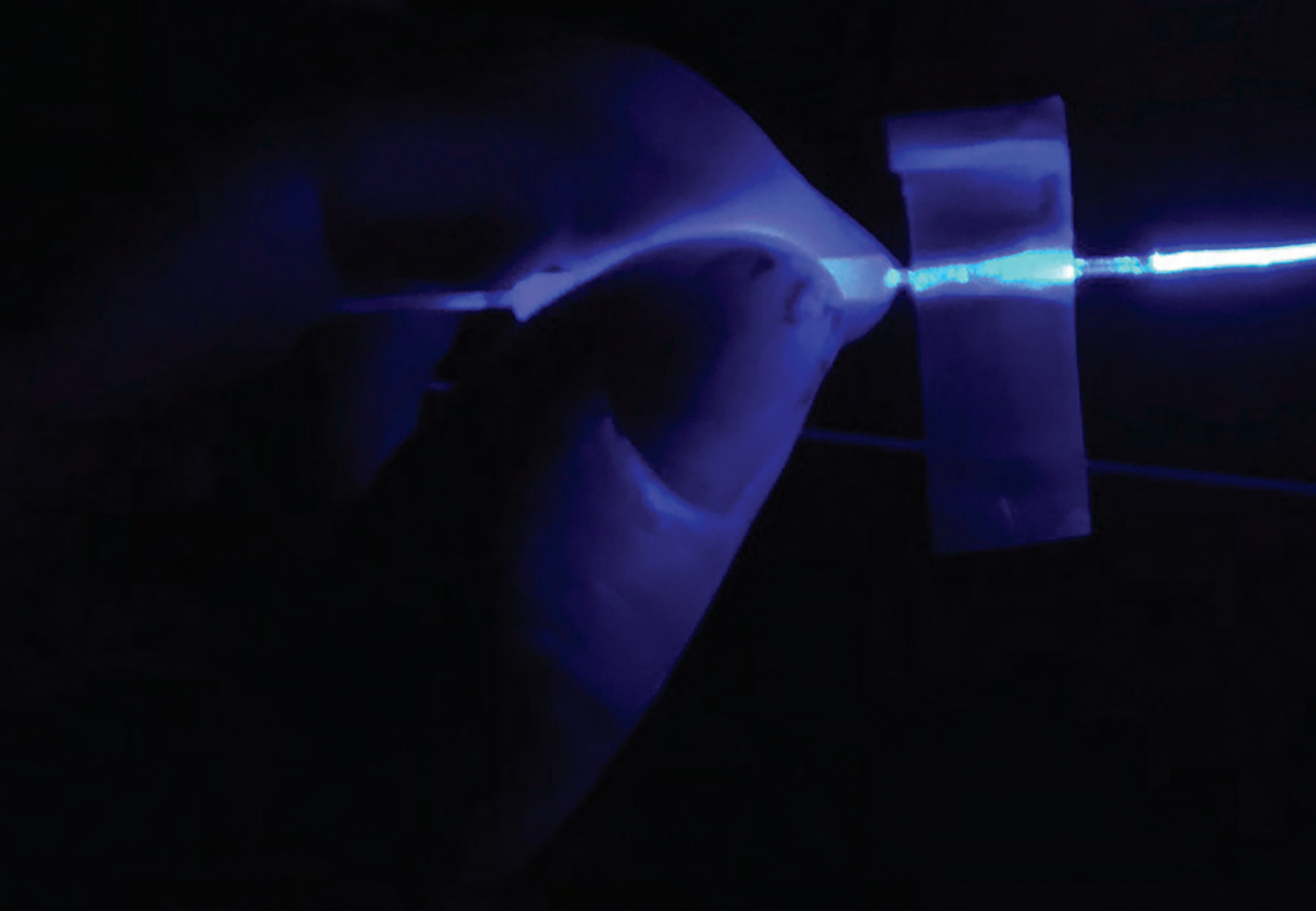
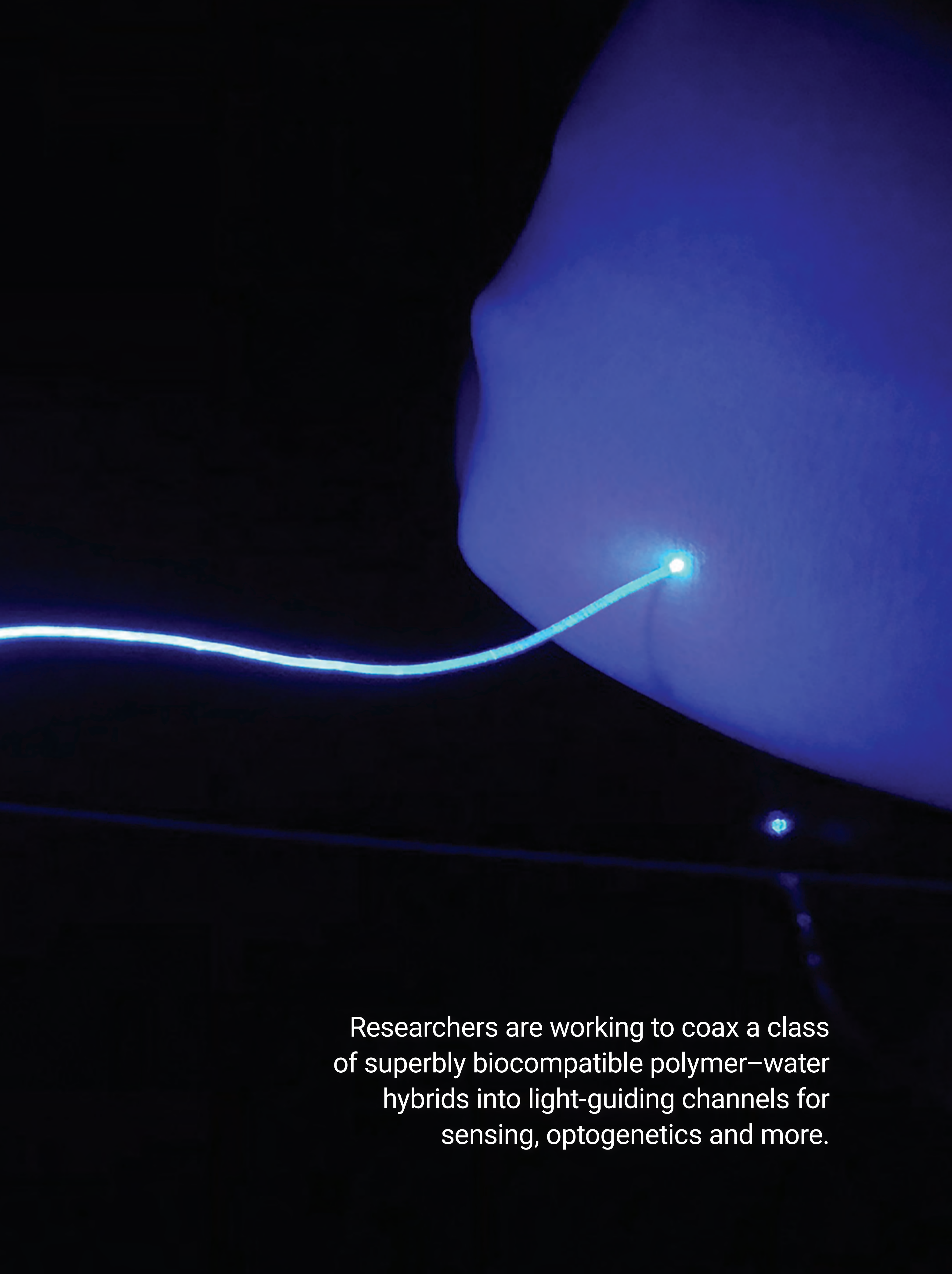
Stewart Wills

