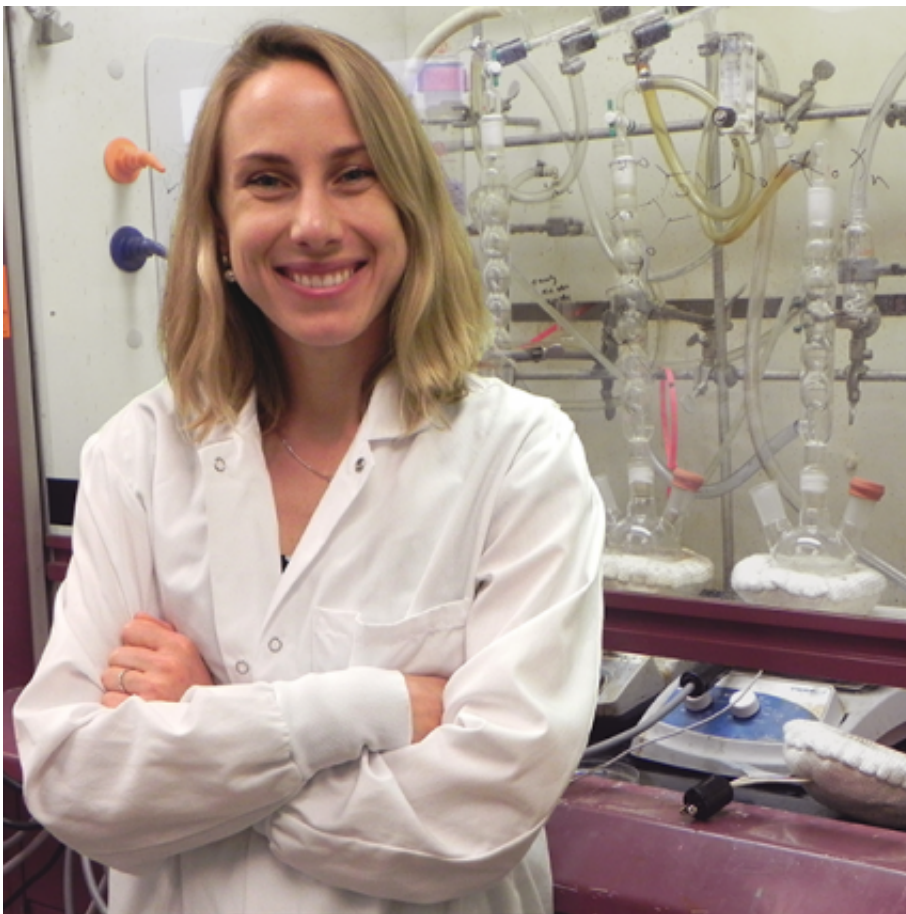


Flexible polymer probes and magnetic nanoparticles promise breakthroughs for treating paralysis, brain disease

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Polina Anikeeva, the AMAX Assistant Professor in Materials Science and Engineering, in the MIT lab where her group studies magnetic nanoparticles for non-invasive neural stimulation. Credit: Denis Paiste/Materials Processing Center

Better control of prosthetic limbs and better treatment of diseases like Parkinson's motivates Polina Anikeeva, the AMAX Assistant Professor in Materials Science and Engineering, to develop both flexible electronic devices and safe chemical methods to manipulate nerve cells in the brain and spinal cord.

Recent developments in Anikeeva's Bioelectronics Group include: polymer-based fiber probes that can optically stimulate nerves in vivo and record their neural activity; and magnetic nanoparticles that can be injected into the brain in vivo, and activated non-invasively by externally applying an alternating magnetic field.

"It is not just brain disorders that motivate me but traumas," Anikeeva says. Such devices may some day benefit returning wounded veterans and car crash victims.

"We are hoping to use our devices to record a pattern of neural activity coming from the brain and translate it across the injury site into a pattern of stimulation. We can do it optically, and that's why we try to incorporate electronic and optical features within these flexible polymer probes," Anikeeva explains. MIT has filed a patent on the device platform, which was developed in collaboration with Yoel Fink, a professor of materials science and director of MIT's Research Laboratory of Electronics. The group has several papers in progress reporting the work.

