber at Harvard University envisions bundling all manner of electronic devices into the flexible contraptions. Researchers may one day use the little gadgets to monitor neural activity during disease or in response to drug treatment, to stimulate neurons, or to provide a scaffold for stem cells.

The development of flexible electronics has taken off in recent years, as researchers have created ever-smaller and more malleable devices. A limiting factor has been that the wiring is often imbedded within a thin-film substrate of some kind, which must be surgically implanted and does not allow for cells in the body to integrate within the structure (see Kane et al., 2011; Kaltenbrunner et al., 2013). Lieber's lab first made progress on the latter front, creating macroporous electronics that allowed cultured neurons to form networks that serve as a scaffold for cells (see Tian et al., 2012). Lieber envisions using this technology to bolster the development of stem cells.

"Then we thought, could we suck up electronics like this into a syringe?" Lieber told Alzforum. That is exactly what the scientists did in the current study. Co-first authors Jia Liu, Tian-Ming Fu, and Zengguang Cheng optimized mesh electronics to roll up tidily when taken up into a syringe. They designed devices consisting of three parts: a sensor (such as an electrode for neural recording), connectors made of polymer and metal mesh, and an input/output pad that sends and receives signals to and from the sensor through the interconnectors (see picture).

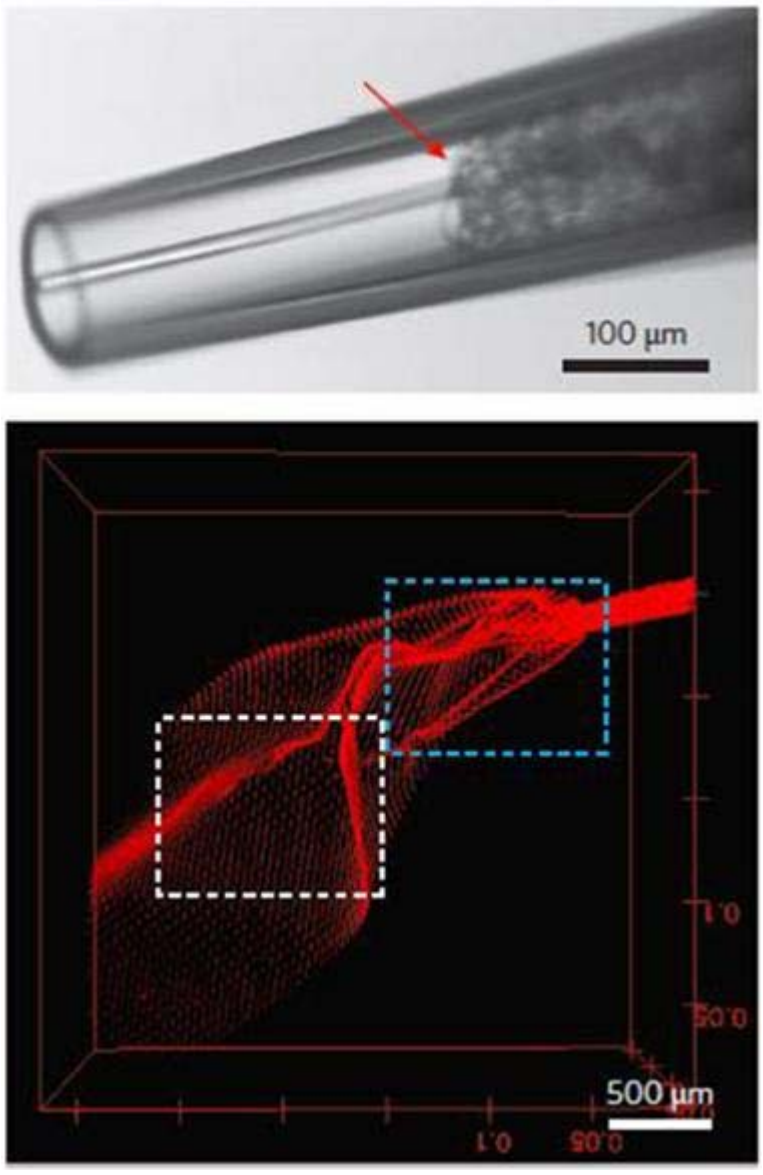


Minute Mesh. *A schematic of typical mesh electronics: Sensors (red), such as electrodes, link up with mesh interconnects (green), which connect with an input/output pad (black) that ultimately*

resides on the outside of the tissue. [Courtesy of Liu et al., Nature Nanotechnology 2015.]

The researchers built the electronics on a flat substrate that they then dissolved away. This left only the mesh electronics consisting of 90 percent open space, much like chicken wire, Lieber said. The meshes can be made in various sizes and squeezed into metal or glass syringes whose inner diameters are 30 times narrower than the width of the devices.