Hydrogel Optical Fibers

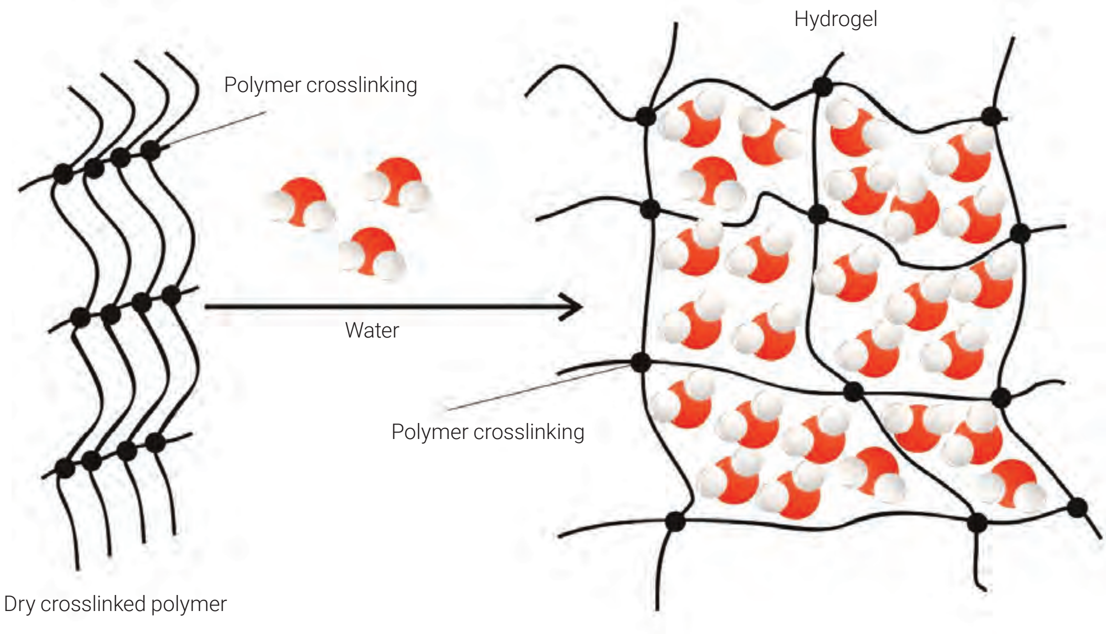


Engineers from the MIT labs of Polina Anikeeva and Xuanhe Zhao designed a soft hydrogel optical fiber that can be used for optogenetic studies of the peripheral nervous system.

Courtesy of the researchers



Researchers are working to coax a class of superbly biocompatible polymer–water hybrids into light-guiding channels for sensing, optogenetics and more.



Hydrogels are networks of crosslinked hydrophilic polymer chains that soak up water molecules, creating biocompatible materials with highly tunable optical and mechanical properties.