A bit of fun in class

Anikeeva teaches the class 3.024 (Electronic, Optical and Magnetic Properties of Materials), which she says is quite challenging, as it combines quantum mechanics, solid-state physics, photonics, and magnetism. Each spring for the last class, instead of a review session, students break into teams and design a superhero comic that has as many

concepts from the class as possible.

"We have an external committee that consists of faculty and graduate students that judges those comics in the last five minutes of the class. This is a bit more fun than just regurgitation of the material," Anikeeva explains in her office, where comics from the most recent competition still hang on the wall. The team that produces the best comic wins a copy of "The Physics of Superheroes," by James Kakalios, a professor of physics at the University of Minnesota.

Last summer, Anikeeva was the inaugural recipient of the Mildred S. Dresselhaus Fund to support women or junior members of the MIT faculty. Dresselhaus, an Institute Professor Emerita of physics and computer science and engineering, established the award after she received a \$1 million Kavli Prize. "Millie's support has made me a better scientist," Anikeeva says.

Flexible neural probes

Materials science and engineering graduate student Chi (Alice) Lu, who is leading development of the flexible polymer probes for spinal cord stimulation, conducted experiments in mice that express a gene that makes their neurons respond to blue light. "When we shine light into the spinal cord of these mice, we can use the device to observe the neurons' electrical response," Lu explains. "My fiber probe incorporates a waveguide and two electrodes. The waveguide is for optical stimulation, and the polymer electrodes are used to record the electrical response."

With Anikeeva and collaborators, Lu is lead author of the paper, "Polymer Fiber Probes Enable Optical Control of Spinal Cord and Muscle Function In Vivo," which has been accepted for publication in *Advanced Functional Materials*.

These polymer-based fiber devices, are almost as thin as human hairs and so flexible that they can be tied in a knot. "The materials that we are using are fully organic, and the structures themselves are designed to interface with neural tissue," Anikeeva says. "Polymer fiber processing has never been applied to neural probe engineering; we are the first ones."

"We use a single device to optically stimulate the neurons in the [spinal cord](#) and evoke leg movement synchronized with light, and simultaneously record the corresponding [neural activity](#). This is a bi-functional device; it both supplies the light and does the recording," she says.

Improving tissue compatibility

Besides being soft and pliable, the fiber-based neural probe is made entirely of biocompatible materials. "Biocompatible means that the device can be inside the body without deleterious effects on the surrounding tissue," Anikeeva explains.

"It means that the device will be stealthy inside the body. It will not trigger an immune response; it will not be toxic; it will not degrade and it will not leach chemicals into the nervous system," she says.

"We have done tissue analysis, and we do see improved tissue viability around our devices as compared to the more traditional metal- and semiconductor-based technologies. There are indications that our platform may solve some of those tissue-compatibility issues, but it is still a work in progress," Anikeeva says.

Magnetic neural control with nanoparticles

Graduate students Michael G. Christiansen and Ritchie Chen are co-authors of papers with Anikeeva and colleagues demonstrating that heat dissipation in ferrite nanoparticles depends on the parameters of the applied alternating magnetic field and opens the possibility of designing customized arrays of iron oxide nanoparticles by matching particles with differing material properties to different alternating magnetic field conditions.

"Magnetic hyperthermia has been explored by many labs, including those at MIT, for cancer applications over the past 50 years. What we have shown, however, that it is possible to tune the materials properties to specific parameters of alternating magnetic field," Anikeeva explains. By manipulating the frequency and amplitude of the alternating magnetic field, researchers can selectively heat different particle types enabling different processes or distinct areas of the nervous system to be stimulated independently of each other.

The new technique, called magnetothermal multiplexing, was reported in the May 26, 2014, *Applied Physics Letters* paper, "Magnetically multiplexed heating of single domain nanoparticles."

