Bio Focus

Neural implant mimics mechanical properties of neural tissue

Neural implants are important and useful for studying the nervous system and even help treat certain neurological issues. However, while compliant, today's implants are still stiff relative to neural tissue, making them unsuitable for long-term use. Researchers at the École Polytechnique Fédérale de Lausanne (EPFL, or Swiss Federal Institute of Technology in Lausanne) have now designed a soft neural implant that mimics the shape and elasticity of *dura mater*, the protective membrane of the brain and spinal cord. Described recently in the journal *Science*, the new implant, called e-dura, doesn't induce inflammation or spinal cord damage after nearly two months of continuous use in rats, and has been shown to restore locomotion, using electrochemical stimulation, to rats suffering from paralyzing spinal cord injury.

"We've developed a technology where the neural implant has the mechanical signature of the natural dura mater, and this allows the implant to be almost transparent to the neural tissue," says Stéphanie Lacour, Bertarelli Foundation chairwoman of neuroprosthetic technology at EPFL and co-corresponding author of the new study published in the January 9 issue of *Science* (DOI: 10.1126/science.1260318; p. 159). "This is an exciting new technology, which we hope will have use as a long-term neural prosthetic solution."

Neural implants serve a wide range of functions in medicine. For example, cochlear implants can help restore hearing to some people who are hearing impaired, and other types of implants can help alleviate Parkinson's disease symptoms, epileptic seizures, and neuropathic pain. These neuroprosthetic devices are often made of soft silicon, but they contain metallic foil electrodes, which make them rigid compared to biological tissue. This biomechanical mismatch between implants and neural tissues can cause sheering and rubbing to occur, potentially resulting in inflammation and neural tissue damage over time, and cause the device's electrodes to eventually fail.

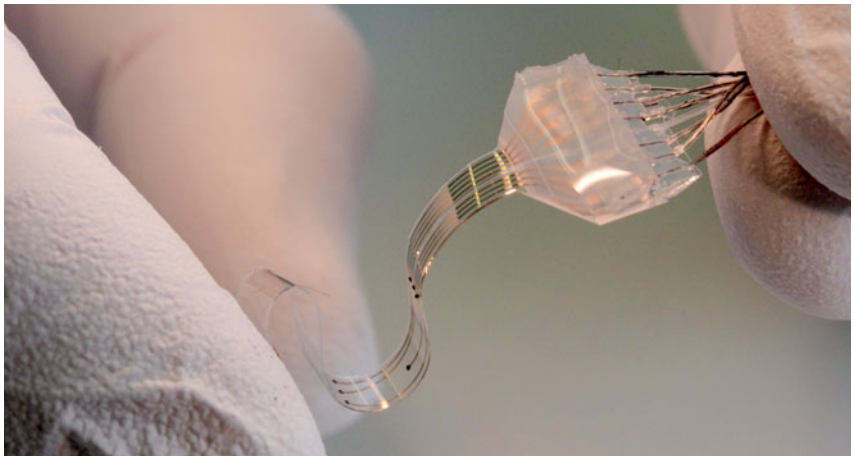
To address this issue, Lacour and her colleagues developed e-dura, which contains interconnects, gold electrodes, and "chemotrodes" (microfluidic channels that can deliver drugs) that can all bend, stretch, and deform with the movement of the neural tissue.

To make their soft implant, the team began by fabricating a transparent substrate by spin-coating polydimethylsiloxane (PDMS) onto a silicon carrier wafer, which they cured overnight. They evaporated tracks of a 35-nm-gold film full of microcracks—which provide a meshlike structure improving flexibility and stretchability—onto the substrate to serve as the electrode interconnects. They also created a secondary PDMS substrate consisting of a thick PDMS slab and two thin (20 μm) PDMS layers, which were full of puncture holes corresponding to sites of the electrodes.

The researchers encapsulated the electrode wiring by bonding the two substrates (making sure to align the puncture holes with the underlying electrodes) and then peeling off the thick PDMS slab, leaving behind two 20-μm-thick PDMS encapsulation layers on top of the interconnects. Next, using a process similar to screen printing, they coated the e-dura electrode sites with a customized platinum-silicon composite. They peeled off the upper encapsulation layer, leaving behind bumps of conductive composite at the active electrode sites, while the bottom PDMS layer remained permanently bonded to the electrode-interconnect e-dura substrate to provide electrical encapsulation. Finally, they bonded an 80-μm PDMS layer that hosted a microfluidic delivery system to their metallized e-dura substrate.

To test the long-term biointegration of the soft neuroprosthetic, Lacour and her colleagues implanted e-dura and rigid implants (the most flexible, non-e-dura implants available) directly onto the spinal cords of rats, beneath the rodents' dura mater. After just one to two weeks, rats with the rigid implants began experiencing motor issues, including coordination problems and trouble walking. When the implants were removed six weeks after implantation, tests showed the rigid devices caused inflammation and spinal cord deformation. Comparatively, rats with the e-dura did not experience motor issues, inflammation, or deformation.