S. Besarab, doi: 10.13140/RG.2.2.35059.86569 (2021); CC-BY 4.0

Researchers in biophotonics and biomedical optics pursue a seemingly endless quest for the ideal biocompatible material—a medium that both can transport light efficiently and can hang out long enough in the body to enable meaningful measurements or treatments. One important clue in the search, it turns out, lies in an elementary-school factoid: the average human body is 50% to 60% water.

To take advantage of that truism, materials scientists and photonics engineers are increasingly investigating the polymer–water hybrids known as hydrogels. These "really hydrated networks," says Carlos Guimarães, a bioengineer with the 3B's Research Group at the University of Minho, Portugal, "are way closer to what we have in living tissues and what we have in organs" than many other light-carrying materials. And that, he observes, "adds a new possibility, the interface of these with biological systems."

As the chemistry and techniques for dealing with hydrogels have matured, lab researchers have played with the gels' unusual properties to build a variety of prototype optical devices and sensors—largely, but not exclusively, with an eye toward biocompatibility. In particular, scientists are molding, squirting, wet-spinning and 3D-printing hydrogels into supple, bio-friendly versions of the ultimate light-guiding medium: optical fiber.

The water-logged road to biocompatibility

Simply defined, a hydrogel is a collection of hydrophilic ("water-loving") polymer molecules that have been chemically, photochemically or physically crosslinked into a self-supporting, 3D gel-like network. Once the network is formed, it will sop up any available water molecules, swelling until the elastic restoring force of the crosslinked polymer cage balances the swelling force exerted by the water molecules. The tight crosslinking of the polymer molecules keeps the hydrogel from dissolving as it becomes increasingly water-logged.

The chemistry and crosslinking structure of the polymer units thus serve as key knobs to turn in controlling the material's level of hydration (as well as in shaping its mechanical and optical properties). Hydrogels can range from relatively dry structures that are 10% water or less by weight, to sopping-wet gels of 90% water or more. The polymer in question can be a natural one, such as gelatin (a collagen derivative extracted from animal parts during meat processing) or alginate (obtained from brown seaweed), or any of a variety of synthetic hydrophilic polymers.

For a hydrogel of a given makeup, the level of water-induced swelling can change with variations in temperature, pH, ionic concentrations and other environmental factors. That has made the materials an intriguing platform for building sensors.

1047-6938/24/11/40/10-$15.00 ©Optica

As the techniques for dealing with hydrogels have matured, researchers have played with the gels' unusual properties to build a variety of prototype optical devices and sensors.

Given their inherent biocompatibility, hydrogels have attained particular traction in the fields of tissue engineering and regenerative medicine, which were born in the 1980s and have gathered steam since then. Hydrogels with cells incorporated into their networks have been used to create tissue scaffolds for the generation or regrowth of artificial bone, skin and other tissues.

More recently, tissue engineers have taken advantage of hydrogels' propensity to react to stimuli such as pH, temperature and electric or magnetic fields to create "smart" hydrogels for targeted drug delivery and regenerative medicine within the body. And a team led by researchers at Harvard University's Wyss Institute for Biologically Inspired Engineering this year created a tough hydrogel "glue" that can attach and bond to tissues, for applications such as sealing blood vessels, bandaging damaged tissues and encapsulating flexible sensors for medical diagnostics.

Soft lenses, Jell-O lasers and sensors

Interestingly, notwithstanding their long pedigree in tissue engineering, perhaps the earliest biomedical use of hydrogels was a decidedly optical one. The soft contact lenses that began cropping up in the 1960s and 1970s and are widely used today are made from various forms of hydrogels.

Shortly after the appearance of the laser, hydrogels and gel materials found other interfaces with optics and photonics. In the mid-1960s, T.A. Shankoff and K.S. Pennington established the use of dichromated gelatin as a medium for recording holograms. In a lighter vein, in 1970, future Nobel laureates Theodor Hänsch and Arthur Schawlow—after unsuccessful attempts to create a laser medium out of the commercial hydrogel dessert Jell-O—instead tried a mixture of "almost nontoxic" sodium fluorescein and clear gelatin. Pumping the mixture with nitrogen laser light, they were able to make the wiggly concoction itself lase—thereby creating what the two scientists described, with memorable deadpan, as "[what] may be the first edible laser material" (see OPN, February 2005, p. 14).

Others soon twigged to the possibility of using transparent hydrogels as optically empowered sensors. By the early 1990s, labs had demonstrated biocompatible surface-plasmon-resonance sensors that combined hydrogels with gold films. Hydrogels embedding photonic crystals made of self-assembling nanospheres have been devised for potential use in temperature, humidity, glucose and protein sensing and in detecting hazardous substances. Moving beyond sensing, in one 2024 project, researchers in the Republic of Korea even created a solar steam generator for freshwater harvesting and water treatment using a composite of a hydrogel and plasmonic gold nanoparticles.