Anikeeva's group is extending that work from establishing the chemical and physical parameters for functional magnetic nanoparticles to testing them biologically. "We're trying to interface with neurons completely noninvasively by using a nanomagnetic material that can act as a transducer for neural stimulation," Anikeeva explains.

An alternative treatment

Current Parkinson's treatments that use deep brain stimulation are highly invasive and have a small risk of stroke, infection, or internal bleeding and the treatment itself is often accompanied by undesirable side effects.

"With our magnetics platform, we are trying to provide a more-effective, non-surgical treatment option, where there is no implant, no leads, no mechanical invasiveness. Instead, there will be an injection of magnetic nanoparticles into an area in the brain, very similar to an MRI contrast agent. Then we can apply external [magnetic field](#) and stimulate the desired brain region," Anikeeva explains.

"Eventually we will seek out biology labs as collaborators to explore applications of our work. If it keeps being promising, we are very interested in clinical translation because the materials are safe and the invasiveness is minimal," she adds.

Blurring lines between electronics and biology

Although she is a materials scientist, Anikeeva says it's important for her lab to engage directly in animal research to prototype devices. "We can make a device and quickly test it in our lab," she says. "If we see a device failing in some way, we can iterate until we have something that is promising. Then we turn to our neuroscience collaborators for more thorough investigations into applications."

Besides being a researcher with the Center for Materials Science and Engineering at MIT, Anikeeva is a principal investigator with the Center for Sensorimotor Neural Engineering, a collaborative center for developing new technologies to help people with sensory and motor disabilities, which is based at the University of Washington in Seattle.

Anikeeva is a co-author of "Bioelectronic medicines: a research roadmap," published June 2014 in *Nature Reviews Drug Discovery*. Bioelectronic medicines promise to reach diseases that are not traditionally considered neurological, such as high blood pressure, infertility or diabetes. However, recent findings indicate these disorders may have a neurological component that can be treated using

neuromodulation. "We may be able to address hypertension by stimulating a peripheral nerve, such as the vagus nerve, for example. However, it is challenging to build a device, which can optically and electrically interface with nerves in these environments, hence our focus on novel flexible neural probes," Anikeeva explains.

Future challenges

Anikeeva would like to extend the fiber work to enable intimate materials interfaces for future prosthetic devices. "By improving biocompatibility and having more specificity with respect to the targeted neurons we can potentially interface with a prosthetic limb in a manner that blurs the line between the human and the bionic," Anikeeva explains.

Student Lu notes that while her optical probe works with genetically altered mice, the technology is not yet directly transferrable to people, whose neurons are not sensitive to visible light (with the exception of those in the eye). To date, researchers have used transgenic mice, which express the protein channelrhodopsin 2 that is sensitive to blue light. The same effect can be achieved by viral gene delivery in genetically intact organisms. This is a challenge for the entire field of optogenetics, and Anikeeva expects that the electrical stimulation capabilities of the fiber-based neural probes will be the first to see clinical applications.

Anikeeva says her [materials science](#) skills were essential to making these breakthroughs. "Most high quality polymer photonic devices are made on flat substrates, but by using a drawn fiber we can create devices which are flexible, implantable, and biocompatible while maintaining their optical qualities," she says. "It turns out that the materials aspect of the neural interface is extremely important, and successful devices must match the mechanical, optical and electrical properties of the surrounding tissue."

"The brain is a very complicated system and we are trying to develop tools which can improve our understanding and treatment of neurological disorders," Anikeeva adds. "As an engineer, we can reduce the problem to electrical potentials across neural membranes, and we can manipulate those potentials and change their function."

More information: "Magnetically Multiplexed Heating of Single Domain Nanoparticles." Michael G. Christiansen, Ritchie Chen, Polina Anikeeva arXiv:1403.1535, arxiv.org/abs/1403.1535

"Bioelectronic medicines: a research roadmap." Karen Birmingham, et al. *Nature Reviews Drug Discovery* 13, 399–400 (2014) [DOI: 10.1038/nrd4351](https://doi.org/10.1038/nrd4351). Published online 30 May 2014

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