The team also tested the functionality of the e-dura system on rats that were paralyzed from spinal cord contusions. They implanted the device below the site of injury along the spinal cord. "Then, using electrochemical stimulation, we woke up the dormant spinal circuit that controls the limb movement," Lacour says. "By applying controlled stimulation, we



E-dura is a soft neural implant that does not cause inflammation or spinal cord deformation after nearly two months of continuous use. The implant was shown to deliver electrochemical stimulation to help restore locomotion in rats with paralyzing spinal cord injury. Credit: EPFL.

elicited non-voluntary movement in the legs." With help from a machine, the rats could, in effect, walk again, though they weren't controlling their own movement. Previous work by Lacour's co-corresponding author, Grégoire Courtine, suggests that electrochemical stimulation can encourage some of the fibers in the injured spinal cord to connect, promoting voluntary leg movement.

"This work represents a significant advance in the development of biocompatible devices that can be used for modulation of the functional properties of the spinal cord and brain," says Reggie Edgerton, a bioengineer at the University of California–Los Angeles, who wasn't involved in the work. "It is now apparent that there can be multiple strategies to neuromodulate the spinal cord and brain, ranging from indwelling electrodes within the spinal cord to stimulating transcutaneously. Ideally, each can be developed to include in a clinical toolbox from which the best option for a given patient under a given situation can be selected." He adds that the next challenge is to establish the real-world durability of e-dura.

Lacour says her team now has a number of parallel experiments to conduct, including testing the longevity of the device and trying to design a completely implantable system that does not have wires leading out of the patient. If successful, e-dura could have a range of important brain–interface applications, such as the long-term monitoring of epilepsy.

Joseph Bennington-Castro

Ion bonding in organic scaffolding promotes biomineralization

The seashells you pick up at the beach might not seem extraordinary, but they are a source of inspiration for researchers searching for efficient ways to store extra atmospheric carbon. Through a process called biomineralization, organisms like mollusks, clams, and corals crystallize excess carbon in their environment into hard calcium carbonate shells. Understanding on a molecular level the way that inorganic minerals interact with a framework of biological macromolecules is a critical step toward mimicking the process in artificial systems—and one that has proven challenging.

Now, an international team of materials researchers has demonstrated that these organic scaffolds influence the crystallization process by binding clusters of positively charged calcium ions, inducing mineral formation in specific locations. The results, published recently in *Nature Materials*, challenge previous assumptions about the molecular-level mechanisms responsible for biomineralization.

"This work is of great value in the realm of fundamental materials science—in particular in the world of living systems, where soft matter controls hard matter," said Jim De Yoreo of Pacific Northwest National Laboratory.

De Yoreo and his colleagues used liquid-phase transmission electron microscopy (TEM)—a relatively new imaging technology that visualizes atomic-level activity in liquid samples—to monitor the crystallization process in real time at nanoscale resolution.

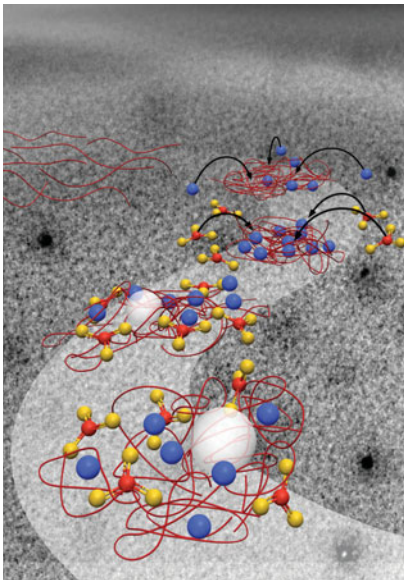
They first observed vaterite and a little bit of calcite, two different calcium carbonate crystal structures, forming in a solution in the TEM.

Then, they repeated the experiment with added polystyrene sulfonate (PSS), an organic polymer with negatively charged side chains that is structurally similar to the macromolecules that guide biomineralization in natural systems.

This time, the mineralization process looked different: Amorphous calcium carbonate (ACC) formed first, then later transformed into vaterite. ACC is a precursor to many biologically based minerals.

To understand how the PSS scaffold interfered with vaterite formation, the researchers mixed the calcium with the macromolecules without the carbonate. The macromolecules clumped together, absorbing the calcium ions to form globules. Once the carbonate was added, ACC crystals only formed within the calcium-PSS globules, and stopped growing once the calcium ran out. The finding suggested to the team that calcium binding to the organic macromolecules mediated how and where the ACC formed.

Having monitored the crystallization process step by step, they concluded that the negatively charged polymer side chains act as a sponge for the positively charged calcium ions (or counterions), concentrating them in specific regions.



Large charged molecules (red) lure in calcium ions (blue), which position carbonate ions (yellow and red) and form amorphous calcium carbonate (white ball).

Biomineralization then readily occurs where the calcium is clustered.

"The sponge makes it possible to locally increase the ion concentration, which makes nucleation easier," said Nico Sommerdijk, a collaborator in the study from Eindhoven University of Technology in Eindhoven, The Netherlands.

Previous work had suggested an alternate route to crystallization: the scaffold might guide biomineralization by providing a low-energy surface upon which the crystals could deposit themselves in an ordered fashion. The crystals would form