NTU Singapore

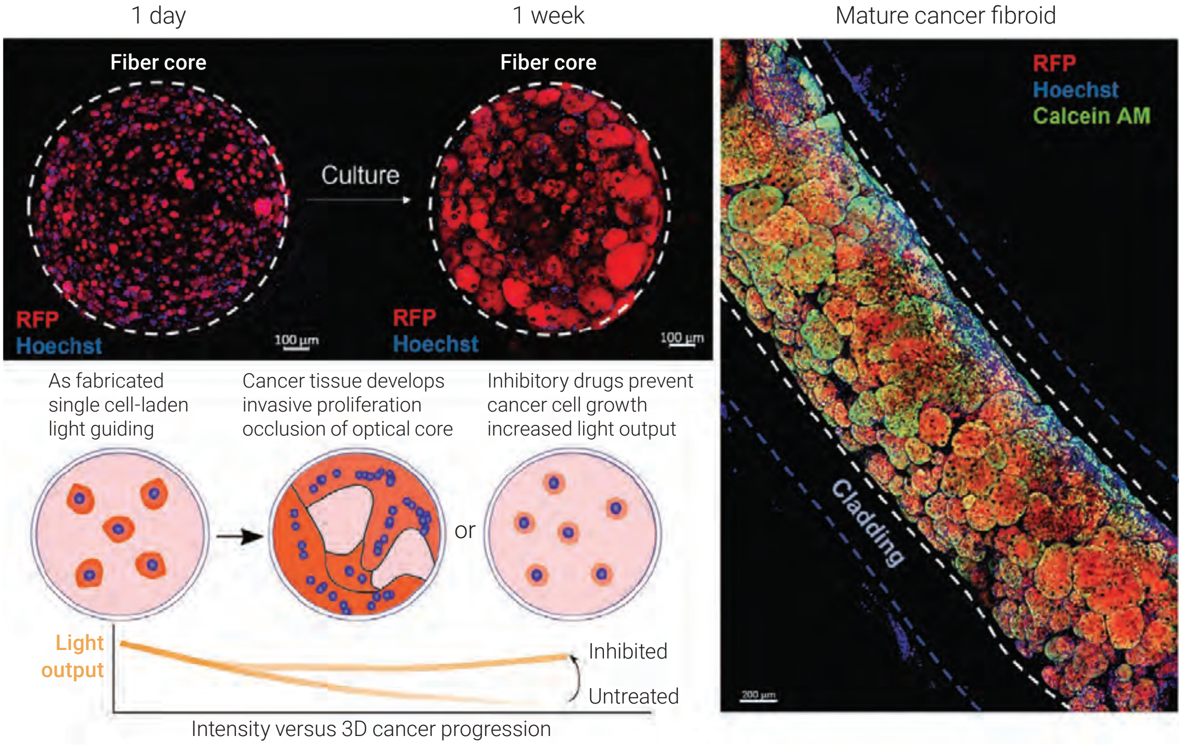
A laser-spiked hydrogel sensor

Outside of the realm of optical fibers, researchers have investigated myriad other ways to marry photonics with the flexibility of hydrogel materials.

In a study this year, for example, a team at Nanyang Technological University, Singapore, reported a way to encapsulate liquid-crystal microdroplet lasers into a wearable hydrogel patch. The patch, sitting on the skin, was able to absorb molecules in human sweat—and light–matter interactions within the laser-spiked gel afforded novel way of sniffing out metabolites, offering the prospect of a noninvasive, wearable glucose sensor for diabetic patients.

From waveguides to optical fibers

Despite these long-standing efforts, Guimarães says, it took quite a while for scientists to seriously explore using hydrogel networks in waveguides and fiber optics as a direct interface to biological systems. One reason, he suggests, is that the technology for fabricating hydrogels needed to catch up.



Carlos Guimarães and colleagues used bio-friendly hydrogels to fashion "living" optical fibers with cancer cells in the core. The fibers enabled monitoring of the effects of various cancer drugs simply by measuring transmission of light through the fiber.

C.F. Guimarães et al. Adv. Mater. **33**, 2105361 (2021); ©2021 Wiley-VCH GmbH

"I think it starts with that for sure," he says. The 1990s and early 2000s, he notes, saw "a very big explosion" of work—driven by the interest in tissue engineering—toward developing new combinations of biomaterials, efficient techniques for spinning, layering and otherwise shaping hydrogels, and advanced chemistry for tweaking compositions and properties. The result was substantial gains in "the knowledge and toolbox … for how to structure [hydrogels] in a way that makes sense for optical purposes." (Especially tricky for making hydrogel optical fiber, it turns out, is ensuring a sufficient refractive-index contrast to allow total internal reflection—as both the fiber core and cladding are predominantly made of water.)

A number of experiments in the 2000s and 2010s started to put those ideas into practice, fashioning hydrogels into waveguides. In one study, published in *Optics Letters* in 2012, the group of David Erickson at Cornell University, USA, fabricated an agarose slab including hydrogel waveguides that were embedded within microfluidic channels, and that could encapsulate live cells—creating what the team described as "an integrated optofluidic system" made entirely of the gel. The device, the researchers suggested, could offer a platform for laboratory force experiments on cells in a more realistic, 3D matrix.

Of particular interest, according to Guimarães, was a 2013 *Nature Photonics* study led by Seok Hyun Yun of the Harvard Medical School, USA, and the Korea Advanced Institute of Science and Technology (KAIST), Republic of Korea. Here, the team developed a 4-cm-long planar hydrogel waveguide from polyethylene glycol (PEG), tweaking the composition for good optical transparency and embedding live cells for potential sensing or therapeutic applications. Tying the slab to a length of standard optical fiber to pipe light into the cell-containing hydrogel, the team then implanted the planar waveguide into lab mice and demonstrated its use for *in vivo* nanotoxicity sensing—and even, using optogenetically modified cells, in a potential light-driven therapy for diabetes.