After first trying out their gadgets in cultured neurons grown in Matrigel, the researchers injected them into two regions of the mouse brain: the lateral ventricle and the hippocampus. Five weeks after injection into the lateral ventricle, confocal microscopy of brain sections revealed that the mesh had fanned out following injection. Neurons had interjected their processes in and out of the mesh and formed tight junctions with the structure. It appeared that some neural progenitors had migrated from the subventricular zone to bolster themselves upon the mesh scaffold. Importantly, levels of glial fibrillary acidic protein (GFAP)—a marker of activated astrocytes and chronic inflammation—were the same in the injected lateral ventricle as they were in same region on the other brain hemisphere. This indicated that the mesh structure had integrated into the brain tissue without triggering a chronic inflammatory response.

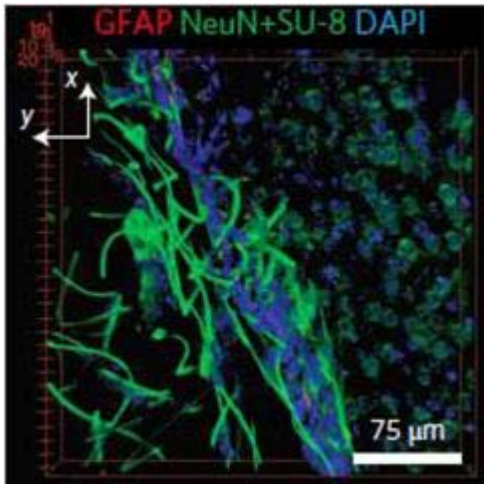


The Great Unfurl.

Mesh electronics squeezed into syringe (top panel) just prior to injection into saline solution (bottom). [Courtesy of Liu et al., Nature Nanotechnology, 2015.]

The researchers obtained similar results after injecting the devices into the hippocampus,

although the densely packed cells in that region prevented the electronics from expanding much further than the diameter of the needle. Neurons intermixed with the mesh, which did not disturb the boundaries between the dentate gyrus and CA1 layers.



Neural Integration.

Mesh electronics (green) create a habitat for neurons (also green, nuclei blue) at the border of the subventricular zone. Few activated astrocytes (red) are present. [Courtesy of Liu et al., Nature Nantotechnology, 2015.]

The researchers next injected similar devices with 16-channel electrodes attached. Upon initiating injection into the hippocampus, the researchers gradually pulled the syringe out of the brain, so that the input/output pad was ejected last and landed outside the skull. The electrodes thus interacted with neurons in the hippocampus, while signals could be measured using standard electrophysiology equipment outside. The researchers picked up consistent local field potentials that are characteristic of the hippocampus, as well as single neuron action potentials in all 16 channels. Lieber is currently measuring how stable and long-lived the electrodes are. He told Alzforum that his colleagues have so far recorded neural signals for 100 days, adding that according to statistical analyses, each channel has recorded the same neuron for the duration. Lieber said this aspect excites him most, as it allows for remarkably consistent measurements over time. He noted that the electronics could be designed to accommodate far more than 16 channels in the future.

Lieber envisions a panoply of applications for these miniature devices. Researchers could monitor neural activity in response to treatments, or use them to stimulate neurons in applications such as deep-brain stimulation. Because the devices cause little harm to surrounding neurons, Lieber said they may be well-suited for implantation within damaged or sensitive brain tissue, such as following brain injury or during neurodegeneration. He believes the electronics could even form artificial junctions or synapses, thus connecting regions of the brain whose circuitry is faltering. The devices could be fitted with sensors to detect biomarkers as well, Lieber said. Antibodies or other detection reagents could be loaded onto the sensors, which would activate electrochemically when the target (such as Aβ or tau) is engaged.

John Cirrito of Washington University in St. Louis has helped design implantable thin-film biosensors that measure CSF Aβ (see Prabhulkar et al., 2012). He called the new technology "incredible." "The fact that it is flexible and doesn't cause damage or inflammation is a huge advance in itself," Cirrito said. While Cirrito said the devices could be used to measure biomarkers in the future, he was most pleased about the possibility of recording the electrical activity of many neurons at once. For example, neural activity regulates the release of toxic Aβ and tau species, he said, so the ability to measure such activity over multiple channels could

allow researchers to better understand how electrical signals relate to AD pathology, and to track how neurons respond to treatment, he said.

Improvements on Lieber's injectable electronics are sure to stimulate even more innovation, wrote Dae-Hyeong Kim and Youngsik Lee of Seoul National University, South Korea, in an accompanying editorial. "Further integration of the injectable electronics with other functional units and/or wireless components is expected to lead to promising pathways for innovations in implantable bioelectronics and continuous biomonitoring," they wrote.—Jessica Shugart

COMMENTS

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REFERENCES

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FURTHER READING

No Available Further Reading

PRIMARY PAPERS

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