Yun's Harvard/KAIST team followed up this work with a 2015 study in which the researchers combined PEG and alginate, via a molding-and-dipping process, to create a step-index optical fiber that used biocompatible hydrogels for both core and cladding. The fiber, Guimarães sees hydrogel fiber as a way to use the power of light—which already enables efficient readouts from 2D microplate readers—to pull data from more realistic 3D models.

the team wrote, sported "excellent light-guiding efficiency in biological tissues," and could be doped with nanoparticles or fluorophores to enable specific sensing and therapeutic applications. A flurry of efforts from other labs followed, showing how the stretchy biocompatibility of hydrogel fibers and waveguides, and their responsiveness to various stimuli, could potentially serve in glucose sensing, colorometric strain sensing, optogenetics, water sensing and more.

Getting information out of 3D models

Guimarães himself became intrigued by hydrogel fibers as a possible window into the complex 3D tissue models increasingly used for high-throughput laboratory drug development. "We can have these really complex models" for various types of cancer, he points out, that might be used to test thousands of drug candidates. "But then how can we get data out of them?" That, he says, is why he is "so interested in hydrogels and optics … using the potential that light has always given us—to extract data, get information, quantify things—and bridging that into three dimensions."

For Guimarães, the prospect of creating such a data pipeline using hydrogel optical fibers clicked at the beginning of the 2020s, when he was wrapping up a Ph.D. in tissue engineering and regenerative medicine with the University of Minho and Stanford University, USA. At Stanford, an optical scientist, looking at Guimarães' work in hydrogels, wondered if he had ever thought of "doing optical fibers with that." Shortly thereafter, the pandemic lockdown started, which gave Guimarães plenty of time to ponder the question and steep himself in previous efforts on hydrogel optical fiber.

Many of those efforts had involved hydrogels made at least partly of synthetic polymers. Guimarães' group, in contrast, was focusing on gels comprising natural materials, such as alginates, gellan gum and polysaccharides, that are friendlier to living cells. As the COVID lockdowns eased, the team got busy in the lab, using a wet-spinning process, combined with ionic crosslinking, to create core–cladding hydrogel fibers, with the refractive-index contrast tunable by adjusting the polymer concentrations in the two layers. (Taking a cue from silica fiber optics, the researchers also added a shield layer of 2% alginate to protect the cladding.)

As a proof of concept—bowing to the spirit of the times—Guimarães and his team embedded gold nanoparticles into the fiber to create a simple plasmonic detector for SARS-CoV-2, the COVID virus. The team also fashioned what it called "living" hydrogel fibers by spiking the hydrogel core with cells. The researchers showed that—via simple measurements of light transmission and output power through the fiber—the system could provide an instant readout on cell growth, and keep tabs on the potential impact of different drugs on the 3D growth of cancer cells.

Guimarães sees the hydrogel fiber as a way to use the power of light—which already enables efficient readouts of chemical assays in 2D microplate readers—to pull data from more realistic, complex biological models. "We're trying to really change the paradigm from 'flat' biology to three-dimensional biology," he says. While Guimarães is focused at present on the hydrogel fibers as a lab tool to supercharge drug discovery, he believes they could ultimately help enable precision medicine in the clinic as well. For example, he suggests, hydrogel fibers embedding cells from a patient's biopsy might be used to rapidly test and compare the relative efficacy of different kinds of drugs for that specific patient.

Hydrogel channels for optogenetics

The lab of Polina Anikeeva at the Massachusetts Institute of Technology (MIT), USA, meanwhile, has spent years focusing on a different problem: developing multifunctional fibers to study brain activity in living animals. And in several projects, the biocompatibility of hydrogels proved a draw.

"I would say hydrogels are actually not a really big part of our materials repertoire," Anikeeva says, noting that her lab focuses mainly on polymer composites and magnetic materials. "We got interested in hydrogels largely for their really interesting mechanical properties that are suitable for interfacing with biological environments … as a mechanical impedance-matching medium for our devices."

The idea of embedding mulitmode optical and electrical fibers for brain research in a hydrogel sheath made sense, because the brain is itself a sort of hydrogel.

One case in point was the lab's efforts to embed a conductive electrical fiber (for electrical neural recording) and an optical fiber (for optogenetics) into a single probe—which would also include a void down the axis, enabling microfluidics for delivery of drugs and gene therapy. Initially, the plan had been to use a polymer cladding to hold the probe's multiple fibers together. But then "we had this thought," Anikeeva recalls. "Maybe we can use a hydrogel to do the integration."

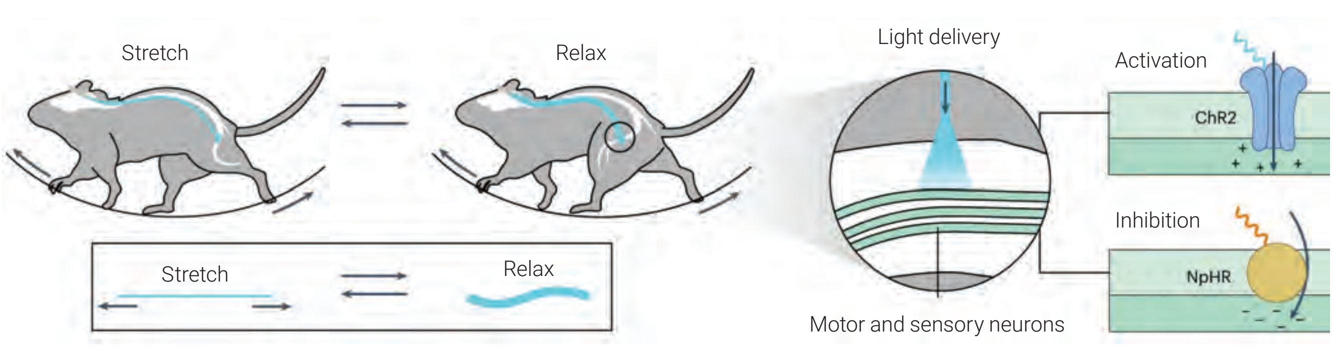
The idea made sense, because the brain, where the probe would eventually end up, is itself a sort of hydrogel. "It is a viscoelastic material; it has very many things in common with hydrogels," she notes. And a hydrogel cladding for the multiple fiber probes, she adds, could be tuned to closely mimic the brain's elastic properties by adjusting the gel's degree of crosslinking or hydration. Anikeeva's team, in partnership with the MIT materials-science group led by Xuanhe Zhao, put the idea into practice in two proof-of-concept studies published in 2021, one of which used natural alginate hydrogel synthesis and one of which relied on a hydrogel built with a synthetic polyurethane-PEG copolymer.

The adjustable mechanical properties of hydrogels turned out to be a plus for practical use of these exotic multimaterial fibers. Anikeeva draws the analogy of a paintbrush bristle, which is stiff when dry but supple when wet. "If we dehydrate the hydrogel, it becomes stiff and mechanically couples all of the fibers," for straightforward insertion into the brain of a lab animal. "But when it gets into the brain, the cerebrospinal fluid flows into the hydrogel, and [the hydrogel] is now again this nice interface" with the biological tissue.

Tough but gentle

Amid this work on fiber probes for brain studies, a postdoc in Anikeeva's lab, Siyuan Rao, was preoccupied by another problem: how to use optogenetics to study the peripheral nervous system—the distant neurons in the body that both act on the brain's instructions and in return send feedback, such as pain signals, to central command. For such studies, Rao notes, "the main limit is how to deliver photons into the tissue and collect photons from the tissue." The hitch is that this must be done in freely moving animals. Any fiber probe thus "needs to be extremely gentle and extremely tough at the same time," according to Anikeeva, to stand up over long periods to stresses in the animal's actively moving limbs, yet not damage tissue or cut the nerve being studied.

Given the application, conventional silica optical fiber seemed a nonstarter. In a conversation over coffee, Rao and Xinyue Liu, a grad-student friend from Zhao's materials lab, started talking about whether a hydrogel fiber might work instead. In the project that subsequently unfolded, the pair developed an annealing process that allowed them to convert amorphous

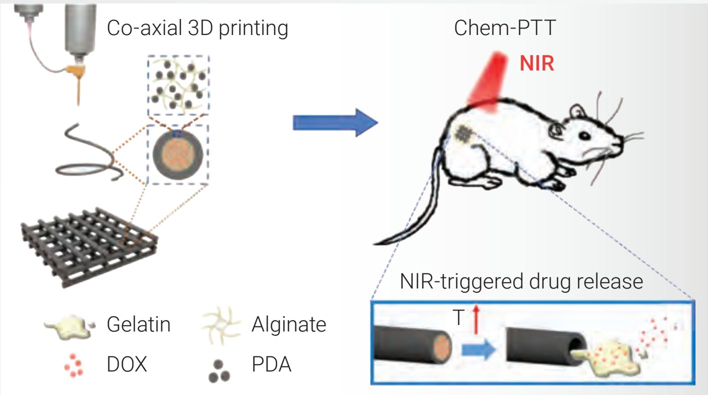


Siyuan Rao and Xinyue Liu were co-first authors on a study that created tough, flexible hydrogels capable of delivering light for optogenetically induced pain inhibition in peripheral nerves (such as the sciatic nerve)—while standing up to the repeated limb movements of a running animal across a period of weeks.

X. Liu, S. Rao et al. Nat. Methods **20**, 1802 (2023); reproduced with permission of Springer Nature.

Photomedicine, sensors and more

Beyond potential applications in optogenetics and 3D cell models, researchers have investigated hydrogel fibers and waveguides for a wide range of other uses in photomedicine, biosensing and more. Here's a random sample of some recent work.



Localized delivery of cancer drugs

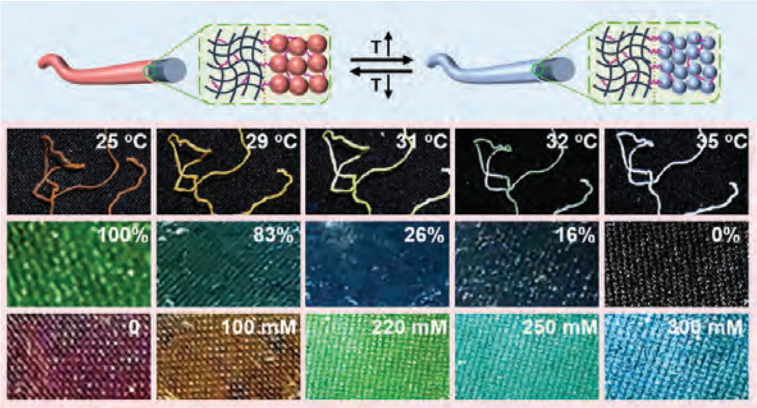
In 2020, a team at Shenzhen University, China, demonstrated a method to create core–shell hydrogel fiber scaffolds, in which the core was loaded with anti-cancer drugs. The resulting fibers, when embedded in cancerous tissue, released the cancer drugs on external irradiation with near-infrared light.

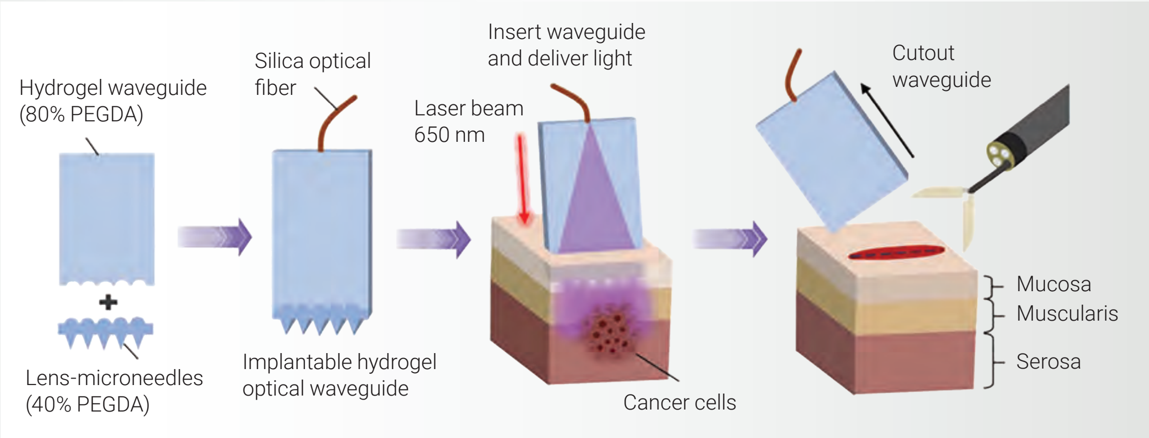
Reprinted from X. Wei et al. Int. J. Pharm. **580**, 119219 (2020), ©2024, with permission from Elsevier

Structural color

A 2024 paper from workers at the China University of Petroleum unveiled "intelligent" hydrogel fibers doped with thermoresponsive microgel photonic-crystal blocks. The blocks caused the fibers to display iridescent structural colors—which could change with changes in temperature, owing to the shrinking or expansion of the microgel blocks. The tunable hydrogel fibers, the team maintained, have "great potential for smart fibers and clothing fabrics and tracking for changes in environmental factors."

L. Zhu et al. ACS Appl. Polym. Mater. **6**, 1720 (2024); ©2024 ACS

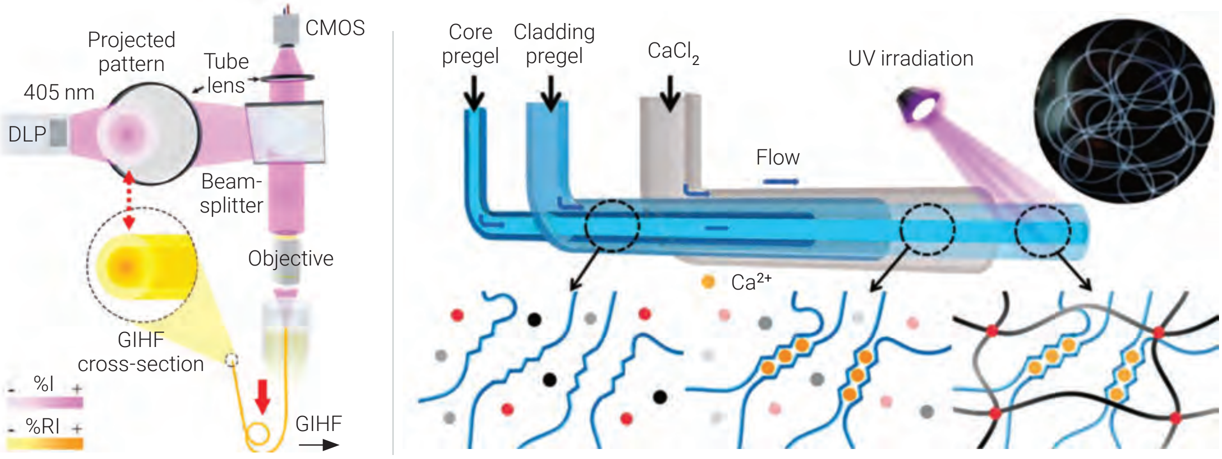




Light for photodynamic therapy

Researchers from three Taiwan universities this year devised a flat hydrogel waveguide—attached to an array of microlens–microneedle probes, also fashioned from a biocompatible hydrogel—that could focus laser light at specific points and deliver it beneath the tissue surface, for potential deep-tissue photodynamic cancer therapy.

L.P. Li et al. Adv. Photon. Res. **5**, 2400031 (2024); CC-BY 4.0



Left: Creating a graded-index hydrogel optical fiber (GIHF) by 3D printing using a digital light processor (DLP).
Right: A microfluidic approach to creating hydrogel optical fibers with consistent properties.
X. Zhuo et al. Adv. Opt. Mater. **12**, 2301613 (2023) / G. Fitria et al. Adv. Opt. Mater. **11**, 2300453 (2023); ©2023 Wiley-VCH GmbH

polymers in the hydrogel fiber core into nanocrystalline domains. That created a new adjustable parameter that could be used to tune both the core's refractive index and its fatigue resistance.

The technique was promising, but it left Rao, Liu and their colleagues with a knotty two-way optimization problem. Increasing the crystallinity would boost the core's refractive index and long-term toughness. But an overabundance of nanocrystalline domains would increase light absorption and scattering and reduce the fiber's flexibility, eventually making it too optically opaque and physically stiff for the planned use.

After substantial effort, the team found a trade-off that worked—a chemically crosslinked polyvinyl alcohol (PVA) hydrogel core with just enough crystallinity to toughen up the hydrogel and boost the core's refractive index, but that still kept scattering to a minimum and enabled a nice, stretchable probe for long-term use in a moving animal. The researchers coated the fiber core in a lower-index cladding made of an amorphous PVA hydrogel, with a dash of black graphene oxide flakes sprinkled in to absorb stray light.

As a proof of concept for the new hydrogel fiber, unveiled last year in a paper in *Nature Methods*, the MIT team chose a particularly difficult application: optogenetic stimulation of the sciatic nerve, in the hind leg of a lab mouse, while the mouse was freely running on an exercise wheel. The researchers implanted a length of the fiber running nearly the entire length of the mouse, with a stub near the animal's skull for coupling external light sources delivering 473- or 589-nm laser pulses. The hydrogel fiber stood up to repeated movement in the running mouse's limb across eight weeks of experiments—and allowed the scientists to use optical stimulation through the fiber to inhibit pain hypersensitivity in the sciatic nerve.

The two lead authors have since moved to faculty gigs at different institutions—Rao at Binghamton University, NY, and Liu at Michigan State University, MI, USA. But they continue to collaborate to move the hydrogel fiber work forward. "I think one of the inspirations … from this collaboration is that [we] always learn which engineering design is most needed to answer biological questions," says Rao. "I think that's a smart design for the next generation of neuroengineering tools."

Toward better fabrication

From a materials-science viewpoint, Liu says she's motivated by the chance to develop hydrogels as "a third generation of optical materials"—a flexible, optically versatile alternative to glass or organic plexiglass in specific applications. But one big hurdle to that vision, she notes, is the need for better manufacturing technologies. Water-logged hydrogels, after all, aren't suited to the high-temperature techniques used to draw kilometers of uniform silica optical fiber out of a single glass preform.

In fact, much of the lab work to date on hydrogel fibers, including that of Liu and Rao, has used basic tube-molding techniques. These, Liu says, produce serviceable fiber but don't allow researchers to "dig into more complex structures," such as in-fiber graded-index (GRIN) hydrogel lenses. Such structures, Rao notes, could enable microscopy deep within

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brain tissue without harming its delicate structures. Liu believes one possible route to such complex structures lies in improvement in 3D-printing techniques for hydrogel fibers.

An intriguing study late last year from the lab of Hua Shen of the Nanjing University of Science and Technology, China, showed just such an approach. Hua's team used "projection-suspended photocuring" 3D printing to fabricate fiber from acrylamide hydrogel, with light energy used to drive the necessary crosslinking of the polymer molecules. In this setup, a digital light processing (DLP) system projected custom printing patterns through a microscope objective on the fiber cross-section. The DLP-shaped light allowed the amount of crosslinking (and thus the refractive index) to be varied across the fiber core, at sub-micron resolution—enabling the creation of a GRIN hydrogel fiber.

Microfluidics could offer another route to larger-scale fabrication of more complex hydrogel fiber structures. A research group led by Jeesu Kim, Ki Su Kim and Jinhwan Yoon at Pusan National University, Republic of Korea, recently demonstrated a method that used a multichannel microfluidic setup, coupled with UV crosslinking of the hydrogel precursors, to create dual-core hydrogel optical fibers. The team showed that the fiber could be used to deliver two different wavelengths of light simultaneously for applications such as *in vivo* diagnostic spectroscopy. And the microfluidic technique, the team believes, allows precise, on-demand control of the fibers' "geometries, sizes, structures and physicochemical properties."

That kind of control and standardization, Guimarães believes, will be essential for hydrogel fibers to meet the needs of the high-throughput pharma applications his group is targeting. "We have these materials that are very compatible, cells like them a lot," he says. "But they are not really that stable or reproducible." Taking things to the next level, he thinks, will demand the ability to create kilometers of hydrogel fiber in an automated and reliable manner. "Then you can slice them," Guimarães says "and take these different pieces and test different things with them."

S. Steinbach / Getty Images

Hydrogels: Pong superstar

The versatility of hydrogels seems to bring out researchers' creative and playful side. A recent case in point: Scientists at the University of Reading, UK, this year "taught" a hydrogel to play the vintage 1970s video game Pong.

The team started with an ionic hydrogel that could react to electrical stimuli, and then hooked it up with a multi-electrode array to a virtual Pong game environment. Using an electrical feedback loop, the researchers were able to coax the hydrogel into sustained Pong rallies. What's more, they found that the ions in the hydrogel functioned as a sort of memory, allowing the gel to improve its gameplay by as much as 10% with practice.

One thing that's clear, Guimarães suggests, is that much work is now afoot toward resolving these problems and taking hydrogel optical fibers closer to practical use in the bio lab and clinic. "There's a lot of development going on in parallel," he says. "Sometimes you'll see a citation of a paper and check it out, and someone is doing something completely different with fibers and hydrogels and photonics … I think it's really a very exciting field." OPN

Stewart Wills (stewart@stewartwills.com), a freelance science writer in Silver Spring, MD, USA, was the senior editor of *Optics & Photonics News* from December 2013 to October 2024.

For references and resources, go online: **optica-opn.org/link/1124-hydrogels**